Emerging Issues in Inflammatory Bowel Diseases

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Abstracts
Poster Abstracts
Falk Symposium 151

EMERGING ISSUES IN INFLAMMATORY BOWEL DISEASES

Sydney (Australia)
March 24 - 25, 2006

Scientific Organization:
A. Fraser, Auckland (New Zealand)
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J. Schölmerich, Regensburg (Germany)
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Asia - The new frontier for IBD
Inflammatory bowel disease: Incidence and prevalence across Asia

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Inflammatory bowel disease has long been considered a disease that affects a Western more than an Asian population. Published studies from Asia show that the incidence and prevalence rates of both UC and CD are lower than that of North America and Europe. However, Asia is a diverse continent and marked differences have been reported from different geographical areas in the region. For instance, very high prevalence rates of UC have been reported from Northern India. There have, however, been a paucity of good studies carried out in Asia. Nonetheless, there have been reports on the increasing incidence of both UC and CD. There appears to be a time-lag phenomenon compared to the West. In addition to geographical differences, ethnic differences have been observed in multiracial Asian countries such as Singapore and Malaysia where the incidence and prevalence amongst Indian race has been consistently reported to be higher compared to the Malays and Chinese.

The genetic background may be different in Asian patients compared to Western patients, which may account for the differences in incidence and prevalence of disease. For example CARD-15 variants have not been found in Asian patients with CD. For UC patients, certain HLA alleles are more commonly found in Asian compared to Western patients.

There does not appear to be any gender differences for both UC and CD. The age of presentation of both UC and CD is between 20-30 years of age and does not differ from the Western experience. Although the detrimental role or conversely the positive association of smoking is well recorded in the Western literature for CD and UC, this has not been established in Asian patients. Although the data on the relationship between IBD and other environmental factors and family history are scarce, there is some evidence to support the inverse relationship of appendectomy with UC. A positive family history of UC and CD however, is less commonly found amongst Asian patients. There is no evidence of difference in the extent and distribution of disease for both CD and UC compared to the Western experience. The prevalence of perianal disease in CD and extra-intestinal manifestation for both UC and CD are both similar as well. However, the clinical course of IBD in Asia seems to be less severe than those reported in Western countries.
Inflammatory bowel disease in Asia - The same as or different to Western IBD? Phenotype and genotype

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The incidence of inflammatory bowel disease (IBD) is lower in Asia than in Western countries and this is likely to be due to both genetic and environmental factors. Can a comparison of genotype and phenotype reveal whether IBD in Asia is the same or different to Western IBD?

It is widely accepted that genetic factors play an important role in the pathogenesis of IBD. While familial clustering of IBD is well recognized in Western countries, there is less evidence this is the case in Asian IBD. [1] A lower level of familial clustering may mean that genetic polymorphisms play a lesser role in the development of IBD in Asia.

The CARD15/NOD2 single nucleotide polymorphisms (SNPs) associated with Crohn's disease (CD) but not ulcerative colitis (UC) have been confirmed in multiple Caucasian studies. [2] As yet genotyping studies have not identified any IBD susceptibility genes in Asians. The prevalence of CARD15/NOD2 mutations in Asian CD is not different to that of controls or UC with prevalence around 0%. [3-7] (Table) Gene sequencing studies have revealed rare novel CARD15/NOD2 mutations in Asians that differ to Caucasians. Other non-IBD CARD15/NOD2 genotyping studies confirm the rarity of these SNPs in Asians. [8-9] It therefore seems unlikely that the CARD15/NOD2 gene SNPs play a causative role in CD in Asians, and that they are relatively recent mutations that followed the genetic divergence of Asia and Europe. More data is required to evaluate other IBD susceptibility genes among different races.

There are no distinguishing phenotypes typical of either Western or Asian IBD. Male predominance of CD is a common feature of Asian IBD and contrasts female gender predominance in Western countries. [1,10] The cause for this disparity is unknown but smoking does not appear to be the confounding factor. [1] Regarding disease behaviour and extent, CD and UC phenotypes appear similar in Asian and Western IBD.

Despite the genotypic differences between Western and Asian IBD, phenotypic differences within a race are greater than that between races. These findings support the concept that IBD is a heterogeneous collection of diseases that are not race-specific. These findings plus the rapid increase in disease incidence suggest environmental factors play a crucial role in the development of IBD.

References


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<tr>
<td>Inoue 2002</td>
<td>Japanese CD</td>
<td>0</td>
</tr>
<tr>
<td>Yamazaki 2002</td>
<td>Japanese CD</td>
<td>0.2 (SNP 8 heterozygote)</td>
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<tr>
<td>Leong 2003</td>
<td>Chinese CD</td>
<td>0*</td>
</tr>
<tr>
<td>Croucher 2003</td>
<td>Korean CD</td>
<td>0**</td>
</tr>
<tr>
<td>Guo 2004</td>
<td>Chinese CD</td>
<td>7 (SNP 13 heterozygote)</td>
</tr>
<tr>
<td>Chong 2004</td>
<td>Chinese SLE</td>
<td>0</td>
</tr>
<tr>
<td>Kim 2004</td>
<td>Korean AS</td>
<td>0.5 (SNP 12 heterozygote)</td>
</tr>
</tbody>
</table>

**Table: CARD15/NOD2 gene in Asia**

CD = Crohn's disease  
SLE = systemic lupus erythematosus  
AS = ankylosing spondylitis  
SNP = single nucleotide polymorphisms  
*2 novel SNPs on whole gene sequencing at 3' untranslated region  
**10 SNPs identified but none significant
Inflammatory bowel disease in Asia - Response to therapy

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In the past 20 years, inflammatory bowel disease (IBD) has been progressively increased in Asia, which gives a great challenge to the clinicians for better management of the disease in this area due to lack of awareness, knowledge of the disease, financial support and completeness of Medicare system in the most of the countries.

A review of literatures from MEDLINE in recent 8 years showed that comparatively less published papers from this area (13.6% of the global) with even less of original articles (39.24% of all). The most of the paper is from Japan with Israel, Australia, China, New Zealand, India and Korea next. A similar principles and guideline used as Western IBD in the most of the countries, but the medications used are rather simple and preliminary for majority of cases with 5-ASA and corticosteroids predominant (57.0%), probably because of mild-moderate case predominant or limitation of the resources. In general the response to therapy is encouraging. The combination of classical and traditional medication have been used in some IBD with satisfactory effects. The prognosis and clinical course of IBD in this area seem to be less severe with less complications, less operating rate and mortality rate than those reported in Western countries.

Some special or alternative therapies have been used in this area. The most of experiences came from Japan such as leucocytapheresis, anti-IL-6R and anti-IL-17 monoclonal antibody, germinated barley foodstuff, nutritional support etc. Traditional Chinese medicine (TCM) including different prescriptions and pattern and different combination with Western medicine have been used mostly in China. Acupuncture has only been tried in a few lab and clinical setting.

Following global research trend, active investigation on pathogenesis of IBD and its therapeutic implication have been persuaded in this area, which generate reasonable therapeutic targets in cell or molecular level, even gene treatment for control or cure the disease, and staminate the development of novel therapeutic agents from local traditional medicine.

In summary, the response to therapy of IBD in Asia is generally the same as those of Western IBD with even better prognosis and less severe clinical course. Some special or alternative treatment play important adjacent role with encouraging efficacy. The exact mechanism and effects need to be studied and evaluated scientifically for better and widespread usage.
State-of-the-Art-Lecture

Pathogenesis - Why is IBD increasing in Asia?

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For approximately 100 years humans have been progressively undergoing changes in social, economical and historical conditions that have had a major impact on the health status of the population at large. Severe diseases with an infection-based acute response have decreased, while more chronic responses manifested by immune-mediated persistent inflammatory responses or neoplasias have become more common. This evolution has not been uniform geographically or temporally, Western societies having been affected first, while developing countries have begun to be affected in the last couple of decades. Typical examples of this scenario are the remarkable rise of autoimmune and allergic diseases, such as asthma, and chronic inflammatory disorders such as ulcerative colitis (UC) and Crohn's disease (CD), collectively named inflammatory bowel disease (IBD).

In regard to IBD, both UC first and CD later, its incidence and prevalence began to increase in the early to mid 1900's in Northern Europe and North America, followed by a steady rise in the rest of Europe, Japan and South America that started after World War II and continues until now, particularly in the pediatric population. Now, it is the time of Asia, where UC, and to a lesser degree CD, are being increasingly recognized and diagnosed. So, as the increase in IBD is spreading from continent to continent, this has become a global trend, and the whole world seems destined to suffer from IBD. Faced with this reality, the question posed in the title of this abstract - Why is IBD increasing in Asia? - must be addressed in the context of the geographical and temporal variations that have occurred and continue to unfold worldwide. Ideally we should begin by answering other questions, such as why has IBD appeared in North Europe and North America first? Why only later has IBD turned up in the rest of Europe, Japan and South America? Why is it that only now Asian countries begin to see this condition? The sum of the answers to these questions may help addressing the original question about the rise of IBD in Asia: does the progressive rise of IBD in space and time hold any clues to its pathogenesis in this part of the world?

We have presently a reasonably solid knowledge of IBD pathogenesis, at least of which are the various components that eventually lead to the clinical manifestations that allow the clinician to make a diagnosis of UC or CD. There is good evidence to implicate environmental, genetic, microbial and immune factors in the causation of IBD, the only problem is - and it is a big problem - that we still do not understand how these various components interact among themselves and what comes first - a primary factor - and what comes later - a secondary factor or event. If this is true for "old IBD" it maybe even more difficult to explain the pathogenesis of "new IBD", i.e., the one that is now emerging in Asia.
If we examine each pathogenic component of IBD, both similarities and differences are noted comparing "old" and "new" IBD. Some of the changes that have occurred in the environment appear to be analogous between what has happened, for instance, in Europe about one half century ago and what is going on in Asia now. This is exemplified by a drastic change in lifestyle in regard to food, smoking, use of antibiotics and other drugs, socioeconomic progress, stress, etc., a change that has been termed "westernization". Exposure to classical infectious agents has certainly decreased in many parts of the world where IBD is now common, and improved hygiene is causing comparable changes in Asia. Little is know about the composition of the enteric flora in European and North American populations back in the early and mid 1900's and little is still known now, and even less in Asian populations. However, there is some evidence that anaerobes and enterobacteria are more common in the flora of patients with IBD, and the same may be happening in the gut of Asian people. The immune response at the systemic and intestinal mucosa immune level has essentially not been studied in Asian patients, and it is difficult to compare with what goes on in the inflamed gut of Western IBD patients. Contrasting with some the above similarities, there is the dramatic difference in genetics, represented by the absence of any association of Asian CD with NOD2/CARD15 mutations, which are found in up to 30% of Caucasian and Jewish Western patients. In addition, IBD clinical manifestations tend to be milder in Asian patients, and familial clustering is rather uncommon.

Considering all of the above, it seems that a series of other questions should be answered first, before going back to the original question of why IBD is increasing in Asia: are the similar clinical manifestations of IBD in Asia caused by the same or different mechanisms of gut inflammation? Because genetic mutations of the West are not a factor in predisposing to IBD in Asia, what other mutations, if any, predispose to IBD in Asia? Is the flora of an Asian IBD patient the same of a North American or European patient? Finally, if the pathogenesis is different, will the response to treatment be the same, or better, or worse?

In summary, it appears that we are not quite ready to answer the original question posed in the title. However, investigation of IBD in Asia offers the unprecedented opportunity to study the "early stages" of the disease - the one we missed in the past - and may provide new clues to its pathophysiology by identifying key environmental factors and new distinct genetic make-ups.
Diagnostic challenges in Asia
Gastrointestinal TB vs. Crohn's disease

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Crohn's disease (CD) and tuberculosis (TB) of the gastrointestinal tract pose major diagnostic problems for clinicians in areas where these conditions co-exist. The clinical, radiological, endoscopic and histological features are similar. In the West, TB is included in the differential diagnosis of all suspected cases of CD. Asian (southern Asian) are 10 times more likely to suffer from TB. Blacks are 8 times more likely to have TB and Hispanic native Americans and Alaskan natives are 5 times more likely to suffer from TB. Hence ethnicity is a factor in making the diagnosis. An earlier age of presentation, presence of peri-anal disease and enteric fistula favour a diagnosis of CD. However, these features are not absolute and fistulation and peri-anal disease have been described in GI TB although they are very rare. Apthoid ulceration, pseudopolyposis and filiform mucosa at endoscopy favour a diagnosis of CD. Ulceration due to TB tends to be asymmetric and have a predilection for the ileo-caecal region and ascending colon. Although the descending colon and sigmoid and rectum could be affected too. The ulcers tend to be multiple, mostly transverse or circumferential in alignment. The depth of ulcers could be superficial (< 2 mm) or deep. Incompetence of the ileo-caecal valve is common in GI TB

In only 20% of TB patients, there is associated acute pulmonary TB. Tuberculin test (Mantoux Test) is positive in 60-80% of patients. Histological features seen in tuberculosis are multiple, large or confluent granulomas with caseating necrosis and epithelioid histiocytes. Crohn's disease tends to produce small granulomas or microgranuloma, without caseation. The differentiation between TB and Crohn's disease before treatment is important, as steroid therapy can be catastrophic with GI TB. A therapeutic trial of anti-TB treatment could be considered in case of doubt. Other therapeutic options include steroid therapy (± anti-TB treatment) with careful monitoring and repeat endoscopy. PCR for mycobacterium have been advocated as a new diagnostic test but DNA from mycobacterium have been found in patients with Crohn's disease and the initial enthusiasm has waned.

The differentiation between GI TB and Crohn's disease is difficult and misdiagnosis of both conditions has been reported in the literature. Careful attention to the clinical, radiological and histological features is required to make the diagnosis. In equivocal cases, therapeutic trial with careful monitoring may be the sensible solution.
Defining ulcerative colitis and infectious colitis in Asia

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Inflammatory bowel disease (IBD) is a relatively uncommon disease among Asians. In the last two decades, however, a progressive increase in the incidence of IBD is noted in the region. Diarrheal disease is a prevalent illness in this population and is one of the major causes of morbidity and mortality. The most common colitides are infectious in nature, but in their most severe form the clinical presentation and colonic lesions can mimic ulcerative colitis (UC). It is therefore imperative to distinguish chronic UC from infectious colitis because the management and natural course of these diseases differ significantly.

Colitis and diarrheal diseases associated with infectious agents are more acute in onset, relatively short in duration and the colonic lesions are less florid. The most important diseases which need differentiation from UC are caused by very common gut pathogens, namely, *E. histolytica*, *Shigella*, *Campylobacter*, and *Salmonella*.

A most common cause of bloody diarrhea in Asia, Amoebiasis is characterized by an acute onset of mucoid, bloody stools. Tenesmus, but not incontinence, is quite a characteristic manifestation. Endoscopic examination will reveal discreet, well defined ulcers distributed between normal intervening mucosa and noted usually in the rectosigmoid or cecum. The intervening mucosa is not friable, and demonstrates the normal submucosal blood vessel array. In the more severe form, the colonic lesions can be substantial and may be difficult to differentiate from idiopathic ulcerative colitis. The isolation of hematophagous trophozoites of *E. histolytica* in the stools is diagnostic and response to metronidazole administration is often dramatic. Migration of amoebic trophozoites to the liver can cause liver abscesses after an episode of amoebic colitis. These are often solitary, right lobe abscesses and are not associated cholangiopathic abnormalities.

Bacillary dysentery, secondary to *Shigella dysenteriae/flexneri* infection, is also a known cause of bloody diarrhea in this region. Its onset is also acute and the colonic lesions are limited to the distal colon. Endoscopically, they appear as wide-based, shallow ulcers with very edematous intervening mucosa. Resolution of the bloody diarrhea is often fast with ampicillin, trimetoprim-sulfamethoxazole, or ciprofloxacin administration.

In its severe form, enteric fever due to *Salmonella typhi*, can manifest with lower gastrointestinal bleeding on the 3rd-4th week of the febrile illness. The bleeds most often come from ulcers in the distal ileum, however, bleeding from severe ulcerations in the cecum and ascending colon have been observed and reported. Copious diarrhea is not observed in typhoid fever patients presenting with lower GI bleeding. Isolation of the Salmonella from blood or stool cultures are key to the diagnosis.
In the West, bloody, mucoid diarrhea in patients with recent travel from the East is often viewed as infectious colitis unless proven otherwise. In the East, the diagnosis of ulcerative colitis is often facilitated by observing closely the clinical presentation, the appearance and distribution of the colonic lesions, the failure to isolate/culture a known infectious pathogen or sometimes, after the failure to respond to anti-infective therapy. In a few patients, the diagnosis is made only when patients come back for an episode of recurrent acute exacerbation. Careful evaluation of the patients' history, clinical findings (including extraintestinal manifestations) and the evolution of the disease on follow-up are helpful in making an accurate diagnosis between infectious colitis and chronic ulcerative colitis.

Most importantly, extraintestinal manifestations like arthritis, erythema nodosum, pyoderma gangraenous, uveitis, sclerosing cholangitis, etc. are not noted in the infectious colitides.
Diagnostic challenges in Asia - Intestinal Behçet's disease

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Behçet's disease is a chronic recurrent systemic inflammatory disorder characterized by triad of oral and genital ulcer combined with typical ocular changes. Many other organs including skin, joints, blood vessels, nerves system, epididymis and gastrointestinal tracts are also involved not infrequently. Although non-specific gastrointestinal symptoms are common in patients with Behçet's disease, intestinal ulcers are occasionally demonstrated. The frequency of intestinal involvement in patients with Behçet's disease was known to be 3-25%, with wide geographic differences. While symptomatic intestinal involvement is rare in Mediterranean patients with Behçet's disease, it is more common in East Asian patients including Koreans. Most common symptom in intestinal Behçet's disease is abdominal pain followed by diarrhea, bleeding and weight loss.

As the diagnosis of Behçet's disease relies on a combination of clinical signs and symptoms due to lack of pathognomic clinical or laboratory findings, the diagnosis of intestinal Behçet's disease also depends on clinical manifestations of systemic Behçet's disease and intestinal ulcerative lesions. We and others have reported that the typical colonoscopic findings in intestinal Behçet's disease are single or a few deep round/oval ulcer(s) with a discrete elevated margin in the ileocecal area or anastomotic site. These colonoscopic characteristics of ulcers including its shape as well as location and the distribution pattern in intestinal Behçet's disease, are helpful in its differentiation from other intestinal ulcerative diseases, including Crohn's disease.

To provide diagnostic objectivity, criteria suggested by the Behçet's Disease Research Committee of Japan and the International Study Group for Behçet's Disease (ISGBD) are commonly used. However, some of patients with typical intestinal ulcers do not fulfill these criteria. And in some patients, it took several months or years for major systemic manifestations to appear after the expression of intestinal ulceration. Therefore, one of the major diagnostic criticisms concerns intestinal involvement in patients who lack the systemic manifestations of Behçet's disease. We consider that most cases of suspect or even possible type could be included in the category of Behçet's disease when typical intestinal involvements are identified, because the clinical and endoscopic characteristics in patients with intestinal involvement who lack the systemic manifestations of Behçet's disease are in accord with those in patients who fulfill diagnostic criteria.

Recently, we have presented that serologic markers including Anti-Saccharomyces cerevisiae antibody (ASCA) and IgM anti-α-enolase antibody may have potential role not only in diagnosis of intestinal Behçet's disease but also in prediction of clinical outcome. To quantify disease activity, we use activity indices for Crohn's disease such as Crohn's disease activity index (CDAI) or Harvey Bradshaw index because intestinal Behçet's disease-specific clinical index has not been developed yet.
In summary, the diagnosis of intestinal involvement in Behçet's disease is not usually difficult because of its characteristic endoscopic findings. However, there is a need for consensus on diagnosis in cases with typical intestinal lesions but lacking systemic manifestations. Finally, we are expecting for the development of an intestinal Behçet's disease-specific clinical activity index to improve management of these patients.
Serodiagnosis of IBD

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Diagnosis of Inflammatory Bowel Disease (IBD), in general, largely depend on compatible clinical manifestation, supportive radiologic findings, characteristic endoscopic findings, compatible histologic findings and in area where prevalence of infectious colitis is high, negative investigations for infectious causes are required. Above all, the most convincing evidence for firm diagnosis probably depend on long term follow-up, response to treatment and/or relapse of disease after withdrawal of treatment. However, 10-15% of patients with IBD cannot achieve the definite final diagnosis despite extensive investigation and the diagnosis of "Intermediate Colitis" is made. In pediatric patients whom IBD is less common and firm diagnosis is also difficult to derive, other means aided in the diagnosis are needed. When other autoimmune colitis e.g. Behçet's disease, SLE and Wegener's granulomatosis are among the differential diagnosis, a combined search for specific seromarkers of each diseases are also required. A variety of immune abnormalities has been identified in IBD eg. pANCA (perinuclear type antinuclear cytoplasmic antibody), ASCA (anti-Saccharomyces cerevisiae mannan antibody, Omp-C (outer membrane porin C), I2 antibody, GABs (Goblets cell autoantibodies), PABs (Pancreatic autoantibodies) etc. These markers are evidence of cross reactivity to triggering pathogenic antigens which reflect the interplay between genetic predisposition, immune reaction and environmental factors as a pathogenetic mechanism of IBD. Initially, when these seromarkers are available their clinical values are questionable due to the inconsistency of test results and the low sensitivity and not high enough specificity. Ethnicity and racial diversity may be responsible for the variability of these test results. pANCA was found in 40-80% of patients with UC, and in 0-20% of patients with CD. ASCA was found in 60-70% of patients with CD and in 10-15% of patients with UC. The combination of ASCA+/- and pANCA-/+ was documented to have a positive predictive value of 86-96% and specificity of 94-97% for CD and the combination of ASCA-/- and pANCA+/+ with a PPV of 75-92% and specificity of 81-97% for UC. In patients with intermediate colitis, combination of serologic markers can be helpful in achieving a differential diagnosis between Crohn's disease or ulcerative colitis in a substantial proportion of patients. Although, almost 50% of patients do not develop ASCA or pANCA, ASCA+/pANCA- predicts CD in 80% of patients with intermediate colitis and ASCA-/pANCA+ predicts UC in 64% of patients with intermediate colitis. Diagnosing intermediate colitis is clinically important because patients with intermediate colitis are more likely to have pouch failure than in patients with definite ulcerative colitis. Hence, testing appeared to have a more significant impact when ordered in cases of differentiating pouchitis from CD, in atypical inflammation, and differentiation of CD versus UC. Moreover, in countries which have low prevalence of IBD but have high prevalence of infectious colitis (especially in Southeast Asia), the use of serologic markers may be used as an adjunct to reach a more definitive final diagnosis of IBD, although datas from this area are still not much available. In countries where prevalence of IBD is high, seromarkers may be used for screening purposes or may be helpful in reflecting genetic susceptibility of the population to IBD.
Some studies have shown the correlation of serologic status with the disease course or severity while others did not. If further studies can elucidate this issue, these serologic markers may hence lead to a proper prediction of therapeutic response. However, their antibody titers seem to be stable over long periods of time. pANCA in UC was shown to persists after colectomy and high titer of ASCA was found in patient whom last flare of CD was > 20 years ago. Finally and excitingly, ASCA and pANCA was shown to predict development of IBD years before the disease is clinically diagnosed.
Anti-MAP therapy in Crohn’s disease - Saviour or nonevent?

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An infectious cause for Crohn's disease has been sought since the disease was first described in 1932. Attention has focussed on Mycobacterium avium subspecies paratuberculosis (MAP) since its isolation from 3 of 11 patients with Crohn's disease in 1984. Numerous reports have appeared since then describing detection of the organism in tissue by PCR and culture. It has also been detected in blood and even breast milk in patients with Crohn's disease. However, while some workers have confirmed these findings other have not found differences between Crohn's disease and controls. Epidemiological and other factors also provide contradictions as to whether MAP is the cause of Crohn's disease and hence the role of the organism remains controversial. Conventional anti-tuberculous antibiotic regimens are generally ineffective in patients with Crohn's disease. However, MAP appears to exist in a cell wall deficient form and this, combined with its intracellular location and slow growth, make it resistant to these antibiotics. Anecdotal open-label studies using antibiotics that are effective against MAP have reported favourable results. However, there have been no large controlled trials until now. The Australian trial of anti-paratuberculosis therapy (APT) randomised 213 patients to receive either clarithromycin, rifabutin and clofazimine or matching placebos in addition to 16 weeks of a reducing dose of oral prednisolone. Patients in remission after that time continued antibiotics or placebos for up to two years. They were then followed for a further one year off trial medications. Although a short term benefit was found for the antibiotic combination at 16 weeks, with fewer subjects having a relapse on active treatment during this period, this benefit was not maintained at one or two years of treatment, with the majority of patients in both groups having at least one relapse. One year after the trial agents were ceased only 13.7% of those who were on active treatment and 9.0% of those on placebo were in remission, a non-significant difference. Disease site, age, smoking status or a history of previous Crohn's surgery did not influence the likelihood of a response. The treatment was generally well tolerated. These findings argue against a role of active infection with MAP as a significant cause in the majority of patients with Crohn's disease.
Key issues in the pathogenesis of Crohn’s disease
The search for an infectious cause

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The search for an infectious agent or agents as a cause of chronic granulomatous intestinal lesions in humans began as early as 1913 when the disease in humans was likened to Johne's disease in ruminants. The detailed description (of regional ileitis) by Crohn et al in 1932 led to repeated attempts to identify a wide range of putative infectious agents as causes of this disease.

Initially research focussed on bacterial cultures of stool and surgically removed intestinal tissue. The increased sensitivity and specificity of diagnostic techniques (including electron microscopy) for identification of bacteria, viruses and other agents widened the search. To date, research appears to have been more successful in excluding putative infectious agents rather than in producing conclusive evidence of the involvement of specific pathogens. For example, numerous studies have excluded many enteric (and other) pathogens, including species of E. coli (ETEC, EPEC, EHEC) Campylobacter, Clostridium difficile, Yersinia, Chlamydia, rotaviruses, reoviruses, adenoviruses, CMV, retroviruses, measles, picornaviruses and herpesviruses.

The advent of molecular biological techniques has shown that the distribution and diversity of micro-organisms infecting humans is much greater than previously realised. The application of these techniques to detection of micro-organisms in tissue from patients with Crohn's disease has resulted in attention being focussed at present on three putative causes of this disease.

Firstly: Mycobacterium avium subspecies paratuberculosis (MAP) has been identified in biopsy tissue and peripheral blood mononuclear cells in a variable proportion of patients worldwide.

Secondly: Adherent/invasive E. coli have been identified in association with the disease in France.

Thirdly: I2 gene sequence (from Pseudomonas) has been identified in lamina propria mononuclear cells in patients in USA.

It is possible that all three organisms are involved in the aetiology of Crohn's disease and that their importance varies from country to country (in an analogous fashion to the changing geographical prevalence of organisms causing acute gastroenteritis). It is also possible that new agents may be identified by future studies using newer molecular biological techniques.
Disturbances in microbiota - Cause or effect?

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IBD are a group of complex polygenetic diseases also involving environmental factors. Evidence for a role for bacteria in IBD include an increased abundance of mucosa-associated bacteria in IBD (which occurs even where there is no intestinal inflammation), and the positive impact of antibiotics on the progress of both Crohn’s disease (CD) and ulcerative colitis (UC) of the pouch - pouchitis. Bacteria are necessary for most animal models of IBD. The increased abundance of mucosal bacteria in IBD is not non-specific because while some mucosal bacteria are more abundant this is not the case for all mucosal bacteria including the very abundant Bacteroides vulgatus. On the other hand, antibiotic treatments are not curative, and the humoral immune Ig response to bacterial antigens which is more evident in CD, appears to be polyclonal. While this argues against a role for specific bacteria causing a classical infection, certain mucosal bacteria may damage the mucosal barrier. This would promote invasion by other commensal mucosal bacteria triggering an immune response. Altered adaptive, and to a lesser extent, innate immunity have been extensively studied, and genetic defects in the CARD15 (or NOD2) gene that encodes a bacterial sensing protein modulating innate and adaptive immunity are strongly associated with ileal CD. However, the penetrance of the homozygous CARD15 frameshift mutation, which is the most strongly CD-associated genotype, is very low with only 4% of humans with this developing CD. Furthermore, mice with the same defects in CARD15 do not develop spontaneous ileitis or colitis. Therefore, there have to be other aetiological factor(s). Altered permeability is a consistent finding in subclinical CD. There are other data to suggest that altered mucin is an early event in UC. We propose that the pathogenesis of IBD is multifactorial involving specific mucosal bacteria, defective barrier function and altered mucosal immunity in an aetiology triangle.
The role of defensins

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Crohn's disease, a chronic inflammatory disease of the intestinal mucosa is usually located in the small intestine (ileum) and or in the colon. Ileal Crohn's disease has been linked to a mutation in the NOD2 gene, a bacterial recognition protein. A disturbed antimicrobial defense as provided by an arsenal of different epithelial defensins seems to be a critical factor in disease pathogenesis. Defensins are antimicrobial peptides and in the ileum, are mainly expressed in Paneth cells, epithelial cells that also express NOD2. In the colon, defensins are expressed by enterocytes or metaplastic Paneth cells. Ileal Crohn's disease patients are characterized by a reduced antibacterial activity and a specific reduction of ileal Paneth cell defensins. In ileal Crohn's patients displaying a NOD2 mutation, this decrease is even more pronounced. In contrast, Crohn's disease of the colon is characterized by an impaired induction of beta defensins in enterocytes. In conclusion, the regional localizations of Crohn's disease, either ileal or colonic disease, can be linked to different defects in defensin expression. In line with these new findings, we predict that future therapeutic strategies aimed at restoring the host-microbe balance at the intestinal mucosa may prove superior to those that broadly suppress inflammation and adaptive immunity.
It seems likely that the responses of intestinal macrophages to bacteria play a central role in the development of Crohn's disease (CD). Macrophages show evidence of active phagocytosis; they migrate to the subserosa or to regional lymph nodes, a pathway that parallels the inflammation of CD; and they form granulomata, a classical feature of CD.

Intestinal macrophages comprise 10-20% of the total cell number in the lamina propria. The resident macrophage population is derived from blood monocytes which migrate through the lamina propria towards the luminal surface beneath the basement membrane. Although they express an "activated" phenotype, and retain avid phagocytic and bacteriocidal activity, they do not express many receptors associated with the innate immune response. Nor do they produce proinflammatory cytokines in response to inflammatory stimuli. This down-regulation is mediated by transforming growth factor beta (TGF-β) produced by stromal mast cells and epithelial cells. The phenotype of the intestinal macrophage has obvious functional implications in the gut, e.g. LPS-unresponsiveness due to down-regulation of CD14 and TLR4.

During acute inflammation there is an influx of blood monocytes. Unlike resident macrophages, these respond to LPS and other stimuli by producing pro-inflammatory cytokines, reactive oxygen and nitrogen intermediates, proteases that degrade the extracellular matrix and other tissue-damaging molecules. Epithelial barrier function is also affected.

Mutations in CARD15/NOD2 confer susceptibility to CD. The protein product of this gene is a cytoplasmic sensor for muramyl dipeptide (MDP), a component of peptidoglycan (PGN), which is present in all bacterial cell walls. CARD15/NOD2 does not appear to be expressed at significant levels by resident intestinal macrophages but is present in high levels in recently recruited monocytes. In fact, CARD15/NOD2 is expressed on all peripheral blood monocytes which migrate into virtually all tissues. Why inflammation is confined mainly to the gut in CARD15/NOD2-variant-expressing CD patients is not known. Understanding the responses of these cells to bacteria in the unique micro-environment of the intestinal lamina propria may help explain the development of CD.

References available on request.
Connective tissue responses

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Crohn's Disease (CD) is frequently complicated by extracellular matrix (ECM) changes that result in fibrosis. Examination of the regulators of ECM degradation and deposition are required in order to understand and potentially modify the healing/scarring process.

Work has shown that functionally different fibroblasts are present in IBD compared to control tissue, but are not disease specific. This supports observations that enhanced expression of the pro-fibrogenic proteins transforming growth factor (TGF)-β1 and insulin-like growth factor (IGF)-1 depends on the presence and location of inflammation rather than IBD subtype. Collagen secretion is enhanced by TGF-β1, IGF-1 and platelet-derived growth factor (PDGF), and TGF-β1/IGF-1 levels are associated with increased collagen type III:I ratios consistent with early scar formation. The levels of TGF-β1 and TGF-β3 may also be important in fibrosis development as a decreased TGF-β1:3 ratio is associated with reduced scarring, but all these findings suggest that fibrosis is still a non-specific response to tissue damage.

Microarray gene expression analysis of CD, ulcerative colitis (UC) and control colonic tissue demonstrated a differential expression between proteins involved in tissue digestion and deposition, and that the ECM regulatory protein, secreted protein acidic and rich in cysteine (SPARC), was also differentially expressed. SPARC appears to play a role in tissue healing and may be anti-fibrogenic. It blocks TGF-β1 activation, through activation of plasminogen activator inhibitor (PAI)-1, and binds to platelet-derived growth factor (PDGF), thus preventing activation of its receptor. SPARC can increase tissue digestion through the induction of COX-2 and indomethacin inhibits COX-2 activity and can induce intestinal fibrosis. Retinoic acid (RA) induces SPARC and is known to be anti-fibrogenic (see figure).
In the murine model of trinitrobenzene sulfonic acid (TNBS)-induced intestinal fibrosis, SPARC mRNA and protein expression was inversely related to fibrosis. RA reduced and indomethacin induced fibrosis. SPARC expression was induced by both RA and indomethacin, but as indomethacin blocks COX-2 the induced SPARC was potentially unable to inhibit fibrosis. In the SPARC-null mouse, TNBS induced similar levels of fibrosis to the SPARC wild-type mice treated with indomethacin/TNBS. RA reduced fibrosis, but to a lesser extent suggesting pathways other than SPARC are involved.

The intestine has a limited response to injury. Either tissue regeneration occurs without scar formation or repair with scarring. The processes involved in scarring are yet to be unraveled, but investigating the interplay between SPARC, the TGFβs and other ECM regulatory proteins may lead to effective therapies for its prevention.
State-of-the-Art-Lecture

How do genes influence susceptibility to inflammatory bowel disease and phenotype?

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Chronic inflammatory diseases of barrier organs (inflammatory bowel disease (Crohn's disease, ulcerative colitis), brochial asthma, psoriasis, periodontitis) share important elements in their inflammatory pathophysiology. It appears that increased expression and production of TNF and an enhanced state of activation of the NFκB system are main drivers of the inflammatory pathophysiology. It is suspected that activation of the IL-6 system is an important event in the proximal regulation of TNF in these diseases. Crohn's disease can be used as the prototype for diseases in this group. The exploration of inflammatory pathophysiology of Crohn's disease using full genome, cDNA based arrays has generated more than 600 genes that are differentially expressed between inflamed mucosa and normal controls. Real-time TaqMan can verify about 70% of the expression screening results. It appears, however, that the dissection of the inflammatory pathophysiology does not allow to identify the multifactorial etiology of the disease.

The genetic etiology of Crohn's disease represents the pattern of a typical civilization associated disease. This disorder 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 high concordance in monozygot ic twins (> 55%), which is not seen in dizygotic twins (< 5%) points to strong contribution of genetic susceptibility to the overall risk for disease. The current hypotheses propose unknown trigger factors in the life style of Western industrialized nations that interact with a polygenic susceptibility.

Genome-wide linkage analysis has demonstrated eight confirmed susceptibility regions with the one on chromosome 16 being most consistent between different populations. In 2001 three groups presented the first susceptibility gene for Crohn's disease on chromosome 16q. Three coding variations in the CARD 15 gene, which encodes NOD2, are highly associated with development of the disease. Notably, the three disease associated SNPs are never found on the same haplotype. In compound heterozygotes or homozygotes they result in a RR of > 35 to develop Crohn's disease as an adult. A particular subphenotype with localization of the disease in the ileocecal region is highly associated with the variants in the CARD 15 gene.

All three major variants affect a part of the gene that codes for the leucin rich part of the NOD2 protein, that appears to be involved in bacteria induced activation of NFκB in macrophages and epithelial cells. NOD2 however regulates a wide array of target genes. An analysis of the NOD2 regulated proteome identified YB1 as the top molecule, which...
interestingly is also a target gene for GM-CSF, that has recently evolved as a promising therapy for IBD.

Variations in the CARD 15 gene do not fully explain the linkage finding in the pericentromeric region of chromosome 16. After stratification for CARD 15 variants, the broad linkage peak is reduced to two more defined peaks on 16p and 16q, respectively. While the exploration of these regions has led to several association signals that are subject to further fine mapping a further disease gene progress has been greater in the other linkage regions.

Additional disease gene has been discovered in the linkage region on chromosomes 10 and 5, respectively. DLG-5 is the example of a low-risk susceptibility gene with a modest associated odds ratio (1.2-1.5). Interestingly, the association signal appears to be confined to young males. SLC22A4/5 which encode the kation-transporters OCTN1 and 2 have been suggested to represent the disease gene in the 200+ kb haplotype block on chromosome 5q31. MDR1 has also been implicated as a disease gene in IBD. Although the human association studies have resulted in highly controversial findings a knockout mouse with a colitis phenotype makes MDR1 likely as a low risk susceptibility gene.

Alternative splicing appears to be major mechanisms resulting in plasticity of the human proteom. Not to a surprise several splice variants exist for NOD2. A short form of NOD2 (NOD2-S) exists as a natural antagonist for the full length NOD2. NOD2-S is induced by IL-10 and down-regulated by TNF. Its upregulation could have contributed to the therapeutic ineffectivity observed for a therapy with IL-10. The full understanding of these non-genetic regulatory mechanisms may place NOD2 at an important part of the cascades originating from other disease genes, too.

Epidemiologic investigations have clearly identified the existence of trigger factors in the life-style of Western industrialized civilizations that precipitate genetic susceptibility into clinical manifestation of inflammatory bowel disease. While the exact nature of the triggering events is unclear, the hypothesis has been raised that mucosal flora may play an important role. It appears as if chronic inflammatory bowel disease in accompanied by an impressive simplification of the colonic flora as evidenced by a reduced diversity of 16S rDNA amplicons. Most interestingly a reduced diversity in bacterial species on the colonic mucosa in inflammatory bowel diseases in inversely related to an increased diversity in fungi.

The further exploration of Crohn's disease (and other inflammatory conditions following this path) will generate important insights into mechanisms leading from genetic susceptibility to clinical manifestation of complex diseases.
Investigation of the GI tract -
Expanding the horizons
Faecal testing in inflammatory bowel disease

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Traditionally, faecal testing has been used in inflammatory bowel disease (IBD) to exclude gastrointestinal infection. However, recent years have seen the emergence of a variety of diagnostic faecal tests aimed at quantifying inflammation non-invasively. These tests reflect both the presence and degree of intestinal inflammation, and are usually derived from faecal leucocytes. They include calprotectin, lactoferrin, polymorphonuclear neutrophil-elastase, lysozyme, myeloperoxidase α1-antitrypsin and luminal nitric oxide. These tests are characterised by high sensitivity for the presence of inflammation, although low specificity for the cause. Therefore, they currently have two potential roles in IBD. Firstly, they may be used to aid in IBD diagnosis, triaging patients into those who do, and those who do not, require more invasive testing. Secondly, they may be used to distinguish between inflammatory and functional gastrointestinal symptoms in patients with known Crohn's disease, allowing for the appropriate use of pharmacotherapy.

The two diagnostic tests that have been most intensively researched are faecal calprotectin and lactoferrin. Each of the faecal tests has different characteristics, although both are stable (allowing for delayed analysis at centralised laboratories) and require small samples of faeces. Both of these tests have been shown to be able to differentiate between IBD and functional bowel disease in large groups of ambulatory patients. Furthermore, for IBD patients in clinical remission, both tests can predict whether or not a patient is likely to relapse over the coming year. Increasingly, these tests are being used in clinical trials as surrogate markers of remission and even mucosal healing. Studies have also shown that these markers are sensitive to the effects of pharmacotherapy such as corticosteroids, thiopurines and newer biological agents. Comparative testing between these tests and more invasive and expensive procedures such as colonoscopy with biopsy, small bowel permeability tests and measurements of faecal white cell excretion show high specificity and sensitivity. Both also perform significantly better than serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in similar testing.

In conclusion, faecal testing provides clinicians with a non-invasive means of assessing both the presence and degree of intestinal inflammation. It is especially useful in patients for whom invasive testing is undesirable (the paediatric age group or those with significant comorbidity). The judicious use of these tests may also ensure that IBD patients with co-existing functional disease are not exposed to potentially harmful medications when they are not indicated.
MRI based imaging

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At least in Europe, MRI of the small bowel has become widely accepted at centers dedicated to the diagnosis and treatment of inflammatory bowel disease due to its diagnostic efficacy, which is comparable to conventional radiological methods (enteroclysis or small bowel follow through) and the avoidance of radiation. Additionally, the extraluminal visualization of pathologies such as abscesses or fistulae is superior to the conventional methods in most of the cases. From the technical viewpoint, as demonstrated recently in several studies, similar diagnostic results can also be obtained if patients just drink oral contrast rather than being intubated with a nasogastric tube as originally described for the conventional enteroclysis by Sellink. The value of MRI in assessing the intestinal inflammatory activity in patients with IBD is still not standardized and needs further evaluation.

MR based imaging can also be used to perform virtual enteroscopy. This 3D technique currently does not provide more information regarding small bowel pathologies than the conventional 2D images as recently shown by our group. The more promising approach of the 3D technique may be virtual colonography in patients with proven IBD, which may even performed in combination with MR-enteroclysis (“one stop shopping”) 3-6. However, since virtual colonography currently just depicts intraluminal morphology (at least 5 mm in size), subtle changes of the surface such as erosions or flat polyps cannot be appreciated by sectional imaging techniques. Because of these limitations, at least for the moment, virtual colonography does not present an alternative to colonoscopy in patients with IBD nor may it be used as a screening method for colon cancer in patients with longstanding ulcerative colitis or Crohn’s colitis.

Literature:


Capsule endoscopy was first described in 2000 and has rapidly developed since then. Initial evaluation focussed on its diagnostic yield in obscure gastrointestinal bleeding. More recent publications have addressed its potential role in inflammatory bowel disease (IBD). There are several potential roles for capsule endoscopy in IBD, which will be discussed:

1. Diagnosis of suspected small bowel Crohn's disease where Crohn's has not been diagnosed previously and standard investigations are negative. The yield of capsule endoscopy in this situation depends heavily on the selection criteria used. For example, individuals with chronic abdominal symptoms, persistent anaemia and raised inflammatory markers have a much higher yield than patients with symptoms alone. The yield of capsule endoscopy is higher than that of enteroclysis and push enteroscopy.

2. Diagnosis of suspected small bowel Crohn's disease in individuals with known Crohn's disease, but where small bowel imaging is negative. Published information shows a high yield and useful role for capsule endoscopy.


4. Indeterminate colitis. Capsule endoscopy has been suggested to look for small bowel disease to clarify whether these individuals have Crohn's disease. There are small studies suggesting this is useful in some individuals.

Capsule retention due to a stricture is a potential hazard of capsule endoscopy in small bowel Crohn's disease. This possibility must be considered carefully and discussed with the patient. Although capsule retention rarely causes symptomatic bowel obstruction, it is generally considered necessary to remove a retained capsule, which may require surgery. A patency capsule composed of barium is available and is helpful in some patients. The patency capsule dissolves within 48 hours and if passed whole, indicates that a video capsule will pass safely.

Capsule endoscopy is potentially very useful in diagnosing and evaluating small bowel Crohn's disease. More work is needed to clarify its role and safety. Funding and reimbursement are currently unavailable for this indication in Australia.
The small bowel - Total direct enteroscopy

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Background: We devised a new insertion method of enteroscopy "the double-balloon method" in 1997. In this method, two balloons at the distal ends of both an endoscope and an overtube are operated in combination and the endoscope is inserted while shortening the intestine. Double-balloon endoscopy is a new type of enteroscopy using this method. It was developed in cooperation with Fujinon Company and first released to the market in 2003.

Methods: We performed 459 enteroscopic examinations in 259 patients using the Fujinon double-balloon endoscopy system between September 2000 and December 2005. The spectrum of the small intestinal diseases in our experience was analyzed.

Results: Of 259 patients, ulcerative and/or erosive lesions were found in 82 cases, including 18 cases of Crohn's disease, 8 cases of NSAIDs-induced injuries, 4 cases of ulcers associated with Meckel's diverticulum. Of 259 patients, tumors / polyps were found in 48 cases, including 9 cases of adenocarcinoma, 9 cases of GIST, and 3 cases of enteric invasion of the malignant tumor from other organs. We also found 27 cases of angiodysplasia in the small intestine. Endoscopic treatments, including hemostasis using clipping devices or electrocoagulation, polypectomy, endoscopic mucosal resection, balloon dilation, and stent placement were successfully carried out in the small intestine. Balloon dilation for strictures of Crohn's disease was performed 21 times for 12 patients. Major complications such as perforations were not experienced from the endoscopic treatments.

Conclusions: Double-balloon endoscopy enabled total enteroscopy by combining both the oral and anal approaches. It features an excellent maneuverability even in the distal small intestine, and enables back-and-forth observation, biopsy, and endoscopic treatment at any given site. Double-balloon endoscopy is both feasible and useful technique for the diagnosis as well as treatment of small intestinal disorders. Double-balloon endoscopy has improved the accuracy of the diagnosis of small intestinal Crohn's disease. It has also provided endoscopic treatments for small intestinal stenoses from Crohn's disease.
The basics on how-to-treat IBD
The basics on how-to-treat IBD - Mild-to-moderate ulcerative colitis

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Therapeutic decision-making in mild-to-moderately active ulcerative colitis (UC) has to consider colonic extent of the disease and duration of activity - acute flare or chronic. Mainstay of treatment in naïve (not pretreated) patients are aminosalicylates. Patients with distal UC are primarily treated topically (enemas, foams, suppositories), while patients with a more proximal disease are treated orally. Rectal application of aminosalicylates is therapeutically more effective than oral therapy. In patients with extended disease combined (rectal and oral) treatment is superior to oral therapy alone.

The active moiety in aminosalicylates is 5-aminosalicylic acid (5-ASA). Free 5-ASA gets rapidly absorbed in the upper intestines. For delivering 5-ASA to the inflamed large bowel different formulations of aminosalicylates have been developed. In principle, 5-ASA can either be linked to a carrier molecule of which sulfapyridine in sulfasalazine is the most traditional, or 5-ASA is enveloped in a special galenic formulation (mesalazine/mesalamine), thus protecting 5-ASA from proximal absorption. In mild-to-moderately active UC mesalazine seems to be more effective and more tolerable than sulfasalazine. Differences between the new sulfa-free formulations have as yet not proven to be clinically relevant. A recent large dose-finding trial has demonstrated a daily dose of 3 g superior to lower as well as higher doses.

The next therapy escalation in patients refractory to aminosalicylates is prednisone/prednisolone either given orally or i.v. Duration of steroid-treatment should be limited. In chronically active or steroid-dependent patients immunosuppressive therapy is indicated. Compounds of first choice are azathioprine or 6-mercaptopurine. In refractory patients alternatives such as methotrexate or infliximab or lastly restaurative proctocolectomy may be considered.
The treatment of severe ulcerative colitis

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Until recently, the majority of patients with severe relapses of ulcerative colitis were hospitalized and often came to colectomy. Currently, only patients with uncontrollable bleeding, perforation and sometimes ‘toxic megacolon’ are operated on immediately.

When patients fail oral corticosteroids (in combination with maximal aminosalicylate) therapy, intravenous steroid treatment is the next step in the therapeutic approach. Patients need to be monitored closely by both surgeons and physicians, fluids and electrolytes need to be corrected and gastrointestinal infections must be ruled out. It is recommended that patients undergo a (careful) sigmoidoscopy the first day, given the prognostic value of the endoscopic appearance and the need to take biopsies to exclude e.g. CMV infection.

Up to 60-65% of patients will improve during IV steroid therapy. In the absence of any improvement, two therapeutic alternatives are available: anti-TNF therapy with infliximab and intravenous cyclosporine. IV Cyclosporine generally 'kicks in' after 3-5 days and is therefore a useful second line agent, with success rates as high as 80-90%. It is given as a continuous infusion at a dose of 2-4 mg/kg/day. Cyclosporin blood levels need to be monitored frequently and must be above 200 ng/ml. The most common side effects with cyclosporine therapy include paresthesias, hypertension, renal insufficiency, headache and various infections. Most patients who respond to cyclosporine will be "switched" to oral treatment with Neoral® and be discharged on steroids (tapered dose) + azathioprine + Neoral®.

Three trials have looked at the effects of anti-TNF therapy for ulcerative colitis. The first trial in Denmark and Sweden was specifically designed for patients with a severe attack who were hospitalized and failed steroids. Ninety days after a single infusion of infliximab, 67% of the placebo-treated patients had undergone colectomy, versus 29% of the infliximab-treated patients. In Act-1 (studying patients with severe UC refractory to immunomodulators and/or corticosteroids), clinical improvement was observed in almost 70 percent of patients after 8 weeks (3 infusions at week 0, 2 and 6), with endoscopic healing in 62%. In Act-2, similar results were obtained in a cohort, which also included 5-ASA refractory patients. Both studies clearly demonstrated the efficacy of anti-TNF treatment in (severely) active UC. Hence, the majority of patients with active disease despite corticosteroid and immunomodulator treatment can successfully be treated with infliximab. Patients who have failed immunomodulators will probably benefit from repeated maintenance therapy, ideally on an every 8-week schedule. Given the immunogenicity of infliximab, it is recommendable that patients are started on immunomodulators prior to or least simultaneously with infliximab treatment. Once infliximab is reimbursed for ulcerative colitis, the use of cyclosporine will likely only be justified in patients who have failed the anti-TNF antibody.
Medical therapy of small bowel Crohn's disease

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The small bowel, particularly the terminal ileum, is a common site of involvement in Crohn's disease. The natural history has been well described in cohort studies and most patients can expect to have a reasonable quality of life, career and family prospects. However, a substantial proportion of patients still require surgery and some will require multiple surgeries.

In the last 5 years, dramatic changes have occurred in the therapeutic approach to the treatment of small bowel disease. 5ASA drugs likely benefit only a minority of patients, such as those with very mild disease, a low likelihood of disease progression or in a minority of patients for prevention of post-operative recurrence. Conventional corticosteroids and rapidly metabolized topically delivered steroids such as budesonide are being used early in the natural course of disease, the former in patients with moderate or severe disease and the latter in patients with disease of the terminal ileum and cecum in attempts to minimize corticosteroid side effects. In patients who become steroid dependent, the addition of immunomodulators such as azathioprine, 6MP and methotrexate permit reduction in corticosteroid use and may also minimize the immunogenencity of biological agents when added to anti-inflammatory cocktails. The new biological agents, chimeric and humanized monoclonal antibodies, such as infliximab have revolutionized the treatment of Crohn's disease and despite their high costs have reduced hospitalization rates and disease complications and improved patients' quality of life. Preliminary findings also suggest greater benefit from earlier use of biologicals but some of the long term risks of biological dependence are not fully elucidated and include opportunistic infections and neoplasms. A variety of new treatments are under investigation in trials, targeting different cytokines and inflammatory pathways and changes in intestinal flora. These efforts are likely to produce additional benefit in the long term treatment of Crohn's disease and further reduce the burden of illness and societal costs.
Hot topics in the medical treatment of Crohn's colitis

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Based on the clinical and pathological features of Crohn's disease (CD) different clinical patterns may evolve into which each patient may fall during the course of the illness and marked variation exist among patients in terms of clinical course, drug responsiveness, symptoms and complications. Thus, appropriate indication for medical treatment is dependent in each patient on a number of clinical and anatomical variables. Disease site is the major determinant of the clinical pattern and, consequently, of the treatment options. Colonic CD (i.e. CD confined to the colon) accounts for approximately 20% of all CD cases.

Specific aims of treatment in colonic CD include inducing and maintaining remission, treating/preventing complications or reaching individual goals (e.g. quality of life improvement, treating diarrhoea, perianal disease, etc).

There is now circumstantial evidence that "active" drug treatment is useful and must be recommended in all colonic CD patients for acute flare up, chronic active course, steroid dependent course and complications. The "active" drug armamentarium is expanding and appropriate regimens can be tailored for all these indications improving the short and long term outcome and possibly changing the disease "natural history". Mucosal healing can be achieved with the most recent biological drugs (e.g. anti-TNF-alpha monoclonal antibodies) and this represents a novel goal to be met in treating these patients. Whether mucosal healing as assessed by endoscopy is predictive of longer and more stable periods of quiescent disease is not established.

The role of "active" drug treatment for maintenance of remission, is controversial. The majority of patients have an intermittent course and stay in relatively stable remission for most of the course of their illness. Thus, proper modes of treatment for preventing relapse are badly needed. Maintenance studies have consistently demonstrated that not all "active" drug are equally effective. Much discrepancy exists in terms of response rates with different drugs possibly related to discrepancies in remission assessment criteria, anatomical patterns, disease course prior to remission (chronic active vs long-term remission), treatments for inducing remission and different schedules for maintenance. Most of these studies have concordantly shown a high response rate to placebo (or non active treatment) suggesting that among patients with stable quiescent disease a subset exists not requiring any "active" drug treatment for at least some time. Recurrence prevention trials have yielded uncertain results using mesalamine (2.4 gr/day) (although a benefit was shown for patients with small bowel disease) and with azathioprine/6-mercaptourine. Independent studies concordantly indicate an approximately 2-fold increased risk of recurrence in active smokers, thus suggesting that by simply asking patients to quit smoking the likelihood of recurrence would be reduced by one half (i.e. much more than with any reported drug regimens) (10). Finally, no evidence indicate the efficacy of any treatment in preventing post-operative recurrence after proctocolectomy and permanent ileostomy. These patients represent the only subgroup of CD patients with no evidence of benefit from any from of medical treatment.
References:


The basics on how to treat perianal Crohn's disease

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Introduction

The major perianal (perineal) complications of Crohn's disease include fissures, anal ulceration, fistulas, abscesses, and anal canal stenosis. Fistulae, fissures and abscesses affect approximately 35 to 45 percent of patients during the course of the disease and are associated with significant morbidity and impaired quality of life. Perianal disease develops prior to or at the time of diagnosis of intestinal disease in half of these patients (1). The cumulative risk of fistula has been estimated to be 21% after 10 years and 25% after 20 years (1). Anal stenosis is uncommon.

Abscesses

Patients with perianal abscesses present with severe, constant pain in the anal area, along with fever and malaise. On examination, an area of erythematous, indurated or fluctuant skin overlying the perianal or ischiorectal space may be seen. There is usually an underlying fistula. The goal of therapy is immediate drainage of the abscess cavity while protecting the anal sphincters. The surgical approach can include local incision and drainage, catheter drainage, or seton placement if a fistula is identified.

Fissures and Ulcers

Fissures and ulcers are associated with active rectal disease. Steroid suppositories are helpful to control rectal disease and intralesional injection of long acting steroids has been shown to heal ulcers and reduce pain (2). Skin tags are common but treatment should be conservative.

Fistula Pathogenesis

One hypothesis suggests that fistulae begin as anal ulcers and that intraluminal pressure forces faeces into the subcutaneous tissue resulting in a fistula. Alternatively, fistulae may arise from abscesses within the anal glands (3). Histologically, perianal fistulae have a central fissure that penetrates through the lamina propria and muscularis mucosae and serosal surface (4).

Risk factors for the development of perianal fistulas include active rectal disease, fibrotic or stenosing disease phenotype, previous internal fistula, poor nutritional status and certain mutations in genes encoding TNFα, TNF receptor 1B and NOD2 (c-insertion) (5, 6). The HLA DRB1 allele appears protective (7).
Fistula Assessment

The mainstay of fistula assessment is examination under anaesthetic (EUA) by an experienced colorectal surgeon. Endoanal/rectal ultrasound gives good imaging of the immediate perirectal tissues but is often painful, is operator dependant and may miss supralevator sepsis. Body coil MRI done with a specific perianal protocol will identify supralevator sepsis, horseshoe fistula and residual undrained collections. It has been shown to be a more accurate indicator of prognosis than acute EUA (8, 9). Use of EUA in combination with either MRI or ultrasound is the optimal approach for evaluating fistula.

Fistula Treatment

Although healing of the fissures, ulcers and fistulae is the ultimate goal, initial treatment should be aimed at relieving symptoms. Patients should be instructed about appropriate anodermal care. Patients who also have intestinal manifestations of Crohn’s disease should receive treatment with the appropriate antiinflammatory, antidiarrheal, and/or immunomodulator drug therapy.

All perianal fistulae require examination under anaesthetic and drainage of associated sepsis. Antibiotics (metronidazole 400mg tds and/or ciprofloxacin 750mg bd) are helpful to settle residual sepsis after drainage. Uncontrolled trials report healing rates of approximately 50% (10, 11). The data on relapse after cessation are conflicting and the duration of treatment is unknown.

Azathioprine or 6-mercaptopurine have been shown to produce complete healing in a third of patients in randomised controlled trials. However, response was slow with a median time to healing of 3 months and maximal response at 6 months (12, 13). Cyclosporin is effective intravenously but relapse occurs once the drug is switched to oral (14, 15). Oral tacrolimus produces fistula improvement in 43% but only 10% remission, no better than placebo (16).

Infliximab has been a major advance in the treatment of fistula, with rapid onset complete healing in 46% of patients compared to 13% of placebo (17). Perianal abscess formation is the commonest side effect but use of both EUA and setons pre infliximab has been shown to reduce abscess formation and enhance healing rates (18). However, relapse is common by 3 months. Maintenance therapy at 5 mg/kg results in continued remission in 36% of patients (19) but is expensive and a third of patients had infectious complications during therapy requiring antibiotics.

Prognosis is related to fistula anatomy

Understanding perianal anatomy, particularly the relationship of the fistula to the sphincters, is essential to predicting prognosis and choosing therapy. Several fistula classification systems exist. The simplest is to define fistula that originate below the dentate line as low (simple), and those above as high (complex). Defining the perianal fistula anatomy as complex or simple determines the likelihood of healing and the type of surgical approach required. Parks classified fistula according to their relationship to
the external sphincter. This system is helpful in planning surgery for more complex fistula and determining which patients require long term setons (20).

The majority of simple perianal fistulae heal after initial therapy compared with three quarters of complex perianal fistulae, which typically require more episodes of drainage and more intensive medical therapy (21). Healing times vary between 3 and 42 months. Fistula recurrence occurs in a quarter to a half of patients (1, 21, 22). A quarter of patients with perianal fistulae eventually require proctocolectomy (1, 21).

**Treatment algorithm**

Simple fistula identified at EUA should be treated with antibiotics. Low fistulae that do not involve the sphincters can be treated with fistulotomy. Azathioprine or 6-mercaptopurine should be introduced if the fistula has not closed within 8 weeks and continued for at least 6 months. Associated proctitis should be treated with 5-ASA or steroid suppositories if tolerated. If the fistula fails to heal with this approach these patients should then be treated as if they had complex disease.

Complex fistulae require drainage, seton insertion and subsequent therapy with antibiotics and immunosuppression. Once sepsis has been drained induction dosing (0, 2, 6 weeks) with infliximab can be used followed by maintenance either eight weekly or episodically if relapse occurs. Setons should be removed once the fistula is dry and MRI shows no residual collections. Patients should be counselled to stop smoking and immunosuppression maintained during biological therapy.

Complex fistulae that do not heal are best maintained with long term non-cutting setons to prevent abscess formation and sphincter damage that can result in incontinence. Proctocolectomy is a viable option for those with difficult disease and active colitis who are non-responsive or refractory to infliximab.

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Therapeutic challenges in Asia
Inflammatory bowel diseases (IBD) are a public health problem in developed countries as 1 per 1000 people suffers from these diseases. The incidence of IBD has increased considerably in western countries since the Second World War and is still rising in low incidence areas such as Eastern Europe, Asia and developing countries. The effective treatment is still challenging all the practitioners. Traditional Chinese medicine (TCM) has thousands of years of history in China and is the main treatment way for all kinds of diseases including IBD. Since Western Medicine went to China about 200 years ago the combination treatment of TCM and Western Medicine starts being used in the Chinese community. TCM is used by a broad cross-section of the western community as well. It offers some attraction because it provides new options for treatment, an individualized approach, and potentially avoidance of harsh drugs or surgery. In this paper, the aetiology and treatment of IBD is compared from both TCM perspective and the Western biomedicine paradigm. To date, very few studies on the application of TCM to IBD have applied rigorous research methods in western community. The application and researches (randomized, double-blind trial conducted in our hospital) of TCM in IBD in China are identified and more possible treatment choices are considered and discussed in Western community.
**Immunosuppression in an endemically infected environment - Tuberculosis**

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Tuberculosis is a major health burden in Asia-Pacific. Relative poor infrastructure and lack of financial means have been compounded by HIV comorbidity. More than 50% of TB cases in the world occur in Asia-Pacific. Ten of the twenty-two WHO designated high TB-burden countries are located in Asia with India accounting for 30% of the world's burden.

Inflammatory bowel disease is an emerging disease in Asia Pacific. The APDW Working Part on IBD 2004 recorded a discernible increase in both prevalence and incidence of IBD in the region, more so for ulcerative colitis than Crohn's disease. With intestinal tuberculosis being common in many countries, the diagnosis of Crohn's disease can be difficult and often delayed.

The treatment armamentarium for IBD often requires the use of immunosuppressives. Steroids, azathioprine, 6-mercaptopurine and anti-TNF agents are often used in a variety of settings. These agents are well known to activate latent tuberculosis. Many strategies and guidelines have been formulated to screen for TB before the use of immunosuppressives but these may have to be fine-tuned for the region.

A detailed history of TB exposure, current symptoms of chronic cough, fevers, weight loss, ethnicity and migration is critical. Tuberculin skin test (PPD/Mantoux) has been the usual recommendation but suffers from some limitations. Most Asian countries advocate the use of BCG vaccination in childhood that may result in a false positive skin test reading subsequently. On the other hand, anergy from other concomitant use of immunomodulators/steroids may yield a false negative. Severe TB infection may also yield a false negative testing. Co-infection with HIV further impacts on the use of tuberculin skin testing.

The minimum requirement to exclude pulmonary TB is a normal Chest X-ray. Exhaustive studies for TB activity is mandatory if there are lesions on chest radiology. One must also be sensitive to possible extra-pulmonary TB disease. Patients already on immunosuppressives for IBD are to undergo periodic Chest X-rays. All prolonged chest complaints or unexplained fevers should merit a thorough work-up. The index of suspicion for the mycobacterium should remain high.

Finally, given the endemicity of TB in the region, one should appreciate the real difficulties in differentiating Crohn's disease from TB gut. The diagnosis of Crohn's disease should be re-visited early if treatment fails to give optimum result. There have been many accounts of the unmasking of TB in patients thought to have Crohn's disease when given steroids or infliximab.
Therapeutic challenges in Asia - Hepatitis B and C

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It is well recognized that immunosuppressant drugs used in the treatment of inflammatory bowel disease can accelerate liver injury in patients with viral hepatitis. In addition there have been concerns that treatment of chronic hepatitis with interferon may increase IBD activity. These issues are of special importance in Asia and other parts of the world where there is a high prevalence of hepatitis B and C.

**Hepatitis B.** A large number of studies have shown that treatment of HBV carriers with corticosteroids or chemotherapeutic drugs can lead to reactivation of HBV replication, and when treatment with these drugs is stopped, reconstitution of the host immune response can precipitate severe and even fatal liver injury. Thus clinicians need to be aware that the use of short courses of corticosteroids for the treatment of active ulcerative colitis or Crohn's disease may precipitate this clinical syndrome, with the greatest risk occurring in patients with cirrhosis. Recent evidence suggests that treatment of HBsAg positive Crohn's patients with anti-TNF drugs can also produce post treatment flares of hepatitis B. Maintainance therapy of IBD patients with azathioprine, methotrexate or other immunosuppressants may also allow increased levels of HBV replication and worsening liver injury. Anti-HBV nucleoside and nucleotide analogues can prevent immunosuppression induced exacerbations of hepatitis B and the use of these drugs in the hepatitis B infected IBD population will be discussed.

**Hepatitis C.** Although HCV replication is increased by immunosuppressive medications, there is little evidence that treatment of inflammatory bowel disease with steroids or azathioprine has major adverse effects on hepatitis C. In contrast to hepatitis B, anti-TNF therapies do not appear to cause significant disease flares of hepatitis C. There is also little evidence to suggest that these drugs lead to acceleration of HCV mediated liver injury when given on an ongoing basis, but at present there are no long term follow up studies which have examined this issue.

Thus all Asian patients with inflammatory bowel disease should have hepatitis serology checked prior to commencing corticosteroids, anti TNF drugs or other immunosuppressive treatments. Although, the presence of chronic hepatitis does not preclude the use of these drugs, close follow up and monitoring of hepatitis activity is required both during and after treatment.
Can Asia affording the new and emerging therapies of IBD?

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Crohn's disease (CD) and Ulcerative colitis (UC) comprises a series of inflammatory bowel disease (IBD) resulting from chronic up-regulation of the mucosal immune system. Although the pathogenesis of IBD remains elusive, it appears that there is chronic activation of the immune and inflammatory cascade in genetically susceptible individuals, which are directed by genetic, immunological, and environmental factors. Although the prevalence of IBD in Asian countries is still not so high compared to Western countries, the accumulated numbers of patients have been increased years by in Japan as well as the other Asian countries. Corticosteroids, aminosalicylic acid and antibiotics have represented the principal approaches in evidence-based drug therapy for IBD. However, there are cases that do not respond to conventional drug therapy or remain dependent on high doses of steroids associated with severe side effects in the long run. Thus, several efforts have been made against refractory cases, and immunosuppressive agents (Cyclosporin A, 6-mercaptopurine / Azathioprine) and biological agents (anti-TNF-α antibodies) have been generally used. Furthermore an exploratory clinical trial to investigate the safety and efficacy of humanized monoclonal antibody "MRA" to IL-6 receptor in patients with Crohn's disease was performed by a randomized, double-blind, placebo-controlled trial in Japan. By intravenous infusions 2 weeks apart of MRA, 80% of the patients had clinical response and 20% was successfully induced remission (Ito et al; Gastroenterology 2004, 126:989-996). Tacrolimus (FK506) is another calcinineurin inhibitor with immunosuppressive properties similar to those of Cyclosporin A. We conducted a randomized, placebo-controlled, double-blind study to determine the efficacy and safety of oral tacrolimus therapy followed by an open-labeled trial subsequently performed to moderate/severe, refractory active UC. At 2 weeks after study entry, the response rate was 68%, and the steroid-sparing efficacy was also obtained in the open-labeled trial at week 12. Thus, the high potency and rapid onset of oral tacrolimus therapy were demonstrated (Ogata et al; Gut, 2006 in press). Because leukocytes produce inflammatory cytokines, leukocyte removal has been implemented in Japan to treat IBD since 2001. Lymphocytapheresis, granulocytapheresis and leukocytapheresis can induce remission in refractory, steroid-resistant UC, and have a steroid-sparing effect (Naganuma et al; Inflamm Bowel Dis 2004, 10: 251-257). A pilot study of cytapheresis has also been performed in CD, with marked reduction of CDAI and IBDQ (Matsui et al; Am J Gastroenterol 2003, 98: 511-512). To evaluate the safety and effectiveness of the apheresis therapy for the treatment of refractory IBD, randomized, double-blinded, sham-controlled pivotal studies with more intensive and longer treatment are now ongoing in US, Europe and Japan. The results of this study will provide scientific approval of the effectiveness and safety profile of this novel immunoregulatory therapy originated in Japan. There have been more trials and approaches as novel therapeutic strategy for IBD in worldwide. Although some of them still need more confirmatory studies, those immune therapies will provide new insights into cell-based and gene-based treatment against IBD in near future.
Ulcerative colitis was recognised as a chronic relapsing disease by Samuel Wilks in 1859 in 19th Century London when bloody diarrhoea was regarded as infective. Even by the 1920s, it was still widely believed that the disease was related to E. coli and Sir Arthur Hurst, the Founder of the British Society of Gastroenterology, as well as Burrril B. Crohn were treating the disease with polyvalent antidysenteric serum. In 1932, the classical description of regional enteritis was published but it took another 20 years before it was accepted that the disease could be confined to the colon. The granulomatous nature of the disease suggested a mycobacterial aetiology; that hypothesis was rapidly dismissed but has had a resurgence. It now seems likely that DNA specific for Mycobacterium avian subspecies paratuberculosis can be found in the tissues of some patients as can DNA from E. coli, Listeria and Yersinia - i.e. these organisms may be there as secondary invaders. Effective therapy was only introduced for ulcerative colitis in the 1940s and 50s (sulphasalazine and corticosteroids) but rapidly became evidence-based. Clinical trials for Crohn's disease were thought to be too difficult as the disease was so heterogeneous. The introduction of clinical activity indices provided a tool which allowed an objective measure of therapeutic response. Thus, the medical treatment of Crohn's disease has also become evidence-based.

So, what are the mistakes that have been made in the West? Broadly they would include:

- Regarding UC and CD as single homogeneous disorders. Data on genetic associations now available clearly suggest that is not so.
- Failing to follow treatment guidelines. For example, a recent audit of severe ulcerative colitis from a distinct general hospital in the UK reported a mortality of > 24% at a time when specialist centres had a mortality of < 1%.
- Crohn's disease was frequently managed by surgeons prior to effective medical therapy who, not entirely without reason, argued that prognosis could be improved by extensive resection. The consequences were often disastrous and the concept of minimal surgery, and its subsequent validation has made a major contribution to improving management and hence quality of life.
- The consequences of radical surgery induced considerable reluctance on the part of physicians to refer patients for early surgery but, in turn, this led to prolonged courses of corticosteroids. There is now an almost hysterical anti-steroid feeling amongst many gastroenterologists which may well deny patients rapid alleviation of symptoms.
There has been considerable reluctance to adopt new therapies once their benefits have been established. Examples include the early introduction of immunosuppressants for refractory disease and of cyclosporin for severe ulcerative colitis not responding to intravenous corticosteroids.

**IBD in Asia** The following points are made in the hope that the optimal management of these diseases will be achieved more quickly than has happened in the West.

- Define the nature of the disease. Clinical studies of ulcerative colitis from the Indian sub-continent and China have shown differences from Western populations. Genetic studies also highlight major differences both in HLA associations and the lack of association of Crohn's disease in Chinese, Japanese and Koreans with NOD2 mutations or the IBD5 haplotype.

- Define protocols for management. This will involve creating multidisciplinary teams (physicians, surgeons, radiologists, pathologists) but will need an evidence-base obtained on the local population. If the genetic and clinical heterogeneity is different from Western populations, then response to treatments may also differ. Thus, management guidelines based on Western studies may help to a degree but only if they are to be subsequently tested in randomised trials.

- Sub-specialist training may not have a high priority in many Asian countries especially for diseases which are uncommon. Nevertheless, this will be essential to achieve optimal management.
Making sense of emerging therapeutic options
Are biologicals efficacious enough?

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Biological drugs are effective in treating patients with inflammatory bowel disease, to a degree previously not experienced with conventional drugs. Whether they are considered effective enough depends on whether therapeutic goals are attained, and at what cost. Benefit needs to be considered in terms of proportion of patients in whom remission is induced, speed of induction, and duration of response. This benefit needs to be weighed against issues such as immunogenicity, loss of response, safety and cost.

To obtain maximum benefit from these agents certain practical therapeutic algorithms need to be utilised. To a large extent these are based on published clinical trials, but other published information also needs to be incorporated into practical protocols. For example the use of MRI to monitor fistula healing is likely to enhance benefit from these drugs. While there are clear guidelines as to when to start using these drugs, and how to use them, much other information is still lacking: dose adjustment regimes, combination therapy with other simple molecules, when to stop treatment, and how to re-introduce treatment after a treatment-free period.

Those drugs of proven benefit fall predominantly into the mechanistic domains of TNF-\(\alpha\) inhibition [the chimeric antibody infliximab (the only biological drug licensed for inflammatory bowel diseases), the humanised antibody CDP870 (certolizumab), and the human antibody adalimumab] or adhesion molecule inhibition [\(\alpha 4\) antagonist natalizumab or \(\alpha 4\beta 7\) (gut-specific) antagonist MLN02]. A variety of other biologicals are in less advanced stages of development.

When treating luminal disease with infliximab approximately two thirds of patients respond initially. The ACCENT 1 study demonstrated that 28% of initial responders are in remission for one year.

Infliximab has had a major impact on the management of Crohn's anorectal fistulas. The ACCENT 2 study demonstrated initial response in two-thirds of patients. Considering all treated patients approximately one fifth are healed at one year. Infliximab diminished the need for further surgery. MRI scanning allows the extent of deep healing to be assessed and may influence the duration of treatment.

In the treatment of ulcerative colitis, the ACT 1 and 2 studies have demonstrated efficacy of infliximab over placebo in patients in whom other therapies have failed.

The long-term benefits and risks of biologicals remain to be defined.

Biological drugs can offer great therapeutic benefit, but their use must be considered in context.
Step up or step down therapy in Crohn's disease

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Conventional therapy with corticosteroids in Crohn's disease is disappointing in the long term and associated with considerable adverse effects. Corticosteroids do not maintain remission, possibly due to the fact that it does not heal the mucosa. In the last decade the management of Crohn's disease has altered rapidly with a more widespread and aggressive use of immunosuppressive medications such as 6-mercaptopurine/azathioprine and methotrexate. Furthermore, even less reliance is placed on corticosteroids in paediatric practice where defined formula diets are widely used in Europe.

In steroid dependent patients, immunomodulator therapy with azathioprine or methotrexate are generally the accepted option, but the onset of action is slow. The GETAID group in France randomized Crohn's disease patients who were steroid dependent for over 6 months to infliximab (5 mg/kg at 0, 2, 6 weeks) + azathioprine or placebo (at 0, 2, 6 weeks) + azathioprine. Two different strata of patients were recruited, those who were azathioprine naïve and those who had failed azathioprine therapy. At 12 weeks after randomization 75% of patients in the infliximab group were in steroid free remission compared with 38% in the placebo group (p = 0.003). However at week 24, steroid free remission rate in the infliximab group had dropped to 57%, suggesting that continuation of infliximab might have maintained the remission rate. The efficacy was better in the azathioprine naïve stratum. This study provides evidence that infliximab therapy can be a very valuable therapy to wean patients off corticosteroids, but maintenance therapy along with azathioprine might be the best strategy. This therefore is an example where infliximab has been used second-line along with immunomodulator therapy.

The efficacy of infliximab has raised the question of the place of biologicals in the algorithm and whether such therapy should be used earlier rather than as third line therapy. Such a strategy was tested in a trial of top down versus step up therapy presented at the Digestive Diseases Week 2005 in Chicago. In an open multicentre study in 129 patients, 64 patients were randomized to step up therapy (steroid - immunomodulator - infliximab) and 65 were randomized to top-down therapy (infliximab + azathioprine - episodic infliximab - steroid). Though remission rates were similar at 6 and 12 months, steroid free remission was superior in the top down strategy at month 6, as was mucosal healing and emergence of new fistulae. This study provides the first tantalizing evidence that early treatment with infliximab might be beneficial and this is being tested in the context of a randomized controlled trial in immunomodulator naïve CD patients.

In paediatric Crohn's disease patients, there is some suggestion that treatment of early disease may result in better long term outcome as well as catch-up growth. It is likely therefore that at least in selected patients, a top down approach starting with corticosteroid therapy may be beneficial. Evidence from rheumatoid arthritis also suggests that early aggressive therapy with biologicals may alter the natural history of the inflammatory process. Patients with aggressive perianal disease, severe Crohn's colitis and extensive small bowel disease may be especially suitable for such a top down approach.
New therapies and pregnancy

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In inflammatory bowel disease, fetal outcome and maternal well-being during pregnancy is largely determined by disease activity. Infertility, fetal wastage, low birth weight and prematurity are increased when inflammation is active. As a result, the control of inflammation prior to conception, and the maintenance of remission during pregnancy are advisable. Naturally, patients are concerned about the possible harmful effects of drug therapy to the developing fetus, and ideally, a discussion regarding these matters should be undertaken well in advance of conception. Generally, the minimum drug therapy that is effective and safe is preferable, though in certain cases of moderate to severe IBD, immunosuppressives or biological agents may be required.

Animal studies using high doses and early clinical experience from a small number of transplant recipients suggested that azathioprine/6-mercaptopurine may be associated with an increased risk of congenital abnormalities. However, there is increasing evidence from the IBD and non-IBD literature that the development of adverse fetal outcome is no different to that seen in the general population, and that these drugs may be used safely in pregnancy, provided there is sufficient clinical indication. Azathioprine is excreted in breast milk, and there is a small, but potential risk of myelosuppression developing in infants who are breast-fed by mothers treated with this drug. Methotrexate is teratogenic and must be stopped for 3-6 months in men and women prior to conception. All individuals of reproductive age receiving this treatment must be counseled about this requirement, regardless of their immediate intention to become parents.

The safety of newer biological agents in pregnancy, including anti-TNF therapy, is uncertain, since there are no animal data and human experience is limited to small series. Theoretically, anti-TNF therapy is not considered likely to be teratogenic, and available clinical data suggests that the use of infliximab in pregnancy is not associated with an increased risk of congenital abnormalities or other adverse fetal outcomes. Although more information from larger studies are required to verify its safety, the experience to date indicates that infliximab therapy may be optional during pregnancy if the clinical situation warrants its use, and when there is no effective alternative treatment available. Information regarding the safety of infliximab in nursing mothers is too sparse for recommendations to be issued at this stage.
A decade ago the distinction between Irritable Bowel Syndrome (IBS) and Inflammatory Bowel Disease (IBD) was quite clear. Although symptoms were often similar, IBD patients’ symptoms were explained by gut inflammation while the defining characteristic of IBS was an absence of objective abnormalities in the gut. Research in the last decade has started to show important overlaps which indicate that the two conditions may share some common mechanisms.

Both groups of patients experience abdominal pain or discomfort, bloating, urgency, loose and often frequent stools. IBD is usually marked by evidence of inflammation either in peripheral blood (increased CRP/ESR, anaemia or hypoalbuminaemia) or in the mucosa (endoscopic and/or biopsy abnormalities). However more recently the subgroups of IBD are being defined such as microscopic colitis in which endoscopy and blood tests are normal and the only abnormality is a microscopic one. Furthermore subgroups of IBS such as post infective IBS have been shown to have characteristic histological abnormalities and preliminary reports in the last two years have indicated that biopsies from IBS colons release increased amounts of inflammatory mediators such as histamine and serotonin. Increased gut permeability is another well recognised marker of IBD and shown to be increased prior to relapse and also to be increased in asymptomatic relatives of patients with Crohn's disease with the CARD15 3020insC mutation. Both post infective IBS and IBS with diarrhoea have also been shown to have increased permeability and peripheral blood abnormalities indicating immune activation.

One key distinguishing feature of IBS is visceral hypersensitivity, most obvious in IBS with diarrhoea. While this may originate with peripheral inflammatory changes, it also depends on central influences including childhood experiences and early learning. IBS patients may fail to show appropriate descending nociceptive inhibitory control (DNIC), a feature which is usually absent in IBD. Since IBS is over 100 times commoner than IBD clinicians should be aware of the possible coincidence of the two conditions. Thus when symptoms of pain and bowel disturbance are present in IBD patients with no evidence of inflammation clinicians should think of the IBS dimension. Likewise with IBS-D patients the possibilities of anti-inflammatory treatments should also be considered.
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New therapeutic approaches for IBD - Will they make a difference?
Probiotics and inflammatory bowel disease

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The aetiology of inflammatory bowel disease (IBD) remains obscure, currently thought to be associated with a genetic predisposition, dysregulation of the mucosal immune system, and a loss of antigen tolerance to enteric microflora, further influenced by a range of other environmental factors. In many cases, disease activity can be unremitting and refractory to treatment, with an unpredictable response to conventional therapy. To this end, new treatment strategies are being pursued on the basis of our understanding of IBD pathogenesis, and there is increasing evidence that at least some components of the enteric flora are primary contributors. Restoring the balance of the colonic microbiota to a less-pathogenic state is therefore a desirable strategy. Probiotics are currently defined as live non-pathogenic micro-organisms that, when ingested, exert a positive influence on host health beyond basic nutrition. On this basis, probiotics hold the potential to restore normal intestinal homeostasis. Despite more than a century of anecdotal reports of probiotic efficacy in gastrointestinal disease, only relatively recently have well-controlled, scientific studies and clinical trials, been conducted. Whilst reliable in vitro predictors of potential in vivo efficacy of putative probiotics await development, well-characterised animal model systems are proving valuable for the methodical, pre-clinical development of probiotics. Although early probiotic applications focussed largely on lactic acid bacteria (lactobacilli) and bifidobacteria, the range of candidate probiotics has now expanded significantly. Successful clinical application of the probiotic formulation, VSL#3, for treatment of the pouchitis variant of IBD, has instilled new excitement into the applicability of probiotics to IBD treatment, and the potential importance of probiotic combinations. The availability of new recombinant methodologies to develop ‘designer’ probiotics, capable of synthesizing and secreting specific factors, ranging from enzymes through to vitamins and antibodies, further broadens the scope for probiotic application in IBD. Indeed, there are encouraging reports that probiotics may not need to be viable, or even intact, to exert their beneficial effects, with reports of therapeutic benefit from bacterial components such as DNA. In addition to the development of rigorous predictive systems to ascertain probiotic efficacy, challenges for the future will include determining the optimal probiotic, or probiotic combination, and its timing of administration during phases of IBD relapse and remission. At present, our understanding of the intestinal microflora, and the importance of its composition and variability between individuals, is limited. However, once this understanding has been attained, strategically-designed probiotic formulations could ultimately be ‘tailored’ to suit individual IBD patients.
Enhancing barrier function

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Which barrier and against what?
We can list the components of the mucosal barrier (secretory IgA, defensins, mucus, the underlying glycocalyx, cell receptors, cell membrane, tight junctions etc) and catalogue their abnormalities in inflammatory bowel disease but this will not give us much understanding of pathogenesis nor allow targeting of treatment. To do that we need a better understanding of where there are problems with the mucosal barrier and what pathogenic agent(s) is being allowed in as a result.

Crohn’s disease - defective resistance against mildly pathogenic organisms with the M cell as a likely portal of entry
There is something wrong with the defence against the intestinal microbiota in Crohn's disease. Bacteria can be cultured from mesenteric lymph-nodes, they can be seen by immunohistochemistry within macrophages in affected tissue, their DNA can be isolated from granulomas and circulating antibodies against their flagellae can be found in the peripheral blood. The bacteria most consistently found are E. coli and Listeria with Mycobacterium avium paratuberculosis probably found in low numbers in a significant minority.

The earliest lesions in Crohn's disease overlie Peyer's patches in the distal ileum or lymphoid follicles in the colon. These sites have a specialised "dome" epithelium containing M cells that are particularly permeable to bacteria. Moreover, the dome has no goblet cells and hence no surface mucus and its glycocalyx is sparse. The M cell is the essential portal of entry for bona fide pathogens such as Salmonella and Shigella, Cholera, Yersinia and Mycobacteria. If we assume that the M cell is also the portal for bacteria in Crohn's disease then therapies that inhibit interaction between such bacteria and M cells could be effective treatment.

Ulcerative colitis - an auto-immune disease triggered by interaction between intraluminal bacterial and other toxic triggers and the surface epithelium
Ulcerative colitis has features of an auto-immune condition. It is associated with other auto-immune diseases and with circulating auto-antibodies eg pANCA. Relapse can be triggered by bacterial pathogens. It is not usually associated with bacterial invasion or even generally any circulating antibody response against bacterial proteins such as flagellin. It seems likely that the normal gut microbiota plays some role but it has been unclear what this role is. Bacteria can induce release of interleukin-8 from epithelial cells and this might be an important early trigger. Whole bacteria are probably not necessary as we have recently found that much of the activity is secreted in the form of microvesicles. These trigger IL-8 release via MAPkinase signalling. The mucus layer is likely to be important here as a barrier as also is the glycocalyx and there is evidence for abnormalities of both in ulcerative colitis. There is also a separate story that UC may result from an underlying defect in epithelial phenol sulfotransferase activity. Phenols are detoxified by sulfation and this could be important for dealing with intraluminal phenols produced by bacterial metabolism.
Relevant therapeutic targets if these hypotheses are correct would be:

Crohn's disease
- Inhibit bacteria-M cell adherence and invasion.

Ulcerative colitis
- a. Strengthen the mucus layer (eg block bacterial mucus-degrading enzymes).
- b. Inhibit epithelial MAPkinase activity.

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New therapeutic approaches for IBD - Will they make a difference? - Depleting phagocytes

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Although corticosteroids are mainly used as a primary therapy for severe or intractable cases of UC, we often encounter the cases that do not respond well or complicate steroid-induced adverse effects. For such patients with intractable IBD, leukocyte apheresis has been introduced in Japan. A precise mechanism of leukocyte apheresis therapy has not been clarified yet; however, depleting phagocytes from circulating blood may modify immuno-inflammatory responses in the diseased intestinal mucosa. Currently we have three types of adsorptive leukocytes apheresis therapy with different types of equipments; unwoven polyester filter, cellulose acetate beads and centrifugal method.

Multicenter randomized study showed that adsorptive leukocytes therapy yielded 60-70% response for steroid-resistant cases with ulcerative colitis without major adverse effects related to cytapheresis. Adsorptive cytapheresis therapy was also effective for Crohn's disease with colonic involvements. Recent data suggested that intensive use of cytapheresis (more than twice a week) might yield more rapid and more frequent induction of clinical response to the patients with intractable disease with successful reduction of corticosteroid use.

For estimating clinical effectiveness of the adsorptive leukocytapheresis therapy in UC, patients with chronic continuous inflammation with long-term use of low dose corticosteroid are not likely to respond to the therapy. Endoscopic features before the therapy varied and most patients with massive ulceration did not respond to the therapy. Although patients with deep ulceration have been thought as a candidate of poor responder, nearly 50% of the patients with deep ulcer achieved clinical remission by the therapy.

Clinical indication of the adsorptive leukocyte apheresis for IBD still needs to be defined especially in patients with concomitant use of immunosuppressive drugs. In conclusion, adsorptive leukocyte apheresis therapy, which may partly work thorough depleting phagocytes, could be used for controlling moderate to severe patients with UC patients resistant to usual steroid therapy.
Laparoscopic surgery for colitis

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Since 1991, laparoscopically-assisted colorectal surgery has been selectively performed for the treatment of a variety of colorectal diseases, including inflammatory bowel disease.

During that period, Australian Colorectal Endosurgery, based at the Royal Brisbane Hospital, has performed over 1900 laparoscopically-assisted colorectal operations. This report documents the outcome for patients requiring surgery for severe colitis and Crohn's disease.

Methods: Indication for surgery, perioperative data, morbidity and mortality for all patients having laparoscopic colorectal surgery were entered in a prospective computerised database. Outcomes for emergency total colectomy were compared with a matched cohort of patients undergoing the same operation by conventional open laparotomy.

Results: 47 patients with severe ulcerative colitis, and 87 patients with Crohn's disease underwent laparoscopically-assisted colorectal operations.

Since 2003, emergency total abdominal colectomy with ileostomy has been performed for 20 patients for acute, severe or fulminant colitis. The matched cohort included 25 patients from 1999-2003. Median duration of operation was 180 minutes (range 110-300) in the LAP group. Length of stay was median 6 days (range 4-37), mean 9 days in the LAP group, compared with 14 days in the open group (P < 0.001). Two patients in the LAP group required return to theatre for intra-abdominal sepsis and washout, and one for dehiscence of the 5cm incision where the rectal stump had been secured subcutaneously. Overall complication rate was 25% LAP vs. 34% Open (P < 0.01).

A further 25 patients also had restorative proctectomy/proctocolectomy performed laparoscopically (duration 200 min., length of stay 4 days). A stoma and an abdominoperineal resection was also performed for ulcerative colitis. When reoperated for their restorative proctectomy, those patients who had had their colectomy performed laparoscopically were characterized by significantly less adhesions compared with patients who had a previous laparotomy (36% v. 83% previous open colectomy, P < 0.001). The adhesions that may have been present in the LAP group were also characterized by being much less extensive or problematic.

64 of the 87 patients with Crohn's had a laparoscopically-assisted right hemicolecction. The remaining 23 patients had a variable extent/site of resection. The overall operation duration was 115 min., and median length of stay 4 days (range 3-14).

There were no conversions to laparotomy in either laparoscopic groups, no anastomotic leaks and no mortality.
**Conclusion:** Laparoscopically-assisted colorectal surgery can be performed for the majority of patients with IBD who require surgical intervention. Although the duration of operation is perhaps longer than open surgery, it confers a number of advantages particularly in immunocompromised patients. These include low morbidity and shorter hospital stay. There is also less likelihood of adhesions, which can be of great advantage for patients who may ultimately require multiple procedures.
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Differentiation of Crohn's disease from intestinal tuberculosis in India

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Introduction: The clinical, morphological and histological features of intestinal tuberculosis and Crohn's disease mimic so much that it becomes difficult to differentiate them and at many times patients are treated empirically. In India intestinal tuberculosis is common whereas Crohn's disease is much less frequent; however Crohn's disease is being recognized more frequently now. The aim of this study is to study the clinical, endoscopic, and histological variables for differentiation of Crohn's disease from intestinal tuberculosis.

Methods: The diagnosis of Crohn's disease was made on the basis of a constellation of clinical (chronic diarrhea, hematochezia, intestinal obstructive manifestations, perianal disease, malabsorption and extraintestinal features), morphological (skip lesions, deep ulcers, aphthous ulcers, fistula, involvement of ileocecal valve and small intestine) and histological features (acute on chronic colitis, presence of inflammation extending beyond muscularis mucosae, lymphoid follicles and non-caseating granuloma). The diagnosis of intestinal tuberculosis was made on the basis of clinical (abdominal pain, constipation and/or diarrhea, constitutional symptoms, intestinal obstruction), endoscopic (ileocecal area involvement, ulcerations, nodularity, strictures), and histological features (presence of caseating granuloma) and/or demonstration of acid-fast bacilli. Chi square test was used to assess the associations of variables. Bivariate logistic regression was used to compute the odds ratio (95% confidence interval) and to assess the strength of association of variables with the disease. Variables found significant in bivariate analysis were simultaneously considered in a stepwise multivariate logistic regression to determine independent significant predictors of Crohn's disease.

Results: During the last 36 months, 30 patients each with Crohn's disease and intestinal tuberculosis were included in this study. The mean age (SD) and median duration of disease were 31.2 (9.5) years and 33.43 (14.5) years and 4 years and 1 year, respectively in patients with Crohn's disease and intestinal tuberculosis. In the univariate analysis, the following parameters were found significantly more common in patients with Crohn's disease: bloody diarrhea, tenesmus, malabsorption, absence of intestinal obstruction, perianal disease, extra-intestinal manifestations, aphthous ulcers, cobblestoning, pseudopolyps, and non distensible and fixed ileal loops. On multivariate analysis, blood in stool [OR 98.9 (CI 8.2-1183.2)], malabsorption [OR 23.4 (1.1-484.7)], absence of intestinal obstruction [OR 0.06 (CI 0-0.72)] and perianal disease [OR 22.4 (CI 1.6-312.4)]. On multivariate analysis four independent predictors namely blood in stool, perianal disease, malabsorption and absence of intestinal obstruction were found in differentiating Crohn's disease from intestinal tuberculosis.
**Discussion/Conclusion:** On multivariate analysis four independent predictors namely blood in stool, perianal disease, malabsorption and absence of intestinal obstruction were found in differentiating Crohn's disease from intestinal tuberculosis.
Clinical course of patients with ulcerative colitis in a multiracial Asian population

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Introduction: Ulcerative colitis (UC) is an emerging disease in Asia. The aim of this study is to determine the clinical course of disease in an Asian population.

Methods: Patients with UC from 6 centers seen between Jan 2004-Dec 2005 were recruited. Baseline characteristics, extent of disease was recorded as well as clinical course and relapsed disease for every year after diagnosis Clinical course was classified as remission, chronic intermittent disease, continuous disease low activity and continuous disease high activity.¹ Colectomy and complications in particular toxic megacolon and colorectal cancer was recorded.

Results: 102 patients were included. Complete data of the clinical course was available in only 68 patients. Baseline characteristics were as follows: Male 49 (42%), Female 52 (51%); Malay 26 (25.5%), Chinese 32 (31.4%), Indians 44 (43.1%). Median age of presentation was 36 (range,14-72). Extent of disease; proctitis only 17 (16.7%), sigmoid colon 20 (19.6%), descending colon 15 (14.7%), transverse colon 11 (10.8%), ascending colon and pancolitis 39 (38.2%). Median duration of disease was 8 years (range, 1-46).

The clinical course were: chronic intermittent disease with relapse rates of 39.5% by one year and 62.9% by five years. About 25% of patients had continuous activity for at least five years. Toxic megacolon was seen in one patient and colectomy rate was only 6.9%(7).No patient developed colorectal cancer during the follow up period.

Conclusion: Similar to the West, most of our patients have a relapsing pattern of disease. However, the clinical course appears to be milder with low rates of colectomy and no apparent increased risk of colorectal cancer.

Reference:

Years after diagnosis

- Remission
- Intermittent disease
- Continuous low activity
- Continuous high activity

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

1 2 3 4 5 6 7 8 9 10
Mutations in NOD2/CARD15 gene in Crohn's disease: Experience in an Asian population

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Introduction: The NOD2/CARD15 gene is one of the most important susceptibility genes in Crohn's disease (CD) in the Western population but the three major risk alleles identified (R720W, G908R, 1007fs) are not present in the Far East. However, there have been no studies carried out in other ethnic races in Asia.

Aim: To determine if NOD2/CARD15 gene polymorphisms are present in our population.

Methods: 16 patients with CD, 23 patients with ulcerative colitis (UC) and 150 normal controls were included. Baseline patient characteristics including ethnic group was recorded. DNA was extracted from each sample by conventional phenol/ chloroform method. The extracted DNA was then subjected to RFLP-PCR for DNA polymorphism and sequencing detection. Patients were examined for the three major mutations but also SNP5-JW1 (associated with CD in Ashkenazi Jews) and background SNP5. The pattern of the DNA fragment was visualized on 2% agarose gel with ethidium bromide.

Results: None of the three major risk alleles were identified. One CD patient was heterozygote for the SNP5 mutation (Figure) but the JW1 mutation was not seen. The patient was an Indian woman with upper GI CD (no colonic involvement). None of the mutations were identified in UC patients or controls.

Conclusions: As in other Asian countries, the three major NOD2/CARD15 mutations previously identified among the Caucasians are not present in any of the ethnic groups. One patient with CD was heterozygote for the SNP 5 mutation. Larger studies are required to identify disease predisposing mutations in the Asian population.

Figure:
- Lane 1: 100 bp DNA ladder
- Lane 2: Before BamHI digestion
- Lane 3: CD patient - normal
- Lane 4: CD patient - heterozygote SNP5
- Lane 5: UC patient - normal
- Lane 6: Wild type control
Changing pattern of Chinese Crohn's disease phenotype with time

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Introduction: Crohn's disease (CD) is a chronic relapsing and remitting disease that may change in phenotype with time in Caucasians. In the Chinese population, CD phenotypic changes have not been described, and whether this impacts on the requirement for surgery is unknown. This study aimed to assess the CD phenotype and the impact on surgery through longitudinal follow up.

Methods: This was a retrospective study of Chinese CD patients attending an ambulatory IBD Clinic. The behaviour and location of CD were determined by the Vienna classification at diagnosis and after 1, 3, 5, and 10 years of follow up. The evolution of these characteristics and the need for surgery was evaluated.

Results: One hundred and nine consecutive patients were recruited (median follow up: 4 years, range: 6 months - 18 years; median age at diagnosis: 30 years). CD behaviour changed five years after diagnosis with a significant increase in the stricturing and penetrating phenotype (P < 0.05). The proportion of penetrating disease (B3) increased from 28.4% to 42.9%, and stricturing disease (B2) increased from 25.7% to 33.3% after ten years. Disease location, however, remained stable after ten years of follow up. Fifty patients (46%) underwent surgery during follow up and stricturing phenotype predicted the need for surgery (OR = 6.4; 95% CI: 2.2-18.5).

Discussion/Conclusion: The behavioural phenotype of Crohn's disease in the Chinese was unstable over time with an increase in the proportion of stricturing and penetrating complications. Disease location remained stable. The stricturing phenotype was predictive for the need for surgery.
CD Phenotype Evolution

<table>
<thead>
<tr>
<th>Time (Years)</th>
<th>B3 Penetrating</th>
<th>B2 Strictureing</th>
<th>B1 Inflammatory</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>28.4</td>
<td>25.7</td>
<td>45.9</td>
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<tr>
<td>1</td>
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<td>31.3</td>
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</tr>
<tr>
<td>10</td>
<td>42.9</td>
<td>33.3</td>
<td>23.8</td>
</tr>
</tbody>
</table>
Intestinal granulomas in Chinese patients with Crohn's disease - Association with phenotype and smoking

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Introduction: Crohn's disease (CD) is a heterogenous disease characterised by variable manifestations and outcomes, and increasing in incidence in China. Phenotypic classification has been proposed to assist in sub-typing of disease. Non-caseating intestinal granulomas are a hallmark of CD, but whether intestinal granulomas help predict Chinese CD phenotypes or determine severity is not known. The aim of the study was to determine the association between intestinal granulomas with CD phenotype, severity, risk factors and serological markers.

Methods: This was a single-centre study of consecutive definite Chinese CD cases. Granulomas were diagnosed by an experienced GI pathologist. Correlation with the Vienna Classification and other parameters was performed.

Results: Eighty Chinese CD patients were recruited, 40 (50%) of whom had intestinal granulomas. On multivariate analysis, intestinal granulomas were associated with the stricturing behaviour (OR: 4.71; 95% CI: 1.41-15.72), colonic location of disease (OR: 26.96; 95% CI: 2.68-271.14) but not with age of CD diagnosis. Current or previous smoking protected against the development of granulomas (OR 0.16; 95% CI: 0.04-0.59). Granulomas were not associated with peri-anal involvement, extra-intestinal manifestations, anti-neutrophil cytoplasmic antibody or anti-Saccharomyces cerevisiae antibody serology or severity of CD gauged by the requirement of major intestinal surgery or immunomodulating therapy.

Discussion/Conclusion: Intestinal granulomas in the setting of CD may be helpful in determining phenotypic subtypes of CD, but is unhelpful in predicting disease severity. Smoking impairs the formation of granulomas in CD.
Prevalence of inflammatory bowel disease in a multiethnic Asian patient population

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Introduction: In Asia, inflammatory bowel disease (IBD) once uncommon, is now an emerging disease. It would be interesting to ascertain whether the rapid development of Malaysia in the last 20 years has had an impact on the prevalence of IBD.

Aims and Methods: We retrospectively investigated the prevalence of inflammatory bowel disease (IBD) and its complications in all patients attending Hospital Ipoh (a teaching hospital) from 1997-2000. Racial composition of Kinta District (study location) is 46.6% Chinese, 35.6% Malays, 14.3% Indians, 2.3% Others and 1.2% Indigenous people.

Results: The prevalence of IBD amongst all hospital attendees was 4.1/100 000. A total of 23 patients (Indians = 10, Malays = 7, Chinese = 6) were diagnosed with IBD (ulcerative colitis: 19, Crohn's disease: 4). Male to Female ratio was 0.92, mean age at presentation was 41.5 years (range 14-66 years) with a mean duration of follow-up of 32.4 months. The majority of patients with ulcerative colitis (12/19) had left sided disease of whom 9 had proctitis or recto-sigmoid colitis. Two patients (both with Crohn's disease) had proctocolectomy done. Extra-intestinal manifestations (arthritis, uveitis, sclerosing cholangitis and renal calculi) were seen in 6 patients.

Conclusions: Though, the prevalence of IBD has at least doubled amongst hospital attendees in Malaysia since the 1980's, it is still very much less than in the West. Possible reasons include increased Westernization of the diet and/or increased physician awareness. The preponderance of Indians with this disease is in keeping with similar studies done elsewhere in south-east Asia and warrants further investigation.
Inflammatory bowel disease: The Philippine perspective

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Introduction: Inflammatory bowel disease (IBD) is relatively uncommon among Asians, thus, there is a paucity of data regarding the spectrum of the disease process from this region. We aim to describe the clinical presentation of IBD among Filipino patients.

Methods: Consecutive Filipino patients from 14 centers in Metro Manila and Cebu City who presented with recurrent, bloody diarrhea associated with or without abdominal pain and fever were included in this study cohort. Stool microscopy, bacterial and mycobacterial culture were performed to exclude infectious enterocolitis. After a thorough and meticulous investigation of family history, ethnic background and other extraintestinal manifestations, all patients underwent colonoscopy and biopsy. Those with colonoscopic and histopathologic findings compatible with ulcerative colitis (UC) or Crohn's disease (CD) were collated. These patients were then presented to a panel of gastroenterologists, radiologist and pathologist towards making a final consensus diagnosis of IBD, based on established internationally accepted criteria.

Results: Fifty-six (3/10,000 colonoscopies) cases of IBD were documented during the period of 1996-2005. UC is the definitive diagnosis in 43 cases; average age of 45 years (age range, 16-88 years) and M:F, (2.5:1.8). They presented with bloody diarrhoea (74%), chronic diarrhoea (56%), fever (19%), and abdominal pain (12%). Colonoscopy performed revealed pancolitis in 65%, colitis in the rectosigmoid (19%), in the transverse colon to rectum (12%), and proctitis in 2%. Extra intestinal manifestations included arthralgia (2.3%) and pyoderma gangrenosum (2.5%). Forty-two percent has a history of a failed \textit{E. histolytica} treatment. CD was diagnosed in 13 cases; average age of 34.5 years (age range, 14-70) and M:F, ratio of 6:7. The most common clinical presentations were chronic diarrhea (77%), abdominal pain (54%), weight loss (46%), and bloody diarrhea (38%). Endoscopically, the ileum and colon were involved in 69%, 31% had only colonic lesions and 8% had both upper and lower GI manifestations. Six patients had anorectal, rectovaginal and enterointeretic fistulas while 2 had perianal abscess. Eight cases (46%) failed initial empiric treatment for infectious colitides, i.e., 6 for tuberculosis, 2 for amoebiasis.

Conclusion: In our setting, UC is more common than CD. Bloody diarrhoea is more frequent in UC while chronic diarrhoea has a higher occurrence in CD. This patient cohort demonstrates that IBD, while still relatively rare, is noted among Filipino patients as well.
Objective: Endoscopy has an important role in the diagnosis of ulcerative colitis. A dyeing and magnify endoscopy recently developed enables high-power observation of the colorectal mucosa. The aim of this study was to investigate the value of the magnifying endoscopy in determining the severity of ulcerative colitis.

Methods: Observation 142 patients with ulcerative colitis by dyeing and magnifying endoscopy. Then the findings were graded according to network pattern and cryptal openings.

Results: Magnifying coloscopy did not detect network pattern in 57 and cryptal openings in 30 of the subjects. When the two features were observed, patients had a lower clinical activity. And the findings were correlated with histologic severity of the disease.

Conclusions: Observation under magnifying colonscopy can be a avail method to determining the severity of disease in patients with ulcerative colitis
Serologic presentation of *Helicobacter pylori* infection in patients with inflammatory bowel disease

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**Objective**: To investigate serologic manifestation of *Helicobacter pylori* (*H. pylori*) infection in patients with inflammatory bowel disease (IBD) and the role of *H. pylori* infection in pathogenesis of IBD.

**Methods**: We measured anti-*H. pylori*-IgG and anti-*H. pylori*-CagA of 45 IBD patients and their with sex and age matched 45 chronic gastritis (CG) control patients during 4 years, and analyzed the relationship between seroprevalence of *H. pylori* and inflammatory range of ulcerative colitis (UC).

**Results**: There were 40 UC patients and 5 Crohn's disease (CD) patients; the positive anti-*H. pylori*-IgG patients in IBD was 40.0% and in chronic gastritis was 66.7% respectively ($\chi^2 = 6.43$, $P < 0.05$), in UC and its control were 42.5% and 65.0% respectively ($\chi^2 = 4.07$, $P < 0.05$), anti *H. pylori*-IgG positive patients counted for 20 percent. The anti-*H. pylori*-IgG positive rate of pan-colorectal UC was lower than partial-colorectal UC (28.0% versus 66.7%, $\chi^2 = 5.74$, $P < 0.05$). The positive anti-*H. pylori*-CagA patients were 28.9% and 40.0% in IBD and its control respectively ($P > 0.05$), and that were 28.9% in pan-colorectal UC and 40.0% in partial-colorectal UC ($P > 0.05$).

**Conclusions**: The anti-*H. pylori*-IgG positive rate is in high level in IBD patients, but that is lower than chronic gastritis patients. *H. pylori* infection could play a inhibition role in the inflammation range of UC. The anti-*H. pylori*-CagA positive rate of IBD patients and pan-colorectal UC are lower than their controls respectively, but there is no obviously different in statistics.

Key words: inflammatory bowel disease; Crohn's disease; ulcerative colitis; Helicobacter pylori
2005 IBD Epidemiological Report from Department of Gastroenterology of Beijing Hospital

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Beijing Hospital was built in 1905 as "German Hospital". At present, Beijing Hospital is a Grade AAA Hospital under immediate directive from the Ministry of Health, as the dedicated facility for senior officials for Chinese Government.

Department of Gastroenterology in Beijing Hospital has an organized clinical unit for gastroenterological diseases. The Department has sub-divisions in digestive endoscopic unit, laboratory and gastro-kinetics center. In association with Peking University and other international academic institutions, the Department has taken up the practical teaching and researches in modern techniques in gastroenterological therapy through its extensive engagement in geriatric therapeutic duties.

In 2005, the Department of Gastroenterology has admitted 537 in-patients. Among which, there were 56 IBD cases, representing 10.4%. 46 of those cases were diagnosed as ulcerative colitis, and 8 cases were Crohn's disease. 21 of those cases fulfilled the diagnostic criteria as serious.

During the same period, the Department has performed 38,120 specialist's consultations. Counting in both first or follow-up visits, 420 of those were IBD cases. Colonic endoscopic examinations were performed in 1,403 cases. 67 were IBD cases, representing 4.7%.

The major therapeutic measures towards IBD cases include rest, all round nutrition, supplements for anaemia, prophylaxis to infection etc. Pharmaceutical interventions included retention enema, suppositories, oral and intravenous medications. Major classes of drugs applied were sulphasalazine, mesalazine, corticosteroids of particular use to serious ulcerative colitis patients, cyclosporins and anti-immunological therapy. Overall in 2005, only four surgeries were performed towards IBD patients, all of which were Crohn's Disease complications leading to colonic obstructions.

There were 142 cases newly diagnosis of colon cancer. None of which were deteriorations from ulcerative colitis. Only one case of serious ulcerative colitis, patient refused surgery leading to severe anaemia, toxic megacolon, leading to infection, shock and death.
The features of ulcerative colitis in China

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Aim: To analyze the characteristics of ulcerative colitis (UC) in China.

Methods: From 1981 to 2000, a total of 10218 patients of UC reported in Chinese medical literature and including our cases diagnosed were analyzed according to the diagnostic criteria of Lennard-Jones.

Results: The number of cases increased by 3.08 times over the past 10 years (2506 patients were diagnosed from 1981 to 1990 while 7512 patients were diagnosed from 1991 to 2000). Lesion range were described in 7966 patients, 5592 (70.20%) were proctosigmoiditis or proctitis, 1792 (22.50%) left-sided colitis, 582 (7.30%) pancolitis. Among the 8122 patients, 2826 (34.8%) had first episode, 4272 (52.6%) had chronic relapse, 869 (10.7%) were of chronic persist type, 154 (1.9%) were of acute fulminant type. The course of the illness were described in 5867 patients, 4427 (75.5%) less than 5 years, 910 (15.5%) between 5 and 10 years, 530 (9.1%) more than 10 years. Six hundred and sixteen patients (6.1%) had extraintestinal manifestations. The mean age at the diagnosis was 40.7 years (range 6-80 years, and the peak ages 30-49 years). The male to female ratio was 1.09. Among 270 patients diagnosed in our hospital, 36 had histories of smoking, there was no negative association between the severity of UC and smoking (p > 0.05), 21 smokers were followed up for one year, 15 of them had given up smoking when the disease were diagnosed, and one year later, 7 patients relapsed, another 6 patients continued smoking, and one year later, 2 patients relapsed. Among 270 UC patients diagnosed in our hospital, 4 patients (1.48%) from 2 families had familial history of UC. Treatment was mentioned in 6859 patients, only 5-ASA and/or corticosteroid only in 1276 patients (18.6%), only Chinese herbs in 1377 patients (20.1%), combined Chinese and western medicine in 4056 patients (59.1%), surgery was performed in 87 patients (1.3%), other treatments in 63 patients (0.9%).

Conclusions: In China, number of UC patients increased significantly in the past 10 years. Lesions are commonly located to left side colon. The course is short with rare extraintestinal manifestations. The age of onset is relatively high. Males and females are nearly equally affected. No negative relation was found between smoking and severity of the disease. Familial relatives are rarely involved Traditional Chinese medicine (TCM) is widely used in the treatment of UC.

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Different therapy for different types of ulcerative colitis in China

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Aim: To study the different therapy for different types of ulcerative colitis (UC) in China.

Methods: Among one hundred and two UC patients, 42 chronic relapse type UC patients were randomly divided into olsalazine sodium treatment group (n = 21) and SASP group (n = 21). Clinical effects and safety were observed in the two groups. Forty two first episode type UC patients were randomly divided into Heartleaf houttuynia herb treatment group (n = 21) and SASP group (n = 21). Clinical effects were observed in the two groups while ultrastructure of colonic mucosa, ICAM-1 and the pressure of distant colon were studied in Heartleaf houttuynia herb group. Eighteen patients (8 males, 10 females) with refractory UC and unresponsive to high-dose prednisolone and sulfasalazine therapy more than one month were treated with Kangshuanling(7,200 U/d). Prednisolone was gradually stopped and sulfasalazine was maintained. Stool frequency, rectal bleeding, colonoscopy, general well-being, histology were observed and CD62p, CD63, CD54, Pgp-170 (flow cytometry),TXA2 (RIA), blood platelet aggregation rate and thrombosis length in vitro were assessed.

Results: In the forty two chronic relapse type UC patients, the overall clinical effects of olsalazine sodium group (complete remission in 16 , improvement in 4, inefficiency in 1) were better than those of SASP group (complete remission in 10, improvement in 4, inefficiency in 7, p < 0.05). Symptomatic remission of olsalazine sodium group (complete remission in 15, partial remission in 5, inefficiency in 1) was better than that of SASP group (complete remission in 10, partial remission in 5, inefficiency in 6, p < 0.05). The colonoscopic remission of olsalazine sodium group (complete remission in 11, partial remission in 9 , inefficiency in 1) was better than that of SASP group (complete remission in 7, partial remission in 8, inefficiency in 6, p < 0.05). The histologic remission of olsalazine sodium group (complete remission in 13, partial remission in 7, inefficiency in 1) was better than that of SASP group (complete remission in 6, partial remission in 10, inefficiency in 5, p < 0.05). The side effects of gastrointestinal tract in olsalazine sodium group were less than those of SASP group except for frequency of watery diarrhea. No other side effects were observed in olsalazine sodium group while ALT increase, WBC decrease and skin eruption were observed in SASP group. Two patients relapsed in olsalazine sodium group while 8 cases relapsed in SASP group during the flow-up period (from 6 months to one year).

In the forty two first episode type UC patients, the clinical effect of Heartleaf houttuynia herb group (complete remission in 20, 95.2%; improvement in 1, 4.8%) was better than that of SASP group (complete remission in 15, 72.4%, improvement in 5, 23.8%; inefficiency in 1, 3.8%, p < 0.01). The time of stool frequency recovering to normal (5.6 ± 3.3) d, and blood stool disappearance (6.7 ± 3.8) d and abdominal pain disappearance (6.1 ± 3.5) d in Heartleaf houttuynia herb group was all shorter than that in SASP group (9.5 ± 4.9) d, (11.7 ± 6.1) d, (10.6 ± 5.3) d, (p < 0.01). Heartleaf houttuynia herb could inhibit the epithelial cell apoptosis of colonic mucous membrane.
and the expression of ICAM-1 (45.8% ± 5.7% vs 30.7% ± 4.1%, p < 0.05). Compared with normal persons, the mean promotive speed of contraction wave stepped up (4.6 ± 1.6) cm/min vs. (3.2 ± 1.8) cm/min, (p < 0.05) and the mean amplitude of the wave decreased (14.2 ± 9.3) kPa vs. (18.4 ± 8.0) kPa, (p < 0.05) in active UC patients. After treatment with Heartleaf houttuynia herb, these two indexes improved significantly (17.3 ± 8.3) kPa, (3.7 ± 1.7) cm/min, (p < 0.05). In normal persons, the postprandial pressure of sigmoid (2.9 ± 0.9) kPa was higher than that of descending colon (2.0 ± 0.7) kPa and splenic flexure (1.7 ± 0.6) kPa, while the colonic pressure (1.5 ± 0.5) kPa, (1.4 ± 0.6) kPa, (1.3 ± 0.6) kPa decreased significantly (p < 0.05) in active UC patients. After treatment with Heartleaf houttuynia herb, the colonic pressure (2.6 ± 0.8) kPa, (1.8 ± 0.6) kPa, (1.6 ± 0.5) kPa recovered to normal. The pain threshold of distant colon (67.3 ± 18.9)ml in active UC patients decreased significantly compared with that of normal persons (216.2 ± 40.8) ml, (p < 0.05) and recovered to normal after treatment with Heartleaf houttuynia herb (187.4 ± 27.2) ml, (p < 0.05).

In the 18 refractory UC patients with platelet activation, after more than 4 weeks of combined Kangshuanling and sulfasalazine therapy, sixteen patients achieved clinical remission, with a highly significant statistical difference (p < 0.01) between pre- and post-treatment mean scores for all disease parameters: stool frequency (8.2/d vs. 1.6/d), rectal bleeding (score 2.7 vs. 0.3), colonoscopy (score 2.6 vs. 1.1), histology (score 12.0 vs. 5.0), general well being (score 4.0 vs. 0.6) and CD62p (8.0% ± 3.1% vs. 4.1% ± 1.8%), CD63 (6.3% ± 2.1% vs. 3.2% ± 1.6%), TXA2 (548 ± 85) ng/L vs. (390 ± 67) ng/L, platelet aggregation rate (43.2% ± 10.7%) vs. (34.8% ± 8.1%), thrombosis length in vitro (2.3 ± 0.6) cm vs. (1.8 ± 0.3 cm), CD54 in blood (26.9% ± 6.9%) vs. (14.4% ± 5.1%), CD54 in tissues (51.1% ± 6.2%) vs. (23.1% ± 4.1%), Pgp -170 in blood (18.9% ± 3.9%) vs. (10.4% ± 2.7%), Pgp -170 in tissues (16.5% ± 3.2%) vs. (10.2% ± 2.3%, p < 0.01 or 0.05).

**Conclusion**: Based on the characteristics of UC cases in China, different therapy should be given to different types of UC with expected satisfactory results.

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Fecal calprotectin as an indicator of disease activity in ulcerative colitis

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Objective: To evaluate the accuracy of fecal calprotectin as a non-invasive indicator of disease active in ulcerative colitis (UC) in comparison with colonoscopy, erythrocyte sedimentation rate (ESR) and serum C-reactive colitis (CRP).

Methods: Sixty-one outpatients as controls and 76 patients with UC were recruited after colonoscopy. All the patients were asked to collect 5 g of stool sample one week before colonoscopy for determining fecal calprotectin by an enzyme-linked immunosorbent assay. The disease activity of UC was evaluated according to colonoscopic and histological criteria. CRP, erythrocyte sedimentation rate, Hemoglobin, white blood cell and liver function were also measured.

Results: The fecal calprotectin concentration among patients with active UC (median 515 μg/g, n = 69) was significantly higher than of inactive UC group (7.5 μg/g, P < 0.01), and healthy controls (5.7 μg/g, n = 61, P < 0.01), while the difference between the control group and the inactive group was statistically significant (P > 0.05). Significant difference existed between each active grades (I, II, III) and inactive phase of UC. The results revealed a significant correlation between the endoscopes grades of disease activity and fecal calprotectin concentration (r = 0.876, P < 0.01). The correlation coefficient between CRP/ESR and histological grades were 0.725 (P < 0.01) and 0.302 (p < 0.01) respectively. Both were lower than that of calprotectin.

Conclusions: Fecal calprotectin levels reflect the disease activity in UC and can be used to monitor the response to treatment and detect relapses. It was an objective, simple and noninvasive measurement and was better than ESR and serum CRP.

Key words: calprotectin; ulcerative colitis; erythrocyte sedimentation rate; C-reactive protein
Orientation of bone marrow mesenchymal stem cells in the colon of rat with ulcerative colitis after transplantation

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Objective: To investigate the possibility of orientation in the colon of rat models of ulcerative colitis after bone marrow mesenchymal stem cells (MSCs) transplanted into rat.

Methods: The MSCs from SD male rats were purified by culture-expanded in vitro and then were transplanted into SD female rat models of ulcerative colitis (models with TNBS) through caudal vein. Meanwhile, control groups were used. Sex-determining gene (sry) which located on Y chromosome was examined by PCR in colon tissue of female rats at 1st day, 7th day and 21st day after transplantation, respectively.

Results: The positive expression of sry gene was found in 1 of 6 rats (16.7%) at 7th day and in 3 of 6 rats (50.0%) at 21st day. But there were no found sry expression in the colon tissue in the control groups.

Conclusion: MSCs can orientate the colon of rat models of ulcerative colitis.

Key words: bone marrow; mesenchymal stem cell; transplantation
Clinical observation on treatment of Salofalk® for mild-to-moderate active ulcerative colitis in 36 cases

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Aim: To observe the therapeutic efficacy and safety of Salofalk® (mesalazine) treating mild-to-moderate active ulcerative colitis (UC).

Methods: 36 cases with mild-to-moderate active UC come from our hospital OPD. Male 29, female 7, median age 31.8 years (range 17-63), course of disease 1.5 years, all cases diagnosed by endoscopic examination. Treatment efficacy was assessed by symptoms assessment and endoscopic evaluation. Patients were divided into 3 groups. 32 patients in group A treated with Salofalk® 500mg tablets three times a day for 4 weeks, in group B 4 patients suffering for proctitis were treated with Salofalk® 500mg suppositories twice a day for 4 weeks. In group C, 5 patients who relapsed after 6 months, continued treatment with Salofalk® and with prednisone 30 mg/day and a Chinese herbal medicine (baitouweng tang) for another 4 weeks.

Results: After 4 weeks of treatment, the remission rate in group A was 50%. Complete remission was achieved in 37.5%, partial remission rate was achieved in 87.5%. In group B 3 patients achieved remission. In group C, 5 patients who relapsed after 6 months, continued treatment with Salofalk® and with prednisone 30 mg/day and a Chinese herbal medicine (baitouweng tang) for another 4 weeks. These patients responded well to the treatment. Side effect rate was 8.3%. Headache was found in 2 patients, joint pain in one patient.

Conclusion: Salofalk® may be the first choice in the treatment of active mild-to-moderate ulcerative colitis, achieving high remission rates in short-term treatment and low recurrence rates without serious side effects.

Key words: Salofalk®; inflammatory bowel disease; ulcerative colitis
Treatment of left-sided ulcerative colitis with Salofalk® enemas

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Aims: To investigate the therapeutic effect and safety of Salofalk® enema in the treatment of left-sided ulcerative colitis (UC).

Methods: 80 patients of mild to moderate active UC from 4 clinical pharmacological research centers were enrolled in this randomized controlled clinical trial. The patients were divided into 2 groups. Either 4 g (60 ml) of Salofalk® enema (Salofalk® group) or 100 mg (in 60 ml of normal saline) of hydrocortisone sodium succinate (steroid group) were given by retention enema every night for 4 weeks. 1000 mg of Salofalk® enteric coated tablets were given twice a day to every patient in both groups as a basic treatment. Clinical manifestations, laboratory examinations and adverse drug reactions were scored and recorded before and after the trial. Colonoscopy was performed within 2 weeks before the start and 1 week after the end of the trial. 3 biopsies were taken at the most severe part and the degree of inflammation was evaluated by a specified pathologist blindly.

Results: The clinical manifestations as well as the colonoscopic and histopathologic appearances were improved in both groups after the enema. The general scores of improvement were 61.3% ± 17.3% in Salofalk® group and 51.1% ± 28.4% in steroid group without statistically significant difference. The effective rates were 57.5% and 41.0% in Salofalk® group and steroid group respectively. However, there was no statistically significant difference between the 2 groups (χ² = 2.144, P = 0.143). The total improvement rate after 4 weeks of Salofalk® enema reached 97.5% and was significantly higher than that of 79.5% by hydrocortisone sodium succinate enema (χ² = 6.341, P = 0.018). There was no serious adverse event in both groups.

Conclusions: Both Salofalk® enema and hydrocortisone sodium succinate enema could improve the clinical manifestations, the colonoscopic appearance and the histopathological changes of mild to moderate UC. The total improvement rate of Salofalk® enema was significantly higher than that of hydrocortisone sodium succinate enema.
CD4*CD25* regulatory T cells in inflammatory bowel disease

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Introduction: CD4*CD25* regulatory T cells (Tregs) play a critical role in suppressing the development of autoimmune disease, in controlling potentially harmful inflammatory responses, and in maintaining immune homeostasis. This function is lost in Crohn's disease (CD). Thus, we demonstrate that CD4*CD25* T cells with regulatory properties can be propagated in vitro from peripheral blood cells of CD patients in Chinese.

Methods: Human blood mononuclear cells were isolated from freshly drawn human blood by Ficoll gradient centrifugation. The CD4*CD25+, CD4*CD25* T cells were isolated by sorting using a CD4+CD25+ regulatory T cell isolation kit. These cells were cultured alone or together at various ratios in the presence of soluble anti-CD3 and soluble anti-CD28. Proliferation was monitored at day 3, 5 and 7.

Results: Samples of peripheral blood were obtained from 12 CD patients (five males and seven females, mean age 30 years) diagnosed by established clinical, endoscopy and histopathological criteria and 8 healthy donors. Our results revealed that there was almost no detectable proliferation on day 3 and 5. On day 7, the CD4*CD25* T cells inhibited the proliferative response of the cocultured CD4*CD25* cells in a dose-dependent manner in healthy subjects. In contrast, the inhibitory effect of the CD4*CD25* cells from the CD patients was almost no detectable.

Discussion/Conclusion: The CD4*CD25* cells of the peripheral blood from the CD patients lost the regulatory capacity.
Endoscopic features and clinical analysis on ulcerative colitis

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Objective: To evaluate the clinical and endoscopic features of ulcerative colitis (UC).

Methods: The cases of UC were collected from 1975 to 2001. According to the diagnostic criteria of Chengdu conference, 486 and 490 patients were diagnosed as UC in our hospital from 1975 to 1994 and from 1995 to 2001 respectively. Their records were retrieved and the data were analyzed for sex, age, presentation, the course of the illness and lesion range.

Results: In the two groups from 1975 to 1994 and from 1995 to 2001, the proportion of patients diagnosed as UC under colonoscopy was increased from 3.51% to 4.44%. The ration of male to female was 1.67 and 1.25 respectively. The mean age at the diagnosis increased from 42.4 years old to 51.5 years old, and the peak age was between 30 and 49 years old, between 40 and 49 years old and greater than 60 years old respectively. The typical clinical manifestations of UC were bloody mucopurulent stool, diarrhoea and abdominal pain. Proctosigmoiditis or proctitis was found in 269 patients (55.4%) and 316 (64.5%), left-side colitis in 84 (17.3%) and 68 (13.9%), pancolitis in 58 (11.9%) and 70 (14.3%) respectively. In the two groups, there were 437 (89.9%) and 443 (90.4%) patients who had the course of less than 10 years respectively. The definitive diagnosis of UC was dependent on biopsy.

Conclusions: The lesions of UC are commonly located in the left side colon, the course of UC is short, the age of onset is relatively high in the middle-and old-aged group, and the prevalence of both malignancy and complications is low. Colonoscopy with biopsy is considered to be the major means for the diagnosis of UC.
An analysis of 250 inflammatory bowel disease cases

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Objective: To study the clinical features of inflammatory bowel disease (IBD).

Method: A retrospective analysis was performed in 250 in-patients with IBD diagnosed in the past 14 years.

Results: 161 ulcerative colitis (UC) and 89 Crohn's disease (CD) cases were analyzed according to the diagnostic criteria. The male to female ratio was 1.3:1.9 and the peak age on set was 20-50 years. 1% CD had family history. Abdominal pain, diarrhea and bloody stools were the most common symptoms both in UC and CD. 27 (18%) of 161 UC were proctitis and 40 (26%) were proctosigmoiditis, 29 (19%) left-sided colitis, 52 (34%) pancolitis, 4 (3%) regional colitis. 68 (42%) cases of UC had first episode, 53 (33%) had chronic relapse and 35 (22%) were of chronic persist type, 5 (3%) were of acute fulminant type. Among 89 patients with CD, the location of disease were ileitis 28 (31%), colitis 30 (34%), ileocolitis 27 (30%) and the uncommon lesion including esophagus and duodenum 4 (5%). The behaviour of CD were non-stricturing/non-penetrating 25 (28%), stricturing 33 (37%) and penetrating 31 (35%). Extra-intestinal manifestation in IBD were uncommon which usually involved arthrosis and complications were more frequent in CD including ileus, fistula and perforation. 12 (7%) patients with UC performed operation and 42 (47%) patients with CD were diagnosed surgically. The acute presentation of CD may mimic acute appendicitis.

Conclusions: The number of IBD cases increased over the past 14 years. Individual presentations difference diversely. Extra-intestinal manifestations and complications are more frequent in CD which result in the high rate of misdiagnosis.

Key words: inflammatory bowel disease; diagnosis; extra-intestinal manifestation
Extraintestinal manifestations of inflammatory bowel disease -
A clinical study of 33 cases

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**Introduction:** Patients with inflammatory bowel disease (IBD) may develop some extraintestinal manifestations, which can involve multiple organ systems, such as blood, liver, biliary tract, joints, eyes and others.

**Aim:** This study is to investigate the prevalence of the extraintestinal manifestations of IBD.

**Methods:** We reviewed 33 patients with IBD hospitalized in our hospital in the year 2005 retrospectively.

**Results:** From January 2005 to December 2005, 33 patients with IBD were admitted to hospital. 26 of them were ulcerative colitis, 7 were Crohn's disease with colitis, among which were 22 male and 11 female (range 20-76 years). Among them, 24 cases represented with one or more extraintestinal manifestations (UC 17, CD 7), which could be classified as: hemalogical abnormality (thrombocytosis) - 15 cases (45.5%) (UC 11, CD 4); gallstones or cholecystitis - 12 cases (36.4%) (UC 8, CD 4); arthritis or arthralgia - 10 cases (30.3%) (UC 6, CD 4); 5 bronchitis or asthma - 5 cases (15.1%) (UC 3, CD 2); fatty liver - 4 cases (12.1%) (UC 3, CD 1); scleritis, conjunctivitis and keratitis - 4 cases (12.1%) (UC 3, CD 1); kidney stone or calcium oxalate - 4 cases (12.1%) (UC 2, CD 2); aphthous ulcer - 3 cases (9.1%) (UC 1, CD 2); clubbing fingers - 1 case (3%) (CD); phlebitis - 1 case (3%) (UC). And we found that extraintestinal manifestations may have positive correlation with the extent of the lesion in intestine.

**Discussion/Conclusion:** Extraintestinal manifestations are not uncommon in patients with IBD in Shanghai, and associated with the extent of the lesion. Patients with CD involved colitis seemed to have higher incidence of extraintestinal manifestations than those with UC. It is reported that some extraintestinal manifestations would result in serious consequence if they are not diagnosed or treated in time. And as most symptoms mentioned above are not specific, physicians should pay more attention to the diagnosis and differential diagnosis.
Affects of sulfasalazine on colonic mucosal inflammation and inflammatory grading of patients with mild and moderate ulcerative colitis

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Objective: To investigate the affects of sulfasalazine (SASP) on colonic mucosal inflammation and inflammatory grading of patients with mild and moderate ulcerative colitis (UC).

Methods: Changes of colonic mucosal inflammation and inflammatory grading of 106 patients with active UC were observed before and after the treatment with SASP, 1 g, 3 times daily for 6 weeks.

Results: The rate of eosinophil infiltration was 98.2% and 80.4% in mild UC (P < 0.01), and 100% and 91.1% in moderate UC (P < 0.05) before and after treatment. No significant affects of SASP on lymphocyte hyperplasia, lymphoid follicular formation and plasmacyte infiltration were observed before and after treatment. The affect on crypt abscess was 21.4% and 4.4% in mild UC (P < 0.05), and 48% and 13.3% in moderate UC (P < 0.001) before and after treatment. The affect on mucosal inflammatory grading was 2.00 ± 0.84 and 0.91 ± 0.46 in mild UC (P < 0.001), and 2.49 ± 0.84 and 1.31 ± 0.75 in moderate UC (P < 0.001) before and after treatment.

Conclusions: SASP can improve crypt abscesses and reduce neutrophilic and eosinophilic leukocyte infiltration in inflammatory mucosa of UC.
Risk factors for ulcerative colitis associated colorectal cancers in a Hungarian cohort of ulcerative colitis patients. Results of a population based study

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Introduction: There is an increased risk of colorectal cancer (CRC) in ulcerative colitis (UC). The prevalence of UC associated CRC is different in various geographical regions. The risk depends primarily on the duration and extent of disease. The aim of the study was to identify risk factors for and epidemiology of CRC in Hungarian UC patients.

Methods: We retrospectively evaluated the relevant epidemiological and clinical data of all UC patients in Veszprem province in our thirty-year IBD database (723 UC patients, m/f: 380/343, familial disease: 5.2%, non-CRC related colectomies:3.7%).

Results: CRC was diagnosed in 13 patients (m/f: 6/7,13/8564 person-year-duration) during follow-up (age onset in UC-CRC patients: 34.5 [13-61] years vs. 38.5 [11-80] years in patients without CRC), age at diagnosis of CRC was 50.9 (27-70) years. Eight patients are still alive (survival:67.9 months), four died because of CRC (survival: 8.0 months), one died due to unrelated cause. Longer disease duration, extensive colitis, primary sclerosing cholangitis (PSC) and dysplasia in the biopsy were identified as risk factors for developing CRC (in a logistic regression model). The cumulative risk for developing CRC after a disease duration of 10 years was 0.6% (95% CI: 0.2-1.0%), 20 years 5.4% (95% CI: 3.7-7.1%) and 30 years 12.6% (95% CI: 7.0-18.2%). CRC diagnosed at surveillance colonoscopy was associated with longer survival (p = 0.04).

Conclusions: The cumulative risk of CRC was high in our UC patients and CRC developed approximately fifteen years earlier compared to sporadic Hungarian CRC patients. Longer disease duration, extensive colitis, dysplasia and PSC seem to be important risk factor for developing CRC in UC.
The ulcerative colitis patients with pyoderma gangrenosum

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The ulcerative colitis is an illness initiated, among others, by autoimmunological disorders. It contributes to the fact that in its' course, it may display a wide spectrum of symptoms out of the intestine. Pyoderma gangrenosum constitutes, from the surgeon's point of view, one of more essential co-occurring illness. A recently recognised variant of pyoderma gangrenosum is a peristomal form in patients with ulcerative colitis or Crohn's disease who have had abdominal surgery and have an ileostomy or colostomy.

236 patients diagnosed with ulcerative colitis have been operated in Chair and Department of General, Gastroenterological and Endocrinological Surgery, Poznan, Poland since 1985 till 2005. Nine among all treated in our Department patients have been diagnosed with pyoderma gangrenosum (3.8%). 7 patients had dermal syndromes during the pharmacological treatment, accompanied by intensified symptoms in the intestine. In two cases the skin alterations appeared before the typical symptoms of ulcerative colitis, therefore initially patients had received dermatological treatment.

In the group of the observed patients, during the pharmacological treatment, we did not find the entire remission of skin alterations in any of the patients. At 7 patients the symptoms of pyoderma gangrenosum ceased in a few to a dozen or so days after the operation. At two patients the symptoms were visible for dozen or so months after the operation. However, they healed and no remission of the illness has been diagnosed till the present moment (time of observation: 6-48 months). In our material the peristomal variant of pyoderma gangrenosum was not found.

In the examined group of patients with ulcerative colitis, the pyoderma gangrenosum occurrence frequency, was similar to the one described in the literature. The recession of skin symptoms, in most of the cases quickly after operation, seems to confirm the fact that the radical surgical treatment of ulcerative colitis at patients with heavy or long-term symptoms, allows to avoid many complications and it causes the recession of the syndromes accompanying the ulcerative colitis.
Prevalence of amebic infection in patients with ulcerative colitis flare up

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Introduction: Amibic infection can trigger the initiation of inflammatory bowel disease (IBD). In developing countries, amebic infections together with IBD may cause a challenge in the diagnosis and treatment of IBD. Aim of this study is to explore the prevalence of amebiasis among patients with the flare up of ulcerative colitis.

Methods: 31 ulcerative colitis patients with the criteria of activation were investigated for the occurrence of entomeaba histolytica (EH) by microELISA technique.

Results: Six patients were found to be infected by EH by ELISA technique (19%). No correlation was found between the disease activity score and the presence of EH.

Discussion/Conclusion: EH infection is quite common among patients with ulcerative colitis flare up whereas no correlation had been found with the activity.
Thromboembolism (TE), other extraintestinal manifestations of inflammatory bowel diseases (IBD)

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Introduction: Patients with IBD appear to have 3-4 fold risk of developing TE. The mechanisms of this complication in IBD are not completely elucidated, but it has been suggested that the activity of the IBD is related to TE risk

Objetives: To determine clinical characteristics of TE in a group of IBD patients.

Patients and methods: We examinated the clinical setting of TE in 16 patients.

Results: Thirteen UC and three CD patients were included, with median age 43 years (21-72 years), eight female; 11 patients were under 50 years. In UC, nine had pancolitis, all TE were during active phase of the disease, being moderate-severe in all patients. In CD, two patients had inflammatory activity. Nine patients had deep vein thrombosis, three pulmonary embolism, two mesenteric veins/portal vein, one longitudinal venous seno, one cerebral arterial and one braquial arterial thrombosis. The mean interval from time to diagnosis of IBD to TE was between one week-six years. Five patients were hospitalized at the time of TE. None of the patients were on total parenteral nutrition, had central venous cateter or had inherited causes of thrombophilia. All patients were treated with heparin without complications. One patient died as a direct result of TE. There was no previous history of trombosis.

Discussion/Conclusion: TE is an extraintestinal manifestation of IBD and clinicians should have a low threshold for suspecting the presence of these complications. The remission may be the most important factor in the prevention of TE. Heparin should be started early these cases.
Collagenous colitis - Symptomatic and histological response to oral low dose methotrexate

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Introduction: Low dose oral methotrexate was observed to be effective management of collagenous colitis in a patient prescribed the drug for co-existent rheumatoid arthritis. Subsequently it was offered to patients with collagenous colitis with refractory diarrhoea after failed standard therapy.

Methods: A retrospective review of 18 patients with histologically proven collagenous colitis who had been prescribed methotrexate between 1986 and 2004 was undertaken. Methotrexate was commenced at a dose of 5 to 10 mg weekly and then titrated till a clinical response was observed. Symptoms and side effects were assessed at clinical follow-up. Haematological and biochemical indices were monitored. Ten patients underwent a further colonoscopy to determine histological response.

Results: Twelve females and 6 males (37 to 88 years) were prescribed methotrexate between 5 and 25 mg per week (median 7.5 mg) and followed for 1 to 127 months (median 19 months) whilst on methotrexate. A marked clinical response was seen in 13 and improvement in a further 2 patients by the third week. Three patients withdrew, one when on 5 mg weekly due to no response, another due to minor side effects when taking 7.5 mg weekly and the other for unknown reasons. Ten patients consented to a follow-up colonoscopy. Normalisation of histology was seen in 5, improvement in 2 and no change in 3.

Discussion/Conclusion: In this small study, low dose oral methotrexate resulted in a prompt symptomatic response in 83% of patients with refractory collagenous colitis and histological resolution in 50%.
Amoebiasis in ileo-anal pouch 7 years after total colectomy: A case report

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Introduction: Amebiasis, affects almost 10% of UC patients in Turkey, localizes to the large bowel because trophozoites adhere the colonic mucins via surface lectin. A few atypical localizations of the disease has been reported but none in the ileoanal pouch.

Methods/Results: A 70 years old lady, diagnosed severe ulcerative colitis, had undergone total colectomy because of no response to corticosteroids and cyclosporine during first flare of the disease in 1997. Ulcerative colitis and amoebiasis was confirmed by histopathology. Four moths after colectomy, she complained of bloody rectal discharge. Direct examination material had revealed E hystolitica trophozoits. Metronidazole po and per rectum had been prescribed and ileanal continuity had been restored within the ensuing 6 months. Untill 2005, she had two flares of pouchitis treated by ciprofloxacin. She admitted to the hospital because of bloody diarrhea, abdominal pain, nausea, dizziness, weakness and weight loose in 2005. E hystolitica trophozoites, a lot of leucocytes and erythrocytes were seen in direct examination of fresh stool sample. Pouch mucosa was fragile, nodular and edematous on flexible sigmodoscopy. Apthtous ulcers were also seen. Upon institution of metronidazole treatment, stool frequency was decreased and blood was abolished.

Discussion/Conclusion: Here, we have reported a first case of ameobic pouchitis 7 years after the total colectomy and ileoanal pouch anastomosis. Prevalence and fate of amoebiasis in patients had total colectomy and ileanal pouch (no susceptible organ but the same host) might give insight to the pathogenesis of increased incidence of amoebiasis in UC patients.
Use of the sucrose breath test to assess probiotic effects on small bowel injury in the rat

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Introduction: Inflammation, atrophy, and ulceration of the small intestine are features of Crohn's disease. Certain probiotics, bacteria that may benefit the host, possess anti-inflammatory properties. The sucrose breath test (SBT) was employed to non-invasively assess the role of probiotics in 5-fluorouracil (5-FU)-induced small bowel injury.

Methods: Female Dark Agouti rats were allocated to five groups (n = 10): \textit{Lactobacillus fermentum} BR11 + 5-FU, \textit{Lactobacillus rhamnosus} GG + 5-FU, \textit{Bifidobacterium lactis} BB12 + 5-FU, vehicle + 5-FU, and vehicle + saline. Probiotics were administered by oral gavage prophylactically for seven days and concurrently for three days. Intestinal damage was induced on day 7 by 5-FU injection (150 mg/kg; IP) and rats were sacrificed 72 hr following 5-FU administration. The SBT measured breath $^{13}$CO$_2$, expressed as percentage cumulative dose at 90 min (%CD90), on days 0, 7, and 10. Sucrase activity, myeloperoxidase (MPO) levels, and histological damage severity were assessed in the jejunum.

Results: %CD90 was significantly lower (P < 0.001) in 5-FU treated controls (5 ± 0.6%; mean ± SEM) compared to saline treated controls (15 ± 0.7%) on day 10. Administration of 5-FU caused a significant (P < 0.001) reduction in sucrase activity (5-FU:35 ± 2 nmol glucose/min/cm; saline: 213 ± 10), an increase in MPO levels (5-FU:1122 ± 99 units/gram; saline:184 ± 11), and an increase in histological severity score (5-FU: 17 [15-20]; median [range]; saline:3 [1-7]) compared to saline controls. The probiotics tested offered no significant protection by any of the measurements utilised at the dose tested.

Discussion/Conclusion: The SBT is a simple, non-invasive indicator of small bowel injury which may have application in detection and monitoring of intestinal injury in other conditions affecting the small bowel. Further dose-response studies utilising higher probiotic concentrations are indicated.
Blood coagulation in children with inflammatory bowel disease

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Introduction: In pathogenesis of inflammation in inflammatory bowel disease (IBD) the important role belongs to disregulation of coagulation which leads to hemorheology disturbances and microthrombosis in an intestinal wall. Coagulopathy may be associated with intestinal bleeding and prognosis for the disease.

Methods: We observed 38 children aged from 6 month to 17 years (12 with Crohn's disease (CD) and 26 with ulcerative colitis (UC). The UC and CD activity was evaluated by Rachmilewitz scale and PCDIA respectively. Determination of blood coagulation system including fibrinogen, prothrombin time, activated partial thromboplastin time, thrombin time, soluble fibrin monomer complex (SFMC) were performed in all patients.

Results: The evaluation of blood coagulation parameters have shown that in 75% children with CD and 62% children with UC was significantly increased SFMC level, in 25% children with CD and 7.7% children with UC - increased fibrinogen concentration. After corticosteroid and 5-ASA therapy SFMC level was reduced in comparison with the initial data and became normal in 50% children with CD and 75% children with UC. We obtained positive correlation between PCDIA and SFMC level (r = 0.78, p < 0.01) and between PCDIA and fibrinogen concentration (r = 0.75, p < 0.01) in children with CD. Correlation between coagulation parameters and UC activity has not been revealed.

Discussion/Conclusion: Thus, fibrinogen and SFMC possible to use as additional criteria of activity in children with CD. Therapy with corticosteroid and 5-ASA improves blood coagulation parameters in children with IBD.
Life-threatening colitis-related complications in ulcerative colitis

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Methods: Throughout the 1971-2003 period at the Clinic of Gastroenterology - UH "Tzaritza Joanna" and 5th MHAT, some 424 patients with ulcerative colitis (UC) have been monitored. Life-threatening complications due to ulcerative colitis developed in 56 patients, with resulting exitus letalis in 24 patients (43%), as follows:

Results:
1. Vascular complications - 18 patients, exitus letalis - 7 patients (39%)
   1.1 Phlebothrombosis of the veins of the lower limbs - 14 patients, exitus letalis - 4 patients
   1.2 Phlebothrombosis of the parauterine plexus with pulmonary thromboembolism within 24 hours after colectomy, exitus letalis - 1 patient
   1.3 Cerebral insult, exitus letalis - 2 patients
   1.4 Mesenterial thrombosis - 1 patient
2. Massive haemorrhage - 2 patients, exitus letalis - 1 patient - after urgent proctocol-ectomy under circumstances of haemorrhagic shock
3. Colon cancer - 17 patients (4%), exitus letalis within 5 years after diagnosis - 11 patients (65%). Four of the latter died within 6 months after surgery
4. Toxic megacolon - 12 patients, exitus letalis - 3 patients (25%)
5. Pneumonia - 7 patients, exitus letalis - 2 patients

The above complications, except for cancer, developed in patients with fulminant ulcerative colitis and severe activity of chronic occurrences.

Discussion/Conclusion:
1. Complications in fulminant and active chronic UC are life-threatening with high mortality rates.
2. Colon cancer, massive haemorrhage and vascular complications are some of the major reasons for UC-related mortality.
Crohn's disease involving the jejunum or proximal ileum

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Introduction: Crohn's disease (CD) affecting the jejunum or proximal ileum (JPI) is less common than classical CD involving the terminal ileum and/or colon. Reports of its prevalence range from 3.3% to 9.5% in adults. To determine the prevalence and major clinical associations of patients with JPI disease.

Methods: Patients were recruited from the Brisbane IBD database. The cohort with JPI disease was compared with the rest of this population-based CD cohort. Univariate analysis used chi-square or t-test, followed by multivariate analysis. Results are expressed as ratios, means ± standard deviations or odds ratio (OR) with 95% confidence intervals (CI). A significant p-value was defined as < 0.05.

Results: Patients with JPI disease represented 9.9% of the CD population. There was a highly significant male predominance in this subgroup (OR = 3.1; 95% CI: 1.8-6.4). This gender difference was not related to age at diagnosis, smoking history or any other clinical feature. The rate of surgical recurrence was significantly higher in the JPI group (P = 0.018). Granulomas were significantly more prevalent in this group on multivariate analysis when corrected for age, gender, immunosuppression and bowel resection (OR = 1.8; 95% CI: 0.9-3.6).

Discussion/Conclusion: Symptomatic CD involving the jejunum or proximal ileum, leading to investigation of this region, occurred in 10% of our patients. There was a strong male predominance in patients with JPI Crohn's disease, not explained by other potential confounders such as sex, age or smoking. Surgical recurrence rates were almost double in patients with JPI involvement, despite high rates of immunosuppression use.
Pouchitis - The new simple method of recognition using fecal pyruvate kinase (M2-PK) activity

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Introduction: The inflammation of the intestinal J-pouch mucosa ("pouchitis") occur at the 10-75% patients after restorative proctocolectomy. In recognition of pouchitis PDAI/Pouchitis Disease Activity Index/score is mostly used. Diagnostic method are unpleasant, time-consuming, expensive and requires special expertise. There is still looking for simple and objective method of recognition of pouchitis. The aim of our study was to evaluate the usefulness of fecal pyruvate kinase (TuM2-PK) activity in stool as a new diagnostic method of pouchitis

Methods: The investigated group consider of 27 patients after restorative proctocolectomy. During the control examination modified PDAI was determined in all patients. The single stool samples was taken in all cases and TuM2-PK activity (U/ml, ELISA, ScheBo-Biotech, Germany) was determined. The TuM2-PK activity was also investigated in control group of 70 healthy persons.

Results: Enzyme activity was significantly higher in group of patients after restorative proctocolectomy than in control group. In examined group of patients after surgery fecal TuM2-PK activity was significantly higher in patients with PDAI ≥ 7 pts than in the group with PDAI < 7 pts (211.2 ± 42.5 vs 48.5 ± 19.4 U/ml, p < 0.002). No correlation was found between TuM2-PK activity and time passed since the operation

Discussion/Conclusion: In our study we observed significant correlation between fecal TuM2-PK activity with the disease activity in patients with pouchitis (p < 0.00001). The enzyme activity stool test is simple, non-invasive method. TuM2-PK seems to be a simple and objective method in recognition of pouchitis. However, further validation of test in patients with pouchitis is necessary.
Value of a scanning submicroscopy in diagnostics of a Crohn’s disease of a colon

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One of cardinal microscopic tags of a Cronhn's disease (CD) is the diffusion of an inflammatory infiltrate on all layers of an intestinal wall. Characteristic for a light microscopy of change at CD dominate in a mucosa and on limit with under mucous by a layer, which express as "of incomplete granulomas" and granulomas sarcoid of a type consisting from epithelioid and colossal cells of a type a Peerogov-Langhance, surrounded fibrosis by circle and girdle from lymphocytes. In a muscular coat the phenomena of an edema dominate. However at visual survey with the help of a colonoscopy at CD near to the struck part of an intestine the visible pathological changes are not always taped. The light microscopy of an operational stuff nor allows to find here initial tags of disease. With the help of a scanning submicroscopy (SSM) studied samples of a tissue of a colons taken for 32 patients CD. Samples macropreparations researched in a supermicroscope "Hitachi S-405A" (Japan) at an accelerating strain 25 sq. With the help SSM with CD in fields of an intestine extending on the average on 10 sm from zones of an inflammatory lesion, and which macroscopic and with the help of a light microscopy are determined as not changed, it was possible to find appreciable changes of a microrelief of connecting tissue of cells of a mucosas indicating their awake secretion and an englobement. It is known, that to an operative measure are exposed about 70% of the patients with CD, thus the relapses of disease after the operation arise for 90% of the patients. Our researches with the help SSM have formed the basis for the guideline of usage of amplate operative measures at CD with seizure more than 10 sm not changed proximal and distal of fields of an intestine what to lower to prevent relapses of disease on 15.4% and postoperative complications on 27.3%.
Utility of faecal S100A12 as a non-invasive screening test for children with gastrointestinal symptoms suggestive of inflammatory bowel disease

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Introduction: We have recently shown that faecal levels of the calcium-binding protein S100A12 are increased in children with IBD and that this test provided a sensitive and specific non-invasive marker of gastrointestinal inflammation in children when 10 mg/kg was used as a cut-off. We hypothesised that faecal A12 offers enhanced utility over standard tests to distinguish IBD from non-inflammatory bowel disease (such as functional disorders) when used as a screening test.

Methods: Stools were obtained from 37 children (2.2 to 16 yrs) with gastrointestinal symptoms and suspected IBD before undergoing upper gastrointestinal endoscopy and colonoscopy. Faecal levels of A12 were measured by immunoassay. Results were correlated with standard blood tests and histological findings.

Results: In children with IBD (n = 20) faecal A12 level were elevated (143.5 ± 122.2 mg/kg) compared to the non-IBD group (n = 17, 6.8 ± 14.5) (p < 0.0001). When < 10 mg/kg was used as upper reference limit faecal A12 had sensitivity of 100% and specificity of 89%, which were superior compared to the sensitivities and specificities of standard blood tests (ESR, CRP, PLT, albumin). There was no linear correlation between A12 and the standard tests.

Conclusion: Faecal S100A12 is a highly sensitive and very specific non-invasive marker of gut inflammation in children presenting with gut symptoms. S100A12 may be an additional simple test to screen and select children who warrant further invasive and laborious procedures such as endoscopies for investigation of their symptoms. Further larger studies are required to confirm these findings.
Changes in faecal S100A12 (a novel non-invasive marker of gastrointestinal inflammation) in children treated for active Crohn disease

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Introduction: We have previously shown that the calcium-binding protein S100A12 is elevated in the serum and mucosa of children with IBD and have recently validated a sensitive and specific stool-based immunoassay for the detection and measurement of A12. The aims of this study were to measure faecal A12 levels in a group of children with active Crohn disease (CD) prior to and after treatment with exclusive enteral nutrition (EEN).

Methods: Stools were collected from 22 children with active CD and from 25 healthy children. Serial stools were collected from children with CD before and during therapy with EEN and A12 levels were measured by ELISA. Patterns of disease location and severity were defined, disease activity assessed (Pediatric Crohn Disease Activity Index: PCDAI) and standard serum inflammatory markers recorded.

Results: Faecal A12 was elevated at the time of diagnosis (median 85.69, range 6.19 to 349.9 mg/kg) compared to controls (median 0.69, range 0.69 to 17.73 mg/kg) (p < 0.0001). Ten children reached clinical remission (PCDAI < 15) with normal CRP (< 3). Faecal A12 levels (median 111.7, range 6.19 to 311.3 mg/kg) fell following treatment (median 28.51, range 4.49 to 275.5 mg/kg) (p < 0.05). Faecal A12 levels correlated closely with PCDAI (p < 0.0001) and serum markers, particularly with colonic involvement.

Discussion/Conclusion: S100 A12 faecal levels correlate with disease activity, decrease with therapy and accurately reflect the pattern of colonic disease in children with active CD. This protein provides sensitive and specific non-invasive assessment of gut inflammation. Further evaluation of this marker is now required in additional contexts.
Th1 cytokine pattern determination in patients with inflammatory bowel disease: A novel tool for differential diagnosis

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Introduction: Crohn disease (CD) and Ulcerative colitis (UC) are inflammatory bowel diseases (IBD) with an uncontrolled pro-inflammatory response to commensal and food antigens. CD shows an elevated TNF-alpha production and a predominant Th1 cytokine pattern compared to UC with a Th2 response. Between 10-15% IBD patients are not fully diagnosed becoming an indeterminate condition to be properly diagnosed. The aim of this research was to evaluate the Th1 immune pattern as a change in CD4+/INF-gamma expression in CD and UC patients, and to compare it in terms of type and activity of the disease.

Methods: Whole blood samples were taken from 16 IBD patients: active UC (6), inactive CU (3), active CD (4), inactive CD (3) and 4 controls. Whole blood was exposed to phytohemaglutinin (PHA) and further the percentage of CD4+ T lymphocytes that produced INF-gamma was determined by multiparametric flow cytometry. INF-gamma production by CD4+ T cells from patients was compared in terms of type and activity degree of the disease.

Results: INF-gamma production trend by T lymphocytes from patients with IBD was: active UC = 9.36 ± 2.31, inactive UC = 3.16 ± 1.76, active CD = 20.55 ± 6.44, inactive CD = 6.94 ± 3.96, and control = 1.63 ± 0.77.

Discussion/Conclusion: Our preliminary findings suggest that flow cytometry determination of cytokine production pattern by CD4+ T cells is a promising tool to assist IBD diagnosis in particular during indeterminate conditions and might differentiate the activity level of the disease. FONDECYT 1050451.
Abdominal ultrasonography in the diagnosis and followup of IBD

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Introduction: The process of diagnosis of the two main elements of IBD is based on endoscopic and histological findings. Ultrasonography (USG) is rarely utilized in this process, thus the majority of clinicians may be unaware of the benefits of this method.

Method: Our results are drawn from a group of patients treated over a 14-year period, with 30 patients (3 x 10 pts) selected to illustrate various aspects of the disease. Group I consists of patients who were being examined for the first time by ultrasound, Group II is made up of patients who had previously been diagnosed with serious IBD and were undergoing continued USG observation, and Group III was patients who had been symptom-free for some months but had experienced some recurrence of previous symptoms. For all these cases, colonoscopy and histology were considered the definitive diagnostic tool.

Results: IBD was confirmed in Group I in 80% of the cases. USG was sufficient for 100% of patients in Group II to assess the progress of the disease as well as any probable complications (e.g. perforation), while in Group III USG made it possible with all patients to determine whether reported returning symptoms were caused by the previous IBD or by other conditions.

Note: video recordings will be used to illustrate the features of the different stages of the disease

Conclusion: USG, when conducted by doctors with rich clinical knowledge, can assist gastroenterologists in the diagnosis of IBD. USG is also a convenient and benign way to track the development of the disease and to differentiate between IBD and other conditions which cause colonic symptoms.
Anti-Saccharomyces cerevisiae antibody does not differentiate between intestinal tuberculosis and Crohn's disease

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Introduction: The clinical, morphological and histological features of intestinal tuberculosis (IT) and Crohn's disease (CD) mimic so much, that it becomes difficult to differentiate them. The sensitivity of anti-Saccharomyces cerevisiae antibody (ASCA, IgG and IgA) in CD is 60-80%, whereas specificity is almost 90%. There are neither reports of study of ASCA in patients with intestinal tuberculosis nor it ever has been used to differentiate between IT and CD.

Methods: Patients with UC (n = 25), CD (n = 62), IT (n = 31) and 21 healthy controls were included in this study. Five ml of blood was taken from them and serum was stored at -70°C. ASCA antibodies (both IgG and IgA) were estimated using commercially available ELISA kits (Genesis Diagnostics, UK). Anti neutrophilic cytoplasmic antibody was done by indirect immunoflorescence.

Results: ASCA IgA in 4.7%, 28%, 33.8%, 41.9% and ASCA IgG in 4.7%, 24%, 51.6%, and 48.3% were positive in healthy controls and patients with UC, CD and IT, respectively. Either ASCA IgG or IgA were positive in 9.5%, 33.8%, 61.2% and 67.7% in healthy controls, UC, CD and IT, respectively. ANCA was positive in 0, 33.8%, 10.4%, 7.1% in healthy controls, UC, CD and IT, respectively. ASCA IgG was positive in significantly higher number of patients with CD (p < 0.0001) and IT (p < 0.0001) in comparison to healthy controls. ASCA IgA was positive in significantly higher no. of patients with UC (p < 0.04), CD (p < 0.013) and IT (p < 0.006) in comparison to healthy controls. On comparison between diseases, ASCA IgG was positive in significantly more no. of patients with CD (51.6%, p<0.005) and IT (48.3%, p < 0.02) in comparison to UC (24%). No such significant difference was observed with ASCA IgA. There was no significant difference in ASCA IgA (33.8%, 41.9%, p > 0.05), ASCA IgG (51.6%, 48.3%, p > 0.05) and ANCA (10.4%, 7.1%, p > 0.05) in patients with CD and IT, respectively.

Discussion/Conclusion: ASCA IgG and ASCA IgA does not help in differentiation between intestinal tuberculosis and Crohn's disease.
IBDchip: A new strategy to predict clinical course and development of complications in patients with inflammatory bowel disease (IBD)

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**Introduction:** Accurate prediction of disease phenotype in IBD patients is not available. The IBDchip is a DNA array, allowing the simultaneous study of 61 single nucleotide polymorphisms (SNPs) of 40 genes, selected by their potential impact on IBD.

**Aim:** To evaluate the usefulness of the IBDchip to predict disease phenotype and development of complications in IBD patients.

**Methods:** The genetic profile of 579 patients (335 CD and 244 UC), with > 5 years of follow-up, was assessed by the IBDchip. Relationship between several clinically relevant outcomes and the patient’s pattern of SNPs and clinical characteristics was analyzed by logistic regression. An optimal predictive model for each one the clinical outcomes, based on a weighted combination of SNPs and clinical characteristics, was identified.

**Results:** At abstract submission we have completed the analysis of the IBDchip predictive value for some clinical outcomes. The IBDchip was able to discriminate between fistulizing and inflammatory phenotype in CD patients with a specificity (Sp) 95%, sensitivity (Se) 58%, positive predictive value (PPV) 92%, negative predictive value (NPV) 65%, overall accuracy (OA) 74%, and likelihood ratio (LR) 11.7. Need for colectomy in UC patients was predicted with a Sp 95%, Se 70%, PPV 66%, NPV 96%, OA 93% and LR 15.3.

**Discussion/Conclusion:** The IBDchip is able to discriminate between fistulizing and inflammatory phenotype in CD patients and to identify a significant proportion of UC patients requiring colectomy. The IBDchip could be useful in the clinical setting, selecting a subgroup of patients who might benefit from specific treatment.
High rate of Crohn's disease in Canterbury New Zealand - Results of a population-based study

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Introduction: Inflammatory bowel disease (IBD) has increased exponentially in industrialised nations over the last fifty years. Previous New Zealand studies have shown that IBD is less common than in other countries, however, clinical observations suggested a high incidence and prevalence of IBD in Canterbury, particularly Crohn's disease (CD). This study aimed to determine the descriptive epidemiology of IBD in Canterbury.

Methods: Canterbury IBD patients, recruited using multiple strategies, gave informed consent, permission for clinical record review, completed a questionnaire and were bled for DNA extraction as part of the Canterbury IBD Project. Cases were confirmed using standard criteria and completeness of recruitment was validated using capture-recapture methods. Demographic and phenotypic data were extracted from case notes.

Results: 1420 patients (715 CD, 668 ulcerative colitis [UC]) were recruited (> 91\% of Canterbury IBD patients). In 2004, age-standardised (WHO World Standard Population) IBD, CD and UC incidence rates were 25.2, 16.5, and 7.6/100,000/year respectively. The IBD, CD and UC point prevalences on 1 June, 2005 were 308.3, 155.2, and 145.0/100,000 respectively. CD patients were more likely than UC patients to be female (61.4\% v 47.1\%) and to be younger (median age: 39.9 years v 43.7 years). 97.5\% of IBD patients were Caucasian.

Discussion/Conclusion: IBD is at least as common in Canterbury as in other western regions. CD incidence and prevalence are amongst the highest ever reported and are higher than for UC. IBD population characteristics are otherwise similar to other countries. The Canterbury IBD Project will be a valuable tool for future population-based IBD epidemiology and genetics research.
Inflammatory bowel disease in the pediatric East Indian population in British Columbia

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Introduction: The incidence of ulcerative colitis (UC) and Crohn disease (CD) is linked to ethnicity and geography. The geographical differences, population migration and changing epidemiology suggest an environmental role in prevalence, modulation and phenotypic expression of the diseases. We sought to determine the prevalence and phenotypic expression of IBD in the paediatric East Indian immigrant population in BC and compare it to the total paediatric IBD population in BC.

Methods: A retrospective review was undertaken with data collected from medical charts of East Indian Paediatric patient's =16 of age diagnosed with IBD at BC Children's Hospital between 1985 and 2004. Age, gender, family history of IBD, type and extent of disease were included in the analysis. Provincial population statistics were obtained from Statistics Canada.

Results: 62 East Indian patients were diagnosed with IBD from 1985 to 2004 (11% of total); 31 (50%) with CD, 23 (37.1%) UC and 8 (12.9%) IC, in contrast to 65.2%, 17.1% and 17.7% respectively in the total. The incidence rates for IBD between 1996-2001 for the East Indian population was 14.06/105 (6.80/105 for CD, 5.44/105 for UC and 1.81/105 for IC) vs. 5.5/105 for the total IBD group (3.8/105 for CD, 0.91/105 for UC and 0.79/105 for IC). The East Indian male/female ratio was different from that observed with the total (2.15:1 vs. 1.22:1, P < 0.04). No first-degree relatives in the East Indian group had CD. The East Indian population had more colonic disease, however significant differences were not observed with extent of CD, age of diagnosis or duration of symptoms prior to diagnosis.

Discussion/Conclusion: This data suggests a higher incidence of IBD in the East Indian paediatric population with a different pattern of phenotypic expression and male predominance. Moreover, this data indicates a difference in phenotypic expression from previously published East Indian adult IBD data. These results suggest an effect of migration, environmental and life style change on the incidence and phenotypic expression of IBD.
Epidemiology of inflammatory bowel disease in Turkey

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Introduction: The aim of the present study was to assess epidemiological characteristics and the disease pattern of IBD in Turkey.

Methods: All records of patients' attended to the gastroenterologists of Turkey, diagnosed and treated in the hospitals are prospectively written to the web page of IBD Society beginning from September 2004. The majority of patients were followed up regularly. We analyzed age, sex, education, job, socioeconomic status, geographic distribution, family history, environmental influences, colitis extent, and coexistence of other disease.

Results: During the period of time studied, we diagnosed 1785 IBD [1307 (73%) ulcerative colitis, 450 (25%) Crohn's disease and 28 (2%) indetermined colitis], with 767 females, 1018 males, and female/male: 0.75. Histogram of the age of the patients showed the monophasic distribution with one peak between 31-50 years for ulcerative colitis and Crohn's disease. The predominant form of UC was distal colitis, which affected almost 49% (10% proctitis, 39% rectum and sigmoid) of the studied population. Pancolitis was present in 33%, in left colitis 15%, in CD colon only in 24%, 22% terminal ileum, 32% ileo-colon, 18% ileo-ceacum of the patients. In distribution according to the sub-divisions of Turkey, most of the patients were in Marmara and Egean (northern west and west) part. Patients were mostly from urban areas with medium socioeconomic situation. Family history of IBD for both UC and CD is 4%. History of appendectomy was 13% in CD, 2% in UC and 4% in IC which is significantly different than the others. Extraintestinal findings were present in 13.8% of the UC cases, 24% of the CD cases. Most common finding was peripheral artropathy and sacroileitis in both groups. Second most common finding was cholecystopathy.

Discussion/Conclusion: Occurrence of UC in Turkey is much higher than CD. The majority of IBD are diagnosed in the middle aged patients (31-50 years) with the predominance of males. The most common clinical forms of UC is distal colitis, and CD is ileo-colonic form.
Design and initial experience with a web based clinical database

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Introduction: Databases have been invaluable tools for progressing clinical and epidemiological research of IBD. However, common limiting factors include:

- Inability to follow the disease longitudinally
- Diagnostic bias due to preconceived ideas of subtypes of IBD
- Complexity

Methods: We enlisted the professional services of a business analyst/programmer together with two IBD specialists to design a web based clinical database which ensures a 'clean', non-biased diagnosis ready for analysis to avoid some of the problems faced with current databases.

Results: The clinical database pursues longitudinal data with fixed descriptor fields that are not determined by a particular diagnosis, and thus has the ability to derive a diagnosis based on different classifications such as the Montreal or Vienna. Its modular construction overcomes some issues of complexity; only patient demographics and physician-diagnosis are compulsory fields with the remainder of the sections optional. Other sections include imaging and clinical assessments, medical and surgical treatments, histology, family and environment modules. Security features include:

- Ability to predetermine sections a user can open
- Ability to predetermine view, edit, write (delete or add) options
- Ability to view de-identified data and security between different hospital users
- Full activity audits

Discussion/Conclusion: The web based clinical database will provide a secure site for data collection with a user-friendly modular construction. Fixed descriptor fields ensure a 'clean', unbiased diagnosis ready for analysis.
Inflammatory bowel disease, analysis of presenting phenotype by age distribution in Australian children

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Introduction: We are in a unique position in Australia to have established in 1996 a comprehensive national database of paediatric and adolescent IBD with the aim of establishing epidemiological influences on the disease. The purpose of this study is to examine the influence of age at diagnosis on the relative frequency and phenotype.

Methods: Clinical, demographic and laboratory data at diagnosis is collected for IBD patients <18 years. In this analysis comparison was made of disease distribution, demographic data, nutrition, family history of IBD and laboratory data in the age range 0-4, 4-8, 8-12 and 12-16 years for Crohn's disease (CD), ulcerative colitis (UC) and indeterminate colitis (IC).

Results: Total of 1463 children available for analysis, mean age 10.5 ± 3.7 yrs, 54% male.

<table>
<thead>
<tr>
<th>Disease Frequency by Age of diagnosis (years)</th>
<th>0-4</th>
<th>4-8</th>
<th>8-12</th>
<th>12-16</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD</td>
<td>41 (36%)</td>
<td>92 (42%)</td>
<td>310 (61%)</td>
<td>352 (61%)</td>
<td>826 (57%)</td>
</tr>
<tr>
<td>Male</td>
<td>(59%)</td>
<td>(65%)</td>
<td>(53%)</td>
<td>(53%)</td>
<td>(54%)</td>
</tr>
<tr>
<td>UC</td>
<td>50 (44%)</td>
<td>92 (42%)</td>
<td>141 (29%)</td>
<td>173 (30%)</td>
<td>466 (32%)</td>
</tr>
<tr>
<td>Male</td>
<td>(42%)</td>
<td>(52%)</td>
<td>(56%)</td>
<td>(53%)</td>
<td>(52%)</td>
</tr>
<tr>
<td>IC</td>
<td>24 (21%)</td>
<td>33 (15%)</td>
<td>57 (11%)</td>
<td>57 (10%)</td>
<td>171 (12%)</td>
</tr>
<tr>
<td>Male</td>
<td>(46%)</td>
<td>(70%)</td>
<td>(60%)</td>
<td>(46%)</td>
<td>(55%)</td>
</tr>
<tr>
<td>Total</td>
<td>115 (8.1%)</td>
<td>217 (15.2%)</td>
<td>508 (34.9%)</td>
<td>623 (41.9%)</td>
<td>1463</td>
</tr>
</tbody>
</table>

The frequency of CD increases significantly from age 8-12 years. The frequency of pancolitis decreases with age for CD, the frequency of terminal ileal disease increases, while for UC the frequency of pancolitis increases with age. Minor variation noted in the frequency of family history in first degree relatives, nutrition, laboratory parameters, perianal, upper gastrointestinal involvement, hepatobiliary, ocular and cutaneous involvement over the age distribution.

Discussion/Conclusion: Significant age related changes in the frequency of CD vs UC and IC and in disease distribution occur in the paediatric and adolescent age group.
Epidemiology and clinical characteristic of IBD in Indonesia: A multi-centre study

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Background: In recent years a significant increase in the incidence of Inflammatory Bowel Disease (IBD) has been witnessed in Asian Pacific countries. However the incidence of the disease in Indonesia has been scarcely reported.

Aims: to determine the incidence and characteristic of IBD patients in Indonesia.

Methods: From January 1998 to December 2005 all patients who underwent colonoscopy in Dr. Cipto Mangunkusumo Hospital and eight other surrounding hospitals were reviewed. The diagnosis and classification of IBD was based on clinical and endoscopy criteria.

Results: Of 2397 patients who underwent colonoscopy, 294 patients were diagnosed as IBD (12.3%), and 703 (29.3%) as colitis. Among IBD patients 163 had ulcerative colitis (UC) (55.4%, 80 male and 83 female, age range, mean + SD at diagnosis 5-84, 43.99 ± 17.57, respectively) and 131 had Crohn's disease (CD) (44.6%, 73 male and 58 female, age range, mean ± SD at diagnosis 15-81, 41.39 ± 15.85, respectively). Four most frequent symptoms of IBD patients are chronic diarrhea (34.7%), hematochezia (32.0%), abdominal pain (15.3%), constipation (4.1%), and others. Hematochezia (38.0%) and chronic diarrhea (37.4%) are the most frequent symptom in UC and CD consecutively. Though the incidence of UC more frequent in female and CD in male patients, but such associations were not significant, statistically (p = 0.704, p = 0.186, respectively).

Conclusion: The incidence of IBD in Indonesia seems to be increased in the last decade. Occurrence of UC is higher than CD.

Key words: epidemiology; IBD; clinical characteristics
Protective effect of lactulose on dextran sulfate sodium-induced colonic inflammation in rats

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Introduction: Promising results have recently been obtained with probiotic therapy in ulcerative colitis (UC). Orally administered lactulose has been shown to increase the colonic levels of Lactobacillus species associated with probiotic activity. The purpose of the present study was to examine the effect of lactulose on a rat UC model induced by dextran sulfate sodium (DSS).

Methods: Experimental colitis was induced in male Wistar rats by 3% DSS-solution added to drinking water for 7 days. Lactulose (300-1000 mg/kg) was administered PO twice daily for 6 days. Colonic ulceration area, colon length, body weight changes, diarrhea/bloody feces, colonic mucosal myeloperoxidase activity (MPO), thiobarbituric acid reactive substances (TBARS) and histology were examined.

Results: DSS-treatment of control animals resulted in severe colonic lesions accompanied by diarrhea, bloody feces, decrease of body weight, shortening of colon length, and increase in MPO activity as well as TBARS, compared to normal rats. The histological examination showed deep erosions, ulcerations, and infiltrates of leucocytes as well as lymphocytes. Lactulose treatment ameliorated DSS-induced colitis in a dose-dependent manner, and at 1000 mg/kg all of the parameters examined, except TBARS, were shown to improve significantly as compared to controls (p < 0.01). The microscopical grading in the severity of damage was remarkably reduced by lactulose.

Discussion/Conclusion: These results demonstrated the protective effect of lactulose in this rat colitis model and suggested that the background of this lactulose effect may be due to alterations of colonic microflora. The ongoing determination of the changes in colonic microflora induced by lactulose may clarify the mechanism of action.
Prebiotic supplementation with fructooligosaccharide increases the severity of experimental colitis in rats

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Introduction: Fructooligosaccharide (FOS) has been reported to possess prebiotic characteristics and provide protection from TNBS-induced colitis in rats. Conversely, increased intestinal permeability and colonic injury has been described following FOS administration. We compared the effects of the prebiotics FOS and maltodextrin, (alone, and in synbiotic combination with \textit{L. fermentum}), on the development of dextran sulfate sodium (DSS)-colitis in rats.

Methods: Rats consumed an 18\% casein diet or diet supplemented with 6\% FOS or maltodextrin for 14 days. Synbiotic treatment groups were gavaged 1 ml \textit{L. fermentum} BR11 (1 \times 10^9 cfu/ml) twice daily. From day 7-14, colitis was induced via 3\% DSS in drinking water.

Results: Disease activity, colon and cecum weight increased, in all DSS-treated groups compared to normal controls. Colon and cecum weight in DSS + FOS and DSS + FOS/BR11-treated rats was further increased compared to DSS + Vehicle-treated rats (Colon: 19\% and 16\%, Cecum: 48\% and 62\%). Myeloperoxidase (MPO) activity was greater following DSS + FOS (204\%) and DSS + FOS/BR11 (150\%) treatment compared to normal controls. MPO activity was increased by 81\% in DSS + FOS-treated rats compared to DSS+Vehicle-treated controls. Histological damage severity scores were greater in DSS + Vehicle (6.8 \pm 1.3), DSS + FOS (9.7 \pm 2.4) and DSS + FOS/BR11-treated rats (8.8 \pm 1.8) compared to normal controls (0 \pm 0). Crypt depth increased in all treatments compared to normal controls (DSS: +Vehicle 137\%, +Maltodextrin: 112\%, +FOS: 130\%, +Maltodextrin/BR11: 135\%, +FOS/BR11: 125\%).

Discussion/Conclusion: No prebiotic or symbiotic assessed in the current study provided protection from DSS-colitis. Indeed, FOS actually increased some indicators of colonic injury. Further studies are required to explore the dose-responsiveness of prebiotics, including FOS, in experimental colitis.
Oral ingestion of *Streptococcus thermophilus* partially attenuates methotrexate-induced small bowel damage in female dark Agouti rats

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Introduction: Crohn's disease is often characterised by inflammation and ulceration of the small intestine. Increasingly, probiotics are being proposed as candidates for the alleviation of small bowel complaints. *Streptococcus thermophilus* is a potential probiotic, which has been shown to reduce the severity and duration of diarrhoea in infants. We investigated the effects of *S. thermophilus* (TH-4) on MTX-induced small bowel damage in rats.

Methods: Gastrointestinal damage was induced with MTX (1.5 mg/kg; i.m.) in 27 female dark agouti rats (148.0 ± 1.0 g) using the non-invasive 13C-sucrose breath test (SBT) to monitor gut function. Rats received MTX or saline at 0 hr; with daily treatment of: TH-4 at doses of 10⁹ (high), 10⁸ (low) cfu/ml, or skim milk (vehicle), 48 hrs pre and 96 hrs post MTX. The SBT was conducted at -24, 24 and 96 hr post MTX. At sacrifice small intestinal tissues were collected for sucrase activity, myeloperoxidase (MPO) activity and histological assessment.

Results: MTX + vehicle and MTX + low TH-4 rats produced a significantly lower SBT and sucrase activity compared to saline controls (p < 0.001). In contrast, MTX + high TH-4 showed no significant differences compared to saline controls, but were significantly higher compared to MTX + vehicle and MTX + low TH-4 (p < 0.05). MPO levels were significantly elevated (p < 0.05) in MTX+vehicle and MTX + low TH-4, but not in MTX + high TH-4, compared to saline controls and histological analysis confirmed these inflammatory changes.

Discussion/Conclusion: Oral ingestion of TH-4 at 10⁹ cfu/ml is capable of partially attenuating small bowel damage in rats. The non-invasive SBT is a useful technique to assess the efficacy of treatments or interventions for small bowel disease.
Dextran sulphate sodium (DSS)-induced small intestinal hyperplasia is prevented by administration of *L. fermentum* BR11 to rats

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**Introduction:** The dextran sulphate sodium (DSS) model of colitis is frequently employed to assess novel treatments for ulcerative colitis. However, few studies have examined the effects of DSS in the small intestine. We investigated the effects of DSS on small intestinal injury in rats, and the concomitant effects of four candidate probiotics.

**Methods:** Rats were gavaged 1 ml probiotic [*L. rhamnosus* GG (LGG), *S. thermophilus* TH-4 (TH-4), *B. lactis* Bb12 (Bb12) or *L. fermentum* BR11 (BR11)] or vehicle twice daily for 14 days (n = 8). Rats consumed 2% DSS in drinking water between days 7 and 14. Crypt cell proliferation (labelling index-LI) was assessed in normal controls, Vehicle + DSS and BR11 + DSS-treated rats by PCNA immunohistochemistry.

**Results:** Ileal crypt depth (CD) increased in Vehicle + DSS (19%), LGG + DSS (15%) and TH-4 + DSS (26%) treated rats, however, administration of BB12 or BR11 did not affect CD compared to normal controls. Ileal villus height (VH) in normal controls was not significantly different to DSS-treated rats (p < 0.1). VH increased in LGG + DSS (17%) and TH-4 + DSS (19%) treated rats, whereas BB12 and BR11 administration did not affect VH compared to normal controls. DSS treatment increased ileal LI by 143%, compared to normal controls. This effect was attenuated by BR11 (LI not significantly different to normal controls).

**Discussion/Conclusion:** The DSS-colitis model produced low-grade hyperplasia in the distal small intestine which was not prevented by LGG or TH-4, although BB12 and in particular, BR11 partially attenuated these effects. Further studies of DSS effects and probiotic interventions in the small intestine are indicated.
The role of zinc supplementation on the alleviation of dextran sulfate sodium-induced colitis in the mouse

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Introduction: Ulcerative colitis (UC) is associated with increased production of reactive oxygen species (ROS) and may be a major contributor to colonic inflammation. An abundance of evidence has demonstrated that zinc (Zn) has the ability to retard oxidative processes and sequester ROS indirectly. The aim of the present study was to determine the role of Zn supplementation on the alleviation of dextran sulfate sodium (DSS)-induced colitis in the mouse.

Methods: UC was induced in male C57BL/6 mice by supplementing 2% DSS (w/v) in the drinking water for 6 days. Zn sulfate (ZnSO₄; 20 mg/ml) and Zn oxide (ZnO; 30 mg/ml) were administered by oro-gastric gavage (0.1 ml) daily, concurrently with DSS treatment. Disease activity index (DAI) was scored daily, comprising of stool consistency, rectal bleeding, general health and body weight. On day six, mice were sacrificed, the colon removed, fixed and embedded in paraffin wax for histological assessment. Myeloperoxidase (MPO) activity was also determined.

Results: MPO levels were significantly (p < 0.05) elevated in DSS-controls (148 ± 39 U/g; mean ± SEM) compared to ZnSO₄-treated (73 ± 20 U/g) and ZnO-treated mice (62 ± 13 U/g). Zn supplementation significantly (p < 0.05) reduced histological damage (ZnSO₄; 1.5 ± 0.1 U, ZnO; 1.1 ± 0.1 U) compared to DSS-controls (1.8 ± 0.1 U). ZnO significantly (p < 0.05) decreased DSS-induced DAI (1.4 ± 0.5 U) compared to DSS-controls (4.1 ± 0.5 U) and those receiving ZnSO₄ (4.0 ± 0.5 U).

Discussion/Conclusion: Daily oral Zn supplementation markedly reduced DSS-induced colonic inflammation. ZnO was more effective at alleviating the colitis as indicated by decreased DAI and improved histological assessment. Further studies of Zn supplements in inflammatory bowel diseases are indicated.
High prevalence of amebiasis in ulcerative colitis patients compared to Crohn's disease; ten year follow-up results from a university hospital, Turkey

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Introduction: Entamoeba histolytica is a common infestation in developing countries. Amebic colitis may be one of the leading causes of IBD reactivation in Turkey. Role and prevalence of amebic colitis in Inflammatory Bowel Disease (IBD) is yet to be explained.

Methods: Retrospectively beginning from 1996 all patients diagnosed as IBD in our clinics were screened for the diagnosis of amebic colitis. Besides clinical presentation, microbiological confirmation were performed with fecal direct wet mouth examination and also by Antigen tests: Ridascreen, (R-biopharm Germany) between 1998 to 2005 and by E. histolytica II (Techlab, Netherlands) after july 2005

Results: A total of 345 patients; 200 ulcerative colitis (UC), 142 Crohn's disease (CD) and 3 indetermined colitis patients were analysed. 57 out of 200 UC (28.5%) patients had at least one attack of amebic colitis whereas that was 2 out of 142 for CD (1.4%) patients (p < 0.001).

Discussion/Conclusion: Amebic colitis seems to be more prevalent in UC patients than that of CD patients. This finding suggest that amebiasis may play role in the disease process in patients with UC.
Modulation of the intestinal microflora ameliorates experimental graft-versus-host-disease (GvHD)

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³University of Munich, Department of Hematology/Oncology, Munich, Germany
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Introduction: Inflammatory Bowel Disease (IBD) and GVHD following bone marrow transplantation (BMT) share similarities. IBD is the result of a genetically determined, unbalanced immune response to luminal bacterial antigens, while in GVHD bacterial lipopolysaccharides (LPS) from luminal bacteria, triggers the secretion of pro-inflammatory cytokines. A disruption of the intestinal epithelial barrier leads to increased bacterial translocation and increased levels of systemic LPS. The aim of our experiments was to evaluate the effect of a modulation of the intestinal microflora on the development of GvHD in an animal model.

Methods: We used a well-described murine transplantation model in which inflammation is induced across a haploidentical major histocompatibility complex mismatch. The effect of Lactobacillus GG (L. GG) was compared with broad-spectrum antibiotics or drinking water. The assessment included clinical features of GvHD, histological grading of intestinal inflammation, measurement of splenic cytokine release and bacterial translocation.

Results: Treatment of recipient mice with L. GG showed significantly decreased mortality (p < 0.01), clinical GvHD (p < 0.02), intestinal inflammation (p < 0.04) and splenic IFN-γ release (p = 0.02) compared to untreated animals. Ciprofloxacin treatment led to delayed mortality, significantly decreased histological inflammation (p < 0.04) and IFN-γ release (p = 0.02) but had no effect on clinical GvHD. Both treatment options resulted in a non-significant reduction of bacterial translocation into MLN but interestingly, no difference in LPS levels was seen.

Discussion/Conclusion: Alteration of the intestinal microflora by probiotic or antibiotic treatment greatly affects the outcome of experimental GvHD following (BMT). Further studies are needed to elucidate the underlying mechanisms.
**Effects of *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* BB12 on indomethacin-induced intestinal ulceration**

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**Introduction**: Crohn’s disease commonly presents with focal ulcerations in the distal small intestine. Probiotics have been shown to reduce inflammation in a range of gastrointestinal disorders. We examined the potential for *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* BB12 to prevent indomethacin-induced small intestinal ulceration.

**Methods**: Sprague Dawley rats were allocated into three groups: Vehicle + Indomethacin (Indo), LGG + Indo and BB12 + Indo (n = 10). Groups received probiotic or skim milk vehicle by oral gavage twice daily for 14 days (LGG: 1 x 10^9 cfu/ml, BB12: 1 x 10^8 cfu/ml). Between days 7 and 14, rats received 6 mg/kg indomethacin. At sacrifice, the small intestine was scored for ulceration and tissue collected for examination by quantitative histology and biochemical means (myeloperoxidase [MPO] activity).

**Results**: Small intestinal length decreased by 13% and weight increased by 54% in LGG + Indo-treated rats compared to Vehicle + Indo-treated controls. BB12 + Indo-treatment had no effect on small intestinal weight and length. LGG-treated rats exhibited a 230% increase in MPO activity compared to Vehicle + Indo-treated controls, whilst BB12 + Indo treatment had no effect. Intestinal ulceration was increased 10-fold in LGG + Indo-treated rats compared to Vehicle + Indo-treated controls. No differences were observed in MPO activity between BB12 + Indo-treated and Vehicle + Indo-treated controls. Crypt cell apoptosis decreased by 82% in BB12 + Indo-treated rats compared to Vehicle + Indo-treated controls, whereas LGG-treated rats displayed a 55% decrease.

**Discussion/Conclusion**: BB12 did not prevent indomethacin-induced intestinal inflammation, whilst LGG actually increased some indicators of intestinal injury. However, both probiotics reduced crypt cell apoptosis. The current study would not support LGG and BB12 as candidate probiotics for the prevention of focal small intestinal injury.
Inhibition of dipeptidyl peptidase activity in DPIV knock-out mice and wild type mice decreases disease activity in experimental colitis

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Introduction: Glucagon-like peptide-2 (GLP-2) is a potent intestinotrophic growth factor; however, it is rapidly degraded by dipeptidyl peptidase IV (DPIV). Previous work in our lab suggests that inhibition of DP-activity reduces disease activity in an experimental colitis model. We investigated the effect of pharmacological DP inhibition in wild-type and DPIV knock-out mice (DPIV-/-) in the jejunum of mice.

Methods: DPIV-/- and DPIV+/+ mice were treated twice daily with 10 mg/kg of the DPIV inhibitor, Isoleucyl-thiazolidine (Ile-thia) or 0.9% saline by oral gavage. Mice were sacrificed on days 0 and 14. Weight and length of intestinal organs were recorded. Jejunal tissue was removed for histological determination of crypt depth and villus height. Proliferative cell labelling index (LI) was determined by proliferating cell nuclear antigen (PCNA).

Results: No differences were observed between all groups for small intestinal length and weight. Crypt depth and villus height remained unchanged between DPIV-/- and DPIV+/+ mice treated with saline or inhibitor at days 0 and 14. At day 14, LI was significantly lower (p < 0.05) in DPIV-/- mice treated with inhibitor compared to DPIV+/+ mice administered inhibitor. However no further statistical significance was seen for LI between DPIV-/- and DPIV+/+ mice at day 14 treated with saline.

Discussion/Conclusion: We conclude that loss of DP activity does not significantly increase jejunal growth. We hypothesise that endogenous GLP-2 levels may be insufficient to promote significant intestinotrophic effects in a healthy intestine. Future studies could determine the effects of DP inhibition concomitantly with exogenous GLP-2 in a setting of small intestinal damage.
Blockade of IFN-γ-inducible protein-10 ameliorates chronic experimental colitis by blocking cellular trafficking and protecting intestinal epithelial cells

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Introduction: The role of chemokines, especially CXCL10/interferon-γ-inducible protein 10 (IP-10), a chemokine to attract CXCR3+ Th1 type CD4+ T cells, was largely unknown in the pathophysiology of inflammatory bowel disease that comprises ulcerative colitis and Crohn disease. We have earlier revealed that IP-10 neutralization protected mice from acute colitis by protecting crypt epithelial cells of the colon.

Methods: To investigate the therapeutic effect of neutralization of IP-10 on chronic colitis, we injected an anti-IP-10 antibody to mice with chronic colitis. B6 nude mice were injected intravenously with lymph node cells from B6 mice infected with LP-BM5 leukemia virus; the virus known as the murine AIDS (MAIDS) virus. This procedure induced chronic colitis mimicking ulcerative colitis in nude mice, which we termed MAIDS colitis. The nude mice were injected every week either with an antibody against IP-10, or with a control antibody.

Results: Anti-IP-10 treatment reduced the weight of colon of mice when compared to those mice which were administered with control antibody. The number of colon infiltrating cells was reduced by anti-IP-10 treatment. The treatment made the length of the lamina propria of the colon greater than control antibody. The number of Ki67+ proliferating epithelial cells was increased by the anti-IP-10 treatment. TUNEL+ apoptotic cells were observed in the epithelial cells of the luminal tops of crypts in control MAIDS colitis whereas TUNEL+ apoptotic epithelial cells were rarely observed with anti-IP-10 treatment.

Discussion/Conclusion: In conclusion, blockade of IP-10 ameliorated MAIDS colitis through blocking cellular trafficking and protecting intestinal epithelial cells, suggesting that IP-10 plays a key role in the development of inflammatory bowel disease as well as chronic experimental colitis.
Azathioprine metabolite levels in paediatric inflammatory bowel disease

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Australia

Introduction: Measurement of azathioprine (AZA) and 6-mercaptopurine (6-MP) metabolite levels may be useful as a clinical tool to optimise AZA/6-MP treatment of paediatric inflammatory bowel disease (IBD). Some authors have shown that 6-thioguanine (6-TGN) levels > 235 pmol/8 x 10^8 red blood cells (RBC) correlated with therapeutic efficacy. The correlations between 6-TGN and therapeutic efficacy, and metabolite levels and drug toxicity were evaluated. The use of metabolite levels in the dose management of AZA/6-MP in a clinical practice setting was also evaluated.

Methods: Forty-seven paediatric IBD patients treated with AZA/6-MP who had metabolite level measurements were retrospectively reviewed. Clinical status, laboratory parameters, and AZA/6-MP dosing-related data were compared with metabolite levels.

Results: There was no significant correlation between 6-TGN and therapeutic response, despite higher 6-TGN levels among patients with therapeutic response than among those with non-therapeutic response (174 v 154 pmol/8 x 10^8 RBC; p = 0.07). There was no significant correlation between 6-TGN levels and white cell count. Six patients (12.7%) experienced side effects caused by AZA/6-MP therapy. Five patients developed leucopenia. No patients with elevated 6-mercaptopurine (6-MMP) developed hepatitis. One patient developed acute pancreatitis. Metabolite level measurements were the main factor in guiding dosing of AZA/6-MP and were helpful in identifying non-compliance.

Discussion/Conclusion: Monitoring of AZA/6-MP metabolite levels allows careful dose adjustment of AZA/6-MP and minimises the risk of drug toxicity when used as adjunct to clinical judgement, and blood count and liver biochemistry measurements. Metabolite level measurements also help identify non-compliance.
Indomethacin and retinoic acid modification of inflammation-induced intestinal fibrosis

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Introduction: Fibrosis complicates chronic inflammation. Indomethacin inhibits COX-2 activity and can induce fibrosis. Retinoic acid (RA) reduces fibrosis and induces Secreted Protein Acidic and Rich in Cysteine (SPARC). SPARC increases tissue digestion through COX-2 and may link the indomethacin and RA effects. This study investigated indomethacin and RA regulation of intestinal fibrosis and SPARC expression in trinitrobenzenesulfonic acid (TNBS)-treated mice.

Methods: CD-1 mice were randomised to 6 groups: Control groups; a) Water, b) Indomethacin-alone (0.2 mg/kg/day orally) and c) RA-alone (100 µg/kg/day orally). Treatment groups; d) TNBS-alone, e) Indomethacin/TNBS and f) RA/TNBS. Mice were given TNBS enemas weekly for 2 or 8 weeks. Colonic tissue was stained with H + E, trichrome and sirius red to assess inflammation and fibrosis. Immunohistochemical staining assessed α-SMA, SPARC, PCNA (cell proliferation) and TUNEL (apoptosis). SPARC mRNA expression was determined by real-time PCR.

Results: No inflammation or fibrosis was seen in the controls. At 2 weeks, indomethacin enhanced and RA reduced fibrosis. SPARC mRNA and protein expression was inversely related to fibrosis except in indomethacin/TNBS mice where SPARC levels were elevated. α-SMA and submucosal PCNA staining were increased in fibrosed sections. TUNEL staining revealed no change in apoptosis. At 8 weeks, fibrosis was similar between the treatment groups. SPARC expression was elevated in all treatment groups, but was still inversely related to fibrosis levels in the TNBS-alone mice.

Discussion/Conclusion: RA and indomethacin enhance SPARC expression. Indomethacin induced, whilst RA reduced fibrosis. Indomethacin, however, blocks any COX-2-mediated SPARC effect. SPARC may, therefore, be potentially anti-fibrogenic.
Inhibition of dipeptidyl peptidase activity does not alter jejunal growth in mice

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Introduction: Glucagon-like peptide-2 (GLP-2) is a potent intestinotrophic growth factor; however, it is rapidly degraded by dipeptidyl peptidase IV (DPIV). Previous work in our lab suggests that inhibition of DP-activity reduces disease activity in an experimental colitis model. We investigated the effect of pharmacological DP inhibition in wild-type and DPIV knock-out mice (DPIV−/−) in the jejunum of mice.

Methods: DPIV−/− and DPIV+/+ mice were treated twice daily with 10 mg/kg of the DPIV inhibitor, Isoleucyl-thiazolidine (Ile-thia) or 0.9% saline by oral gavage. Mice were sacrificed on days 0 and 14. Weight and length of intestinal organs were recorded. Jejunal tissue was removed for histological determination of crypt depth and villus height. Proliferative cell labelling index (LI) was determined by proliferating cell nuclear antigen (PCNA).

Results: No differences were observed between all groups for small intestinal length and weight. Crypt depth and villus height remained unchanged between DPIV−/− and DPIV+/+ mice treated with saline or inhibitor at days 0 and 14. At day 14, LI was significantly lower (p < 0.05) in DPIV−/− mice treated with inhibitor compared to DPIV+/+ mice administered inhibitor. However, no further statistical significance was seen for LI between DPIV−/− and DPIV+/+ mice at day 14 treated with saline.

Discussion/Conclusion: We conclude that loss of DP activity does not significantly increase jejunal growth. We hypothesise that endogenous GLP-2 levels may be insufficient to promote significant intestinotrophic effects in a healthy intestine. Future studies could determine the effects of DP inhibition concomitantly with exogenous GLP-2 in a setting of small intestinal damage.
Lyprinol: A potential preventative treatment for experimentally-induced colitis

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Introduction: Lyprinol, the stabilized lipid extract of the New Zealand Green Lipped Mussel, is currently used for the treatment of arthritis. Its anti-inflammatory properties are thought to be mediated by long chain n-3 polyunsaturated fatty acids (LC n3 PUFA). This study compared the potential for Lyprinol, fish oil (conventional source of LC n3 PUFA) and olive oil (placebo) to reduce the severity of experimental colitis.

Methods: C57BL/6 mice received 150 l of olive oil, fish oil or Lyprinol daily by oral gavage for 13 days. From day 7, colitis was induced by administration of 2% dextran sulphate sodium (DSS) in drinking water. Body weight and disease activity index (DAI) were monitored daily. Gastric half-emptying (t½) times were determined by ¹³C-octanoic acid breath testing on days 0 and 13. At sacrifice, weights and lengths of visceral organs were recorded, and the colon removed for histological assessment of crypt depth, crypt area, and histological damage severity. Colonic inflammation was determined by myeloperoxidase (MPO) assay.

Results: Prior to kill, body weight gain was greater following Lyprinol and olive oil compared to fish oil treatment. DAI was greater following fish oil treatment compared to Lyprinol. Caecum weights were lower following Lyprinol (26%) and olive oil (18%) treatments compared to fish oil. Crypt area in Lyprinol-treated mice was 50% greater than fish oil-treated animals. MPO activity, histological severity scores and gastric half-emptying times remained unchanged between treatments.

Discussion/Conclusion: These findings provide preliminary evidence that Lyprinol can counteract DSS-induced colitis. However, the potential role of LC n3 PUFA requires further investigation.
Do antidepressants have an impact on the course of inflammatory bowel disorders?

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Introduction: The psychology of patients with inflammatory bowel disorders (IBD) has been of great interest to many investigators. A number of studies have indicated that there is a link between the patient's psyche and the course of the disease. However, most studies of psychotherapy in IBD patients have found it ineffective in both treating psychological disorders and relieving somatic symptoms of the disease. Although pharmacotherapy with antidepressants has not been widely explored, some investigators have proposed that treating psychological co-morbidities with antidepressants may help to control disease activity.

Methods: To investigate what evidence already exists to confirm or dispute this hypothesis we performed a systematic review, searching Cochrane, PubMed, CINAHL, PsycInfo, and Embase databases. All relevant papers in English, French, German, Polish and Spanish, issued after 1990 were examined for interactions amongst disease activity, psychological co-morbidities and treatment of psychological co-morbidities.

Results: 11 relevant publications have been identified. This has included 1 pilot open-label study with 8 participants, 3 reviews (theoretical considerations), 5 letters, and 2 articles describing case reports. Analysed antidepressants have included bupropion, phenelzine, paroxetine, and mirtazapine. In 10 articles, bupropion, phenelzine and paroxetine have been found effective for treating both psychological and somatic symptoms in patients suffering from IBD. Mirtazapine has been not recommended for IBD patients. Paroxetine has been found to be a trigger for IBD in 1 article (case report).

Discussion/Conclusion: Due to the lack of reliable data, the efficacy of antidepressants should be verified in further studies. Randomized controlled trials in this area are strongly recommended.
Restorative proctocolectomy - A permissible procedure for Crohn's colitis?

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Restorative proctocolectomy is the procedure of choice for ulcerative colitis. However, it has been contraindicated for Crohn's colitis so far. Yet, it is difficult to distinguish ulcerative from Crohn's colitis in 5-15% of patient before operation. Between 1985-2005, 254 patients with alleged IBD ulcerative colitis were admitted to the Department of General, Gastroenterological and Endocrinological Surgery in Poznań. Additional evaluation revealed Crohn's Colitis in 18 patients (7.1%). They underwent partial resection of the large bowel or total proctocolectomy. In turn, restorative proctocolectomy was performed on the remained 236 individuals. However, ultimate histopathological assessment of the operation specimens showed Crohn's colitis in another 9 cases (3.8%)

Postoperative course was uneventful among all the Crohn's colitis patients. They still remain under continuous control. Three patients developed anal fistula whereas neither required additional operations. In one case resection of J-pouch with ileostomy was necessary. Quality of life of the patients operated for ulcerative colitis was similar to the patients with Crohn's colitis.

In conclusion, it is permissible to perform restorative proctocolectomy for Crohn's colitis despite the risk of relapse into Crohn's disease of the ileal reservoir. Satisfactory quality of life after that procedure exceeds the risk of any complications.
Intraoperative colonofiberscopy as a method of volume resection choice of large intestine in nonspecific ulcerative colitis

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Introduction: At present time approaches to a surgical treatment using roentgen and endoscope findings, used before the operation, are not sufficient for a surgeon, particularly, for an adequate determination of the level of affected large intestine. It is necessary to notice that patients with complications such as toxic dilatation and stricture of large intestine shouldn't be performed colonofiberscopy in order to avoid perforation of large intestine and massive bleeding before the operative intervention. We think that the use of intraoperative colonofiberscopy gives an opportunity to choose a rational method of the extent of surgical intervention.

Methods: 28 patients with nonspecific ulcerative colitis underwent intraoperative colonofiberscopy under the control of abdominal surgeons. Endoscopist and surgeons determined by transillumination of the wall of large intestine the level of affection and evaluated a degree of inflammatory process in this large intestine. Having determined in such a way, pathologically changed part of large intestine, operation was performed in the appropriate extent. The removed part of large intestine was studied morphologically. Obtained results were compared with findings of X-ray examinations conducted before the operations.

Results: Evaluations of received data showed that the level of affection according to irrigography didn't coincide with the results received by intraoperative colonofiberscopy. Earlier 16 patients were planned to undergo total colectomy but after intraoperative colonofiberscopy, the extent of operation was finished by preservation of a part or a segment of the organ. 9 patients underwent one-staged operation. 12 patients were planned to have resection of a distal part of large intestine, but after intraoperative colonofiberscopy total affection was determined and total coloproctectomy was performed. The results of morphological study proved the correctness of using the extent of surgical intervention in patients with nonspecific ulcerative colitis.

Conclusion: Thus, the suggested method of intraoperative evaluation by colonofiberscopy for the affected level in large intestine, which is used in patients with nonspecific ulcerative colitis, allows to determine exactly the extent of radical operation and to reduce the number of post operative complications.
Improving quality of care in patients with inflammatory bowel disease (IBD): Are guidelines sufficient?

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Introduction: Generally agreed guidelines exist for the management of IBD. Doctors,
however, are not always adherent to guidelines and additional mechanisms to improve
compliance warrant investigation. We therefore compared two indicators of quality of
care in IBD - screening for colorectal cancer (managed by a nurse co-ordinator) and
metabolic bone disease (at doctor's discretion).

Methods: The Southern Adelaide IBD database was reviewed (N = 493; 240 Crohn's
disease, 188 ulcerative colitis and 55 indeterminate colitis).
Colorectal cancer screening practice was assessed before and after the introduction of
a agreed protocol managed by a nurse co-ordinator. The number of biopsies taken and
whether a follow up colonoscopy was planned were measured. Screening for metabolic
bone disease (at medical practitioner discretion) was assessed by comparing the number
of patients who had a substantive course of prednisolone (> 3 months) with the number
who had at least one bone density performed within the previous 3 years.

Results: The mean number of biopsies at screening colonoscopy increased from 15.4
(range 0-33) in 26 procedures to 25.9 (range 8-37) in 21 procedures following the
introduction of the nurse co-ordinator role. The number of biopsies increased from 27% to 57% (p = 0.07), with the number having a planned repeat colonoscopy for screening increasing from 58% to 100% (p < 0.005). Screening
for metabolic bone disease, was poor (57 bone densities in 201-28%).

Discussion/Conclusion: Guidelines alone do not ensure best care is delivered;
whereas the development of agreed protocols, case managed by a nurse co-ordinator
does improve the quality of care of patients with IBD compared with standard medical
management.
Efficacy of 6-mercaptopurine (6MP) treatment after azathioprine hypersensitivity reaction in IBD

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Introduction: Both azathioprine (AZA) and its metabolite 6-mercaptopurine (6MP) have demonstrated their efficacy in the treatment of inflammatory bowel disease (IBD).

Methods: 29 patients with a known (AZA) hypersensitivity reaction, and with endoscopically and histologically confirmed Crohn’s disease (CD) and ulcerative colitis (UC), were studied prospectively. The 6MP doses were gradually increased up to 1.0-1.5 mg/kg/day. The Crohn’s disease Activity Index (CDAI), Clinical Activity Index of ulcerative colitis (CAI) and laboratory variables of acute inflammatory process were compared prior to treatment, and in the first, sixth and twelfth month of treatment. Changes in medical therapy (oral ASA, prednisolone, methylprednisolone, and 6MP) were also recorded.

Results: Nine patients displayed a hypersensitivity reaction (drug fever in 4, nausea and diarrhoea in 5 cases) in the first 2 weeks of 6MP therapy. Eight patients were excluded within the first 6 months because of interim infliximab-based regimens. At the end of the sixth month and at the end of the first year the data on 12 and 9 patients were assessed.

Discussion/Conclusion: About one-third of the previously AZA-intolerant patients exhibited adverse effects on taking 6MP. In 20 patients 6MP was tolerated, but it was ineffective in 8 cases, and valuable only in 12 patients.
Efficacy and safety of endoscopic balloon dilatation of symptomatic Crohn's disease strictures

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Introduction: Patients with stricturing Crohn's disease (CD) commonly develop obstructive symptoms secondary to gastrointestinal stenosis. Endoscopic through-the-scope (TTS) balloon dilatation is one of the reasonable alternatives to surgery.

Goals: To evaluate the efficacy and safety of endoscopic balloon dilatation of symptomatic short segment gastrointestinal CD strictures.

Methods: We carried out a retrospective review of TTS balloon dilatations performed in CD patients during the period 2002-2005. A stricture was declared when the scope could not be passed through the luminal stenosis. Technical success was defined as the ability of the scope to traverse the stricture postdilatation. Long-term success was claimed if a patient remained asymptomatic and did not require surgery or further endoscopic dilatation for at least one year.

Results: Within the period of the study, we performed 28 stricture dilatations on 23 patients. The mean follow-up period was 18.1 months. Stricture locations were as follows: surgical anastomosis 12, ileocoecal valve 5, colon 5, jejunum 1, ileum 1, and pylorus 1. Technical success was achieved in 25 of the 28 stricture dilatations (89%). Long-term success rate was 21 of 25 dilated cases, 84%. No perforation occurred during the procedures.

Discussion/Conclusion: TTS balloon dilatation is an effective and safe alternative to surgical intervention in selected cases. The best technical and long-term success rate can be achieved with strictures of surgical anastomosis or the Bauhin valve.
The safety of infliximab use in clinical practice: The experience of an Eastern European clinic

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Introduction: Infliximab (anti TNF monoclonal antibody) is the first and most largely used biological therapy in inflammatory bowel diseases. Due to its biologic nature and immunomodulating activity it has potentially severe side effects. The aim of our study was to evaluate the frequency and severity of the adverse events associated with infliximab treatment in every day clinical practice.

Methods: All patients treated with infliximab in our unit between August 2000 and August 2005 were prospectively followed. The number and frequency of infliximab infusions, concomitant medication, and all the adverse events were recorded.

Results: A total of 40 patients (18M/22F, mean age 37.9 ± 2.72 years, 38 with severe Crohn's disease and 2 with severe ulcerative colitis) received 92 infliximab infusions. All patients were treated episodically (on demand) and 19 of them received a three dose induction therapy. The overall incidence of infusion reactions to infliximab was 5.43% (5 of 92 infusions), affecting 12.5% (5 of 40) of patients. Mild reactions occurred in 3 patients (7.5%), moderate in 1 patient (2.5%), and severe in 1 (2.5%). One serious adverse event was noted: a fatal sepsis with S. aureus. Although in our country tuberculosis is endemic we did not have any case of mycobacterial infection, but all our patients were screened for occult disease prior to infliximab administration.

Discussion/Conclusion: Infliximab is a safe agent providing that patients are carefully screened and also monitored during and after infliximab infusions so that potentially severe adverse events can be avoided or promptly treated.
Surgical predisposition in children with Crohn's disease

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Introduction: Crohn's disease causes chronic inflammation of the gastrointestinal tract leading to extensive medical treatments and surgery, with two thirds of patients having surgery over their lifetime. In this study, we reviewed the pediatric population at BC Children's hospital diagnosed with Crohn's disease and examined their demographics and treatments in particular assessing the antecedent factors of those who ultimately underwent surgery.

Methods: There were two hundred and eighty patients diagnosed with Crohn's disease between the period of January 1994 to December 2003. Demographic data was documented including age, ethnicity, length of symptoms prior to diagnosis, treatment to date and surgical parameters. Comparison was made between the surgical and non-surgical patients including involvement of disease, medical treatment, complications and recurrence of disease leading to repeat surgery.

Results: Fifty-five (19.6%) of these children had surgical procedures. Overall we found no significant difference between the surgical group and non-surgical groups in relation to most features. There was a significant increase in surgery in those patients who were not on immunomodulators therapy prior to surgery (OR 1.95 [CI 1.02-3.73). We also noted that those Crohn's disease patients with extensive small intestinal involvement had less chance of having surgery (odds ratio 0.386 [CI 0.15-1.03]). No significant difference was found between the two groups with regard age of diagnosis (p = 0.41), the duration of symptoms (p = 0.22), gender (p = 0.50) or the ethnicity (p = 0.45) of the groups.

Discussion/Conclusion: There is an increased incidence of surgical intervention in those patients who are not initiated on immunomodulator therapy. In addition children with extensive as opposed to isolated small intestinal disease were less likely to have surgery in childhood.
Sargramostim improves the quality of life of patients with moderate to severe Crohn's disease: SF-36 findings

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Introduction: The quality of life (QOL) of Crohn's disease (CD) patients is significantly lower than in the general population. We investigated the effect of sargramostim on the QOL of CD patients using the short-form 36 (SF-36) questionnaire. Unlike current CD treatments that suppress the adaptive immune system, sargramostim is an innate-immunity activator.

Methods: The effect of sargramostim 6 μg/kg/day on QOL was evaluated in a phase II placebo-controlled trial in 124 patients with moderate-to-severe CD. The SF-36 was administered at baseline; at Days 15, 29, 43, and 57 of treatment; and 30 days after treatment (follow-up).

Results: Sargramostim treatment yielded significant QOL improvements in 6 of the 8 SF-36 domains and in 1 of the 2 summary scores. The physical summary score improved at Day 29 and thereafter by 12%-20% compared to 4%-9% with placebo (P = 0.0006-0.0388). General health improved by 35% at Day 29 and follow-up Day 30 versus 8%-12% with placebo (P = 0.0133-0.0366). Vitality improved by 71%-73% at Day 57 and follow-up Day 30 versus 17%-19% with placebo (P = 0.0121-0.0131). Social functioning improved by 27%-36% on Day 29, Day 43 and follow-up Day 30 versus 3%-17% with placebo (P = 0.0102-0.0471). Bodily pain improved by 39-46% on Day 57 and follow-up Day 30 versus 13-24% with placebo (P = 0.0272-0.0077). Role physical improved by 135% on Day 43 versus 22% with placebo (P = 0.0176).

Discussion/Conclusion: Significant QOL improvements were seen early and were maintained throughout treatment and follow-up. Unlike current CD treatments that suppress the adaptive immune system, sargramostim enhances the innate immune system.
Sargramostim improves the quality of life of patients with moderate to severe Crohn's disease as measured by the IBDQ questionnaire

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Introduction: Quality of life (QOL) assessments are important for evaluating therapeutic agents in Crohn's disease (CD). Sargramostim is being studied in multiple clinical trials as a potential new therapy for CD. Unlike current treatments that suppress the adaptive immune system, sargramostim is an innate-immunity activator that enhances the innate immune system.

Methods: A placebo-controlled phase II study (NOVEL 1) was conducted to assess the efficacy and safety of sargramostim 6 μg/kg/day in 124 patients with moderate to severe CD. The Inflammatory Bowel Disease Questionnaire (IBDQ) was completed at baseline; at Days 15, 29, 43, and 57 of treatment; and at 30 days after treatment. Differences between treatment groups were analyzed by the Van Elteren test controlling for previous use of immuno-suppressants.

Results: Patients treated with sargramostim experienced a 20%-24% improvement in total IBDQ score at Day 29 and thereafter, compared to a 7%-15% improvement in the placebo group (P = 0.0059-0.0397). The bowel and systemic subscores improved by 24%-34% at Day 29 and thereafter, compared to 3%-18% in the placebo group (P = 0.0001-0.0384). The social subscore improved by 17% at 30 days after treatment compared to 4% in the placebo group (P = 0.0288).

Discussion/Conclusion: Treatment with sargramostim improved and maintained QOL in CD patients as measured by the IBDQ. Clinically meaningful improvements in the IBDQ scores, including the social subscore, were seen as early as Day 29 (the second scheduled measurement). Unlike current CD treatments that suppress the adaptive immune system, sargramostim is an innate-immunity activator that enhances the innate immune system.
Treatment with up to six cycles of sargramostim for active Crohn's disease was generally safe and well tolerated: Findings from an ongoing open label trial (N.O.V.E.L. 5)

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Introduction: Sargramostim, an innate-immunity activator that enhances the innate immune system, has been shown to induce response and remission in patients with moderately-to-severely active Crohn's disease (CD). Data from an ongoing open-label experience with sargramostim in CD were evaluated to continue to assess the safety and efficacy of repeated sargramostim treatment cycles.

Methods: Patients who participated in previous sargramostim trials for treatment of CD were eligible. Treatment consisted of repeated 8-week sargramostim (6 µg/kg/day) cycles. Concurrent antibiotics, 5-ASA compounds, and steroids were permitted.

Results: From February 2003 through March 2005, 94 patients entered open-label treatment (median age = 41 yrs; median baseline CDAI score = 312). Sixty two, 32, 18, 8, 5, and 4 patients completed at least 1, 2, 3, 4, 5, and 6 cycles of sargramostim treatment, respectively. The majority of patients were compliant with daily dosing of drug throughout each cycle. The median decreases in CDAI scores relative to study entry were 79, 91, 83, 102, 101, and 191 points after cycles 1, 2, 3, 4, 5, and 6, respectively. The most commonly reported AEs included injection site reactions (ISRs), bone pain, nausea, headache, fatigue, and back pain. The incidence of ISRs and bone pain decreased with repeated treatment (from 71% and 26% during cycle 1 to 25% and 8% during cycle 4, respectively).

Discussion/Conclusion: Treatment with up to six cycles of sargramostim for active CD was generally safe and well tolerated. Patients were compliant with daily dosing throughout multiple cycles of treatment.
Careful patient selection may improve response rates to infliximab in inflammatory bowel disease

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Introduction: Infliximab in Crohn's Disease (CD) is accepted and appears effective in ulcerative colitis (UC). Careful patient selection, resulting in infliximab use only for patients truly refractory disease, may improve its efficacy in inflammatory bowel disease (IBD).

Methods: This study aimed to determine whether careful patient selection improves infliximab efficacy. CD or UC/IBDU patients (Montreal classification) were considered for treatment only after failure of disease control with conventional therapies and confirmation of ongoing disease. Patients with inflammatory disease received a single 5mg/kg infliximab dose. Patients with fistulising disease received infusions at weeks 0, 2 and 6. The Harvey Bradshaw index (HBI) for inflammatory CD and Colitis Activity index (CAI) for UC/IBDU were used to determine response and remission. A fistula remission was sustained cessation of drainage. Findings were correlated to inflammatory marker levels. Adverse effects were analysed.

Results: 70 IBD patients were treated. In CD, 85.2% (46/54) had active luminal and 40.7% (22/54) fistulising disease. Luminal CD responded in 91.3% (42/46) and remitted in 80.4% (37/46). Fistulising disease responded in 77.2% (17/22) and remitted in 50% (11/22). Patients with isolated colonic disease were more likely to remit 13/14 (92.9%) than ileal involvement 23/32 (71.9%). In UC/IBDU, 75% (12/16) responded and 43.8% (7/16) remitted. A total of 11.4% (8/70) of all patients experienced an adverse event and 5.7% (4/70) a serious adverse event.

Discussion/Conclusion: Clinical response and remission rates in CD appear better than the standard published results with careful patient selection, whilst clinical efficacy is suggested in UC/IBDU.
Fructose malabsorption in Crohn's disease: A common contributor to symptoms that benefit from dietary modification

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Introduction: The recognition that some of the symptoms in patients with Crohn's disease may be due to IBS has helped little in the positive management of those symptoms since there is a lack of efficacious therapy. Dietary restriction of short-chain carbohydrates that are poorly absorbed and rapidly fermented (FODMAPs), such as fructose, fructans and lactose, gives considerable relief of symptoms in 75% of patients with IBS. We have hypothesized that dietary FODMAPs also contribute to the symptoms of Crohn's disease via the effects of the osmotic load they present and their rapid fermentation in the distal small bowel and proximal colon. This study aimed to determine the prevalence of fructose malabsorption (FM) in patients with Crohn's disease, to examine the phenotype associated with FM and to examine the effects of the FODMAP diet on symptoms.

Methods: Patients with Crohn's disease underwent breath hydrogen testing with lactulose (15 g), fructose (35 g) and lactose (50 g). Patients were then invited to take dietary advice regarding restriction of FODMAPs, guided by the results of the breath hydrogen tests. Those who took up the offer and have had at least three months to follow the diet were then retrospectively evaluated with regard to their perception of the value of the diet.

Results: 59 patients, aged median 35 (17-80) years, 28 men, underwent breath testing. 9 were non-hydrogen-producers (NHPs), 36 (72% of evaluable patients) had FM, and 16 (32%) lactose malabsorption (LM), 13 of whom had concomitant FM. Neither the predominant symptom profile during active disease nor disease phenotype identified patients with FM. However, those who had continuing diarrhoea, despite apparent remission or mild disease, were more likely to have FM. 36 patients were educated in the FODMAP diet and followed for at least 3 months. The majority (86%) adhered to the diet at least for a few weeks. 18 of 21 patients (94%) with FM reported considerable benefit from the diet, while 3 of 3 NHPs and 4 of 11 without FM had benefit (p<0.001; Fisher's exact). Continued adherence to the diet was noted in those who had responded. Dietary change was associated with improvement in diarrhoea (75%), bloating (58%) and pain (25%).

Discussion/Conclusion: FM and LM are common in patients with Crohn's disease, particularly in those with continuing diarrhoea out of proportion to the degree of intestinal inflammation and/or disease. The presence of FM identified patients likely to benefit symptomatically from dietary restriction of FODMAPs. Prospective randomised trials of the diet in unselected patients with Crohn's disease are required to validate or otherwise the marked benefits perceived in this observational study.
NOD2/CARD15 but not toll-like receptor 4 mutations are associated with Crohn's disease in Hungarian patients: Phenotype-genotype correlations

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Introduction: Mutations of NOD2/CARD15 gene increase risk for Crohn disease (CD) and are associated with fibrostenosing behaviour. One other genetic modifier may be the functional D299G polymorphism of toll like receptor 4 (TLR4). In view of the large geographical differences in frequency of these genetic markers and absence of data in Central-European patients, common NOD2/CARD15 mutations and D299G-TLR4 polymorphism were determined in Hungarian CD patients.

Patients and methods: 527 unrelated patients with CD (m/f: 265/262, age: 37.1 [SD 7.6] years) and 200 healthy subjects were included. DNA was screened for possible NOD2/CARD15 mutations by denaturing-HPLC (confirmed by direct sequencing). TLR4-D299G was tested by PCR-RFLP.

Results: NOD2/CARD15 mutations were found in 185 patients (35.1%) and in 33 controls (16.5%, p < 0.0001). SNP8/R702W (10.8% vs. 6%, p = 0.02), SNP13/3020insC (19.4% vs. 5%, p < 0.0001) and exon4 R703C (2.1% vs. 0%, p = 0.02) mutations were more frequent in CD, while the frequency of SNP12/G908R was not increased. The frequency of TLR4 D299G was not different (CD: 9.9% vs. controls: 12.0%). Variant NOD2/CARD15 allele was associated with an increased risk for CD (OR_{high} = 1.71, 95% CI = 1.12-2.6, p = 0.0001, OR_{two-risk-alleles} = 25.2, 95% CI = 4.37-∞, p<0.0001), younger disease onset (carrier: 26.4 vs. non-carrier: 29.8 years, p = 0.0006), ileal disease (81.9% vs. 69.5%, OR = 1.99, 95% CI = 1.29-3.08, p = 0.02, in presence of NOD2/CARD15 and TLR4: 86.7% vs. 64.8%), stricturing behavior (OR = 1.69, 95% CI = 1.13-2.55, p = 0.026) and increased need for resection (OR = 1.71, 95% CI: 1.13-2.62, p = 0.01), but not with duration, extraintestinal manifestations, familial disease or smoking.

Conclusion: These results confirm in large cohorts of Hungarian CD patients the association of variant NOD2/CARD15 (R702W, R703C and 3020insC) alleles with younger disease onset, ileal disease, structuring disease behavior. In contrast, presence of G908R or TLR4 D299G polymorphism was not different from controls.
**Does the presence of NOD2/CARD15 mutations expressed both in monocytes and Paneth cells influence on the necessity of surgery in patients with Crohn’s disease?**

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**Introduction**: Inflammatory Bowel Diseases (IBD) belong to chronic diseases of the GI tract with still unknown etiology. Genetic research established several susceptibility genes in chromosome 16. Genetic factors seem more dominant in CD but the simple genetic model does not explain the way of heredity of the inflammatory process - the genetic factors play a role on different levels.

**Methods**: In the first step 150 patients with CD were examined physically and a molecular analysis was performed for NOD2/CARD15. The second step was the histopathological and molecular analysis of expression of NOD2/CARD15 in resected specimens from patients after surgery because of Crohn’s disease.

**Results**: The most frequently recognized variant of the NOD2/CARD15 mutation in the studied population was 802 C>T which causes the conversion of proline into serine in position 268 of the protein product. The second most often observed variant was found during analysis of exon 11. A frameshift of mutation 3020insC, which causes the C insertion in the 3020 position of the protein product, was present in 14.9% patients with CD. All the patients with this frameshift mutation were also carriers of the 802C>T mutation.

CD patients with 802 C>T mutation variant were statistically more often operated (partial ileal resection) (79.0%). The specificity of the test for homozygous was 73.8% vs heterozygous 60.8%, with high negative predictive value 81.6%. We managed to collect the post-operative tissue materials from 23 patients. In 18 samples we found the expression of NOD2/CARD15 in Paneth cells.

**Discussion/Conclusion**:
1) CD patients who are not carriers of NOD2/CARD15 (802C>T and 3020insC) mutations are statistically less frequent operated
2) 78.0% operated patients after partial ileal resection presented expression of NOD2/CARD15 mutations in monocytes and Paneth cells.
Frequencies of known functional SNPs in exon 3 and 4 in the microsomal epoxide hydrolase gene of Danish IBD patients compared with controls.

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Introduction: IBD is a combination of a malfunctioning intestinal epithelial barrier and a dysfunctional mucosal immune response. Chemical or oxidative stress might contribute to the disruption of the epithelial barrier. This leads to the hypothesis that functional genetic polymorphisms in biotransformation enzymes are putative candidates for genetic susceptibility to IBD. Microsomal epoxide hydrolase (mEH) is involved in the detoxification of reactive epoxides. Two functional SNPs, a T/C transition in exon3 leading to reduced enzymatic activity, and an A/G transition in exon4 leading to increased enzymatic activity, were investigated in this study.

Methods: Blood samples from 795 controls, 535 patients with ulcerative colitis and 357 with Crohn’s disease were genotyped for the exon3 and exon4 SNP by TaqMan technology using MGB probes on an ABI A7000 instrument.

Results: No differences in the allelic frequencies of the two SNPs were found between the patient groups compared with the control group (p > 0.05). A statistical significant difference was found between the patients having Crohn’s disease compared with the ulcerative colitis patients, regarding the exon3 polymorphism which was more frequent in Crohn’s patients (p = 0.02, OR 1.3 [1.0-1.6]). Thus, the homozygotic variant in exon3 was slightly more frequent in the group of Crohn patients compared to that of ulcerative colitis (p = 0.04, OR 1.7 [1.0-2.8]).

Discussion/Conclusion: No differences were found between genotype frequencies of the two SNPs in mEH between Danish IBD patients and controls, leaving no evidence for a possible genetic predisposition to IBD. The genotype frequencies of the controls are comparable to that of previously published control groups.
Polymorphisms in the Toll-like receptor 4 and CARD15/NOD2 in Chilean patients with inflammatory bowel disease

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Crohn’s disease (CD) and ulcerative colitis (UC) are multifactorial diseases with a significant genetic background. Genes related to the innate immune response such Toll-like receptor 4 (TLR4) and CARD15/NOD2 are involved in IBD pathogenesis. There is no information about these polymorphisms in South America and Chilean populations. We investigated the variations in the CARD15/NOD2 (Arg702Trp, Gly908Arg and Leu1007fsinsC) and TLR4 (Asp299Gly) polymorphisms in Chilean patients with CD and UC.

Methods: DNA was obtained from 22 CD, 22 UC patients and 20 healthy individuals. Genotyping was performed by allele specific PCR and by PCR-RFLP analysis. Indigenous origin percentage was estimated using the ABO groups. We recorded patient's clinical and demographic features.

Results: In CD patients, 14 had inflammatory behaviour, 5 penetrating and 5 stricturing. One had upper gastrointestinal, 5 perianal, 7 ileum terminal and 16 colon compromise. In UC patients, 2 had proctitis, 2 proctosigmoiditis, 4 left-sided colitis and 14 pancolitis. The Amerindian admixture in CD, UC and control were 55%, 62% and 57%. NOD2/CARD15 genetic study showed Arg702Trp polymorphism in 2 CD (both heterocytoge), L1007fsinsC polymorphism in 2 CD patients (1 homocygote and 1 heterocygote). No patients revealed Gly908Arg allele. 299Gly TR4 allele was identified in one UC patient.

Conclusion: This is the first genetic study done with Chilean IBD patients. Until now, alleles associated with IBD shows a similar frequency to European populations. These results suggest a genetic association between CD and NOD2 gene, however other ethnic, environmental and genetic differences may be involved in IBD development. FONDECYT 1050451.
Misfolding mutations in the Muc2 intestinal mucin enhance susceptibility to colitis in mice - A case for protein misfolding and endoplasmic reticulum stress in the aetiology of ulcerative colitis

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Introduction: We have produced two strains of mice with mutations in the Muc2 mucin causing aberrant assembly and accumulation of Muc2 in the endoplasmic reticulum (ER), goblet cell stress, reduced goblet cell numbers and a reduction in secreted mucus, resulting in chronic diarrhoea. We now have examined the coating of luminal bacterial flora with immunoglobulin and the susceptibility of these mice to colitis.

Methods: Faecal bacteria were isolated and immunoglobulin coating determined by flow cytometry. Colitis was induced with 3% dextan sodium sulphate (DSS) for seven days.

Results: A greater proportion of the faecal bacterial flora of Muc2<sup>Win</sup> mice were coated with immunoglobulins (52% vs. 22%, P < 0.01). Following treatment with DSS Muc2<sup>Win</sup> mice developed more rapid induction of rectal bleeding, greater weight loss, shorter colons, lower haematocrits, enhanced leucocytosis, and markedly more severe histological colitis than wild type mice (P < 0.05).

Discussion/Conclusion: Similarities between the phenotype of Muc2<sup>Win</sup> mice and ulcerative colitis include diarrhoea, decreased goblet cell numbers, accumulation of immature Muc2 in the goblet cell cytoplasm, presence of intracellular membrane-bound accumulations, depletion of the secreted mucus layer, and increased coating of the normal flora with immunoglobulins. Furthermore, these mice developed severe inflammation in response to a chemical irritant. ER stress and protein misfolding can be exacerbated by viral infection, bacterial and plant toxins, and psychological stress, and can increase leukocyte infiltration. Enhanced ER stress/protein misfolding in intestinal epithelial cells in UC is consistent with known environmental and systemic contributions to this disease and warrants further investigation.
Mutations in the Muc2 intestinal mucin causing aberrant biosynthesis induce endoplasmic reticulum stress and diarrhoea

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Introduction: We have characterized the phenotype of two strains of mice with chronic diarrhoea, generated by ENU mutagenesis.

Methods: Mutations were identified by positional cloning and sequencing. Protein expression was determined by Western blotting. The N-terminal D3 domain of Muc2 was expressed in COS1 cells and oligomerization assessed using PAGE/Western blotting. Intestinal morphology was examined using light and electron microscopy.

Results: The Winnie the Pooh (Muc²Win) and Eeyore (Muc²Eey) mutations result in single amino acid substitutions in the N- and C-terminal oligomerization domains of the Muc2 intestinal mucin, respectively. Diarrhoea began prior to weaning in all mice, and 10-15% developed rectal prolapses. There were substantial decreases in mature glycosylated Muc2 protein in mutant mice. Wild type recombinant N-terminal D3 domains were secreted mainly as dimers, whereas, the Muc²Win D3 domain was secreted mainly as higher order oligomers suggesting the mutation causes inappropriate homo-oligomerization. Histologically both strains had fewer intestinal goblet cells with smaller thecae, reduced extracellular mucus covering, and increased large intestinal crypt depth (P < 0.05). Strong perinuclear immuno-reactive Muc2 was present in mutant goblet cells. Ultrastructurally, Muc²Win and Muc²Eey goblet cells contained large cytoplasmic accumulations surrounded by rough endoplasmic reticulum (ER) membranes characteristic of protein misfolding and ER stress.

Discussion/Conclusion: Single amino acid substitutions in the Muc2 mucin can lead to aberrant assembly of Muc2 homo-oligomers and accumulation of Muc2 in the ER. Accumulation of Muc2 precursor causes goblet cell stress, reduced goblet cell numbers and a marked reduction in the quantity of secreted mucus, resulting in chronic diarrhoea.
MDR1 as a susceptibility gene in inflammatory bowel disease: results of a large case-control and family-based analysis

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Introduction: The MDR1 gene located at 7q22 has been implicated as a susceptibility gene for both ulcerative colitis (UC) and Crohn's disease (CD). Results of 5 studies (5 case-control, 1 pedigree) are conflicting. At least two functional SNPs have been identified, C3435T and G2677T/A.

Aims: To establish whether MDR1 C3435T and G2677T/A contribute to IBD susceptibility using both case-control and family based approaches.

Methods: A population-based cohort of 1044 IBD patients were recruited for this study from the North Brisbane region. Population controls (405) were drawn from the same geographical region and matched for sex and ethnicity. Genotyping was performed by PCR-RFLP.

Results: Analysis by genotype revealed significant differences in C3435T for UC (p < 0.001) and CD (p = 0.04) compared to controls. An allele association analysis demonstrated significance for CD (p = 0.02) but not for UC. A transmission disequilibrium test (TDT) using 209 IBD trios for analysis of the C3425T SNP did not reach significance either for UC (p = 0.26) or for CD (p = 0.62). Phenotype-genotype analysis demonstrated significant differences in C3435T genotype between patients suffering acute severe colitis, strictly based on the Truelove-Witts criteria, and those with no history of this complication (p = 0.006).

Discussion/Conclusion: This large case-control study supports association between the C3435T MDR1 SNP and UC but this is not confirmed by our TDT analysis. Phenotype-genotype analysis supports a possible role for increased MDR1 expression in patients with severe disease. The issue of population stratification may have been underestimated for this gene, and a larger consortium-based investigation would be appropriate to address this.
Morphological changes of the blood vessels at the patients operated due to ulcerative colitis

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The aim of the study: The aim of our work was the evaluation of the changes of the blood vessels of large intestine mucosa, as one of the crucial factor in the development and the course of ulcerative colitis.

Material and method: The samples of large bowel mucosa were taken from the resected large bowel from 36 patients operated on ulcerative colitis. The histological and ultrastructural examination, using routine techniques, was done in all cases. The controlled group consisted of 12 patient operated on the large intestine cancer. The samples were taken from the proximal cutting line, free from tumorous changes.

Results: In the samples taken from the patients with ulcerative colitis, numerous disorders of the blood vessels have been acknowledged: incorrect routs of the vessels, erythroragia, thrombosis, in the lumen of the some venous vessels, and the increase of the surface of the blood vessels sections in the comparison with the controlled group. In the electron-microscope pictures among patients with ulcerative colitis, we discovered focal leakage of the base membrane and changes of the ultrastructure of the endothelial cells. The observed changes, not found in the control group, were especially intensive among patients with chronic (long-term) disease.

Conclusion: The observed changes constitute one of the elements of the generalised ulcerative process taking place in the large intestine area. The degree of these changes correlates with the clinical course of the illness. Patients with long period of duration of ulcerative colitis have had more intensive changes in blood vessels net. The question: to what extend are the observed changes the cause or to what extend are they the results of the ulcerative process remains unanswered.
Dose dependent transfer of CD4+CD25+ T cells attenuates hFUT1 murine colitis

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Introduction: Human fucosyltransferase 1 (hFUT1) transgenic mice have thymic maturation defects and Th1 colitis. Regulatory T cells (Treg) form in the thymus. hFUT1 mice may be deficient in Tregs and transfer of normal Tregs may improve colitis.

Methods: HFUT1 Balb/c and Balb/c thymocytes were assessed for number and phenotype of Tregs via FACS. hFUT1+ mice received 10⁵ (n = 9) or 10⁶ (n = 8) Balb/c CD4+CD25+ T cells, 10⁵ CD4+CD25- T cells (n = 8) or 10⁵ naïve CD4+CD45RBhi T cells (n = 4) at 4 weeks of age. Control hFUT1 mice (n = 8) were similarly observed and euthanised eight weeks post transfer.

Results: HFUT1 mice were deficient in mature CD4+ (1.92 vs 55.6 [× 10⁶]) and CD4+CD25+ thymocytes (3.76 vs 49.6 [× 10⁴]). CD62L and GITR expression were reduced in hFUT1 Tregs. Foxp3 expression was similar. HFUT1 mice receiving 10⁵ and 10⁶ CD4+CD25+ and 10⁵ CD4+CD25- T cells had greater weight gain with mean weights (± SEM) of 21.1 g ± 0.58, (p < 0.05), 20.4 g ± 0.80, (p = 0.05) and 20.0 g ± 0.58 (p < 0.05) versus HFUT1 controls 17.7 g (± 0.98). (CD4+CD45RBhi group 16.3 g ± 0.81). Colitis improved in the 10⁵ CD4+CD25+ group (1.17 ± 0.17, p < 0.01) and 10⁵ CD4+CD25− group (1.40 ± 0.50, p < 0.05) compared with the 10⁵ CD4+CD25+ group (2.67 ± 0.41), CD4+CD45RBhi group (3.75 ± 0.25) and HFUT1 group (3.00 ± 0.38).

Discussion/Conclusion: HFUT1 mice are deficient in Treg number and transfer of normal CD4+CD25+ T cells improves hFUT1 colitis dose dependently, along with CD4+CD25− T cells but not naïve CD4+CD45RBhi T cells. HFUT1 colitis can be successfully treated with normal Tregs.
Deficiency of CD1d restricted Valpha24+ NK T-cells in Crohn's disease and in ulcerative colitis

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Introduction: A contributing factor to the pathogenesis of inflammatory bowel disease may be a loss of immunoregulation to luminal bacteria. Invariant NK T-cells are immunoregulatory T-cells that are deficient in several autoimmune diseases. They are characterized by having the Valpha24 Vbeta11 T-cell receptor that recognizes alpha-galactosylceramide glycolipid presented by the CD1d HLA molecule. They are unique in responding with rapid production of interleukin-4 and other Th2 cytokines. They may down regulate excessive immune reactivity after viral or other tissue damage that exposes membrane glycolipids.

Methods: Blood was collected from 97 subjects with Crohn's disease, 66 subjects with ulcerative colitis and 152 normal subjects. Invariant NK T-cells were detected by Valpha 24, Vbeta 11 antibodies and alpha-galactosylceramide/CD1d tetramers. Invariant NK T-cells were stimulated with anti-CD3 antibody for 4 h and intracellular cytokine staining assessed. Valpha 24+ T-cells were quantified in ileocolonic biopsies by real time PCR and by immunofluorescence.

Results: Circulating invariant NK T-cells were 0.3% in Crohn's disease (P < 0.001) and 7% in ulcerative colitis (P < 0.001) of levels in control subjects. Interleukin-4 production was markedly impaired in both Crohn's disease and in ulcerative colitis. Intestinal Valpha 24 mRNA was 7% in Crohn’s disease (P < 0.05) and 9% in ulcerative colitis (P < 0.05). Valpha 24+ T-cells were 23% in Crohn's disease (P < 0.05) and 40% in ulcerative colitis.

Discussion/Conclusion: We conclude that invariant NK T-cells are deficient in inflammatory bowel disease. A deficiency of these cells may contribute to loss of immunoregulation in inflammatory bowel disease.
Effects of flavonoids: Quercetin and rutin on the chemiluminescence and apoptosis of neutrophils in patients with Crohn’s diseases and healthy individuals

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Introduction: If reactive oxigen species are postulated to be involved in tissue injury in patients with IBD it should be possible to atenuate this injury by the use of antioxidants.

Methods: In our study the in vitro effects of flavonoids: quercetin and rutin, anti-inflammatory and anti-oxidant phytochemicals, on oxidative metabolism and on caspase-3 activation of neutrophils in patients with ulcerative colitis (UC) (N = 15) and Crohn’s disease (CD) (N = 12) has been investigated. Disease activity was assessed using the Crohn’s disease activity index (CDAI) and the Ulcerative Colitis Symptoms Score (UCSS) for CD and UC, respectively. Twenty healthy subjects were enrolled as controls. Neutrophils were isolated and oxidant production response to 1 μg/ml phorbol myristate acetate, was characterised by using luminol dependent chemiluminescence (CL) and caspase-3-like protease activity measured by a cleavage of the fluorogenic substrate Ac-DEVD-AMC.

Results: Neutrophils from UC and CD patients had a significantly higher chemiluminescence response (p < 0.001) and showed decreased spontaneous apoptosis compared to controls. Flavonoids effected a significant concentration-dependent inhibition of CL in all of concentrations used. We also observed pro-apoptotic effects of these substances. Additional experiments to assess the direct toxic effects of quercetin and rutin were also carried out.

Discussion/Conclusion: The results of the study suggest that quercetin and rutin, the most predominant dietary flavonoids, exert beneficial effects in cells and therefore they may be useful in the treatment of IBD.
Vesicular amine transporter VMAT2 in the gut: From principal mechanism to therapeutic application

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Introduction: Besides the role of classical neurotransmitters, acetylcholine, catecholamines, serotonin and histamine play a key role in the immune/inflammatory processes in the gastrointestinal tract, regulating gut motility, vascular permeability and inflammatory responses. Specific transport proteins pack these neurotransmitters into vesicles so that their release can be regulated by neural activity. Recently, two vesicular amine transporters (VMAT1 and VMAT2) were identified. They are essential components of monoaminergic neurons and endocrine cells, and their expression is pre-determined during the development.

Methods: In our study we investigated VMAT2 distribution in rat small intestine using immunocytochemical techniques.

Results: VMAT2-immunoreactivity was found in neurons of the submucosal plexus. Nerve fibres containing VMAT2 were numerous in the submucosal and myenteric plexuses with high frequency of VMAT2-positive varicosities in the circular muscle layer and around the blood vessels. Some immunolabelled nerve fibres were observed beneath the epithelial cells.

Discussion/Conclusion: This data provide important information about the amine-handling structures in the gut wall, and neuroendocrine and immune/inflammatory cell functions. Moreover, it raises the possibility for development of new pharmacotherapeutic approach to inflammatory bowel diseases.
Regulation of human Paneth cell alpha defensins by microbial stimuli

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Introduction: Crohn's disease and mutations in the NOD2 gene are associated with an increased risk of inflammation affecting the ileum. The NOD2 gene is expressed in Paneth cells of the ileal crypts, which in turn play a role in antibacterial host defence, mediated by production of alpha defensins. Recent data suggest that alpha defensin levels are reduced in Crohn's disease, particularly in the presence of mutations in the NOD2 gene.

Methods: We investigated regulation of the human alpha defensin 5 (HD5) gene in vitro in colonic epithelial cells, to determine the effect of treatment with bacterial products such as lipopolysaccharide (LPS) and muramyl dipeptide (MDP). SW480 cell lines were treated with MDP and LPS, followed by real time RT PCR quantification of HD5 mRNA. A defensin gene reporter construct was transfected in SW480 cell lines and reporter activity measured after exposure to MDP and LPS.

Results: Treatment of the SW480 cell line with LPS and MDP did not increase the expression of HD5 mRNA, which is expressed at low constitutive levels, although the same stimuli did induce the expression of pro-inflammatory cytokines and matrix metalloproteinase 7 (MMP7). Using the reporter gene construct, some regulation of defensin gene expression in response to a subset of microbial stimuli could be demonstrated, although the magnitude was lower than that of nuclear factor kappa B induction.

Discussion/Conclusion:
These findings suggest that microbial stimuli that readily induce inflammatory changes, do not regulate HD5 gene expression to the same extent, and that the observed reduction in alpha defensin expression in Crohn's disease may relate to as yet unexplained alterations in the differentiation and function of Paneth cells.
Enteral nutrition leads to modification of the intestinal microbiota of children with Crohn's disease

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Introduction: Enteral nutrition (EN) induces remission and improved nutrition in children with Crohn's disease (CD). It has been suggested that EN may exert anti-inflammatory effects via modification of the gut microflora. This study aimed to determine whether the use of EN in children with CD was associated with modification of the intestinal microbiota.

Methods: Stool samples were collected prior, during and after treatment with exclusive EN (EEN) from 8 children with CD and from 6 control children without CD (two stool samples, 8 weeks apart. The 16S rDNA was amplified from faecal DNA using primers for the Bacteroides-Prevotella, Clostridium coccoides and Bifidobacteria groups of bacteria as well as the Clostridium leptum subgroup. PCR products were subjected to Denaturing Gradient Gel Electrophoresis (DGGE) to determine changes within each of the 4 bacterial groups over time.

Results: DGGE analysis revealed that one week after the commencement of EEN, a reduced diversity (as shown by DGGE banding numbers) in all bacterial groups occurred. During subsequent weeks of treatment, the number of DGGE bands increased as compared with week 1, however in all cases this did not return to the baseline profile. After ceasing EEN, the DGGE pattern again changed resulting in a pattern different to that at baseline and during EEN. In contrast, control samples showed a stable banding profile over the 8-week period.

Discussion/Conclusion: EEN is associated with modification of the intestinal microbiota in children with CD. This modification may modulate interactions between bacteria and the host epithelium, thereby altering mucosal inflammation.
Do non-gastric *Helicobacter* species play a role in intestinal inflammation?

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**Introduction**: Enterohepatic *Helicobacter* species can initiate IBD in immunodeficient mice. Attempts to detect such organisms in human IBD have given divergent results. This study is to determine the presence and spatial distribution of *Helicobacteriaceae* (*Helicobacter* & *Wolinella* species), in faecal samples and colonic biopsies of children undergoing diagnostic colonoscopy and controls

**Methods**: Three biopsies were collected from 12 children with IBD, 5 with IBS and 4 controls. DNA from 1 biopsy was used for *Helicobacteriaceae* specific PCR, DGGE and sequencing. The 2nd biopsy to examine the spatial distribution of *Helicobacteriaceae* using fluorescent in situ hybridization (FISH) and PAS staining of mucus and the 3rd for histology. Faecal DNA from 10 additional control children and the above 12 CD children was also examined by PCR for the presence of *Helicobacteriaceae*.

**Results**: *Helicobacteriaceae* PCR was positive in 12/12 biopsies from children with IBD, 5/5 with IBS and 2/4 controls. DGGE showed that 71% biopsies contained multiple *Helicobacter* species. Using FISH, these organisms were found to colonize the colonic mucus layer, which in children with IBD was found to be significantly thinner (0.84 ± 0.08 µm) than in children with IBS (3.30 ± 0.22 µm) (p < 0.001). Faecal DNA from all 12 CD children was positive for *Helicobacteriaceae* as compared with 0/10 controls.

**Discussion/Conclusion**: The finding that *Helicobacteriaceae* were significantly more common in children with IBD (100%) and IBS (100%) than control children [2/14(14.2%)] would suggest that these organisms may play a role in colonic inflammation. Further work is required to clearly define their role in specific disease states.
Dipeptidyl peptidases in a murine model of experimental colitis

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Introduction: Glucagon-like peptide-2 (GLP-2)₁⁻³³ is a potent intestinotrophic growth factor. Recent experiments suggest that it may be cleaved to the inactive GLP-2₃⁻³³ not only by dipeptidyl peptidase (DP) IV but other DPs. We hypothesized that these other DPs are present in the colon and that the expression of these enzymes would differ in wild-type (WT) versus DPIV knockout (DPIV⁻⁻) mice and normal compared to colitic colon samples.

Methods: WT and DPIV⁻⁻ mice consumed 2% dextran sulphate sodium (DSS) for 6 days to induce colitis (n = 6 for each group). Mice were sacrificed at days 0 and 6. Messenger RNA (mRNA), protein and enzyme levels of all enzyme members of the DPIV gene family and DPII were measured in the colon using real-time RT-PCR, quantitative western blotting, and DP enzyme activity assays.

Results: All enzyme members of the DPIV gene family and DPII were present in the colon of both normal and colitic mice at the mRNA level. DP8 and DPII mRNA levels were significantly increased (p < 0.05) in WT mice with colitis compared to normal mice. DP enzyme activity but not DPIV protein was significantly increased (p < 0.05) in colitic WT mice compared to normal WT mice, and DPII activity was significantly increased (p < 0.05) in colitic DPIV⁻⁻ mice compared to day 0 DPIV⁻⁻ mice.

Discussion/Conclusion: This study has shown that there is a differential expression of DPs in experimental colitis and further investigation is required to establish DP inhibition as a novel therapeutic option for IBD.
Role of mast cells in acute colitis

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Introduction: Therapy for inflammatory bowel diseases (IBD) has been aimed at the regulation of inflammatory cells and their mediators. Hence we plan to evaluate the role of mast cells in the pathogenesis of IBD by doing a comparative study using the mutant mice lacking mast cells (WBB6F1-W/Wv mice) and their counterpart wild type (WT) mice with colitis.

Methods: Experimental colitis was induced by adding 3% dextran sodium sulfate (DSS) in drinking water ad libium for 7 days. The disease activity index (DAI) and degree of colon injury were determined to know the clinical course of colitis on days 2, 5 and 7. Toluidine blue staining was carried out to identify the mast cells. Histamine content in the colon was quantified by fluorometry. TUNEL staining was done by using a special kit to determine the apoptosis.

Results: A significant increase in the DAI, degree of colon injury, infiltration of inflammatory cells was observed in the WT mice with DSS colitis in comparison to WBB6F1-W/Wv mice on day 2, 5 and 7. Histamine, c-Kit ligand and TNF-alpha levels were elevated in the colons of WT mice compared to the WBB6F1-W/Wv mice after induction of colitis. Presence and degranulation of mast cells were only observed in WT mice. TUNEL staining revealed a marked apoptosis of epithelial cells in the early stage of colitis in WT mice.

Discussion/Conclusion: A marked increase in the pathological changes in WT mice compared to WBB6F1-W/Wv mice during DSS colitis indicating a significant involvement of mast cells in the development of colitis, therefore we propose treatment strategies for IBD must incorporate agents which modify the mast cell activity.
Highly elevated functional MDR-activity of CD8+ lymphocytes in an IBD patient with steroid resistance

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Background: Previous studies showed that there might be a correlation between MDR expression and glucocorticoid resistance in various diseases. As the steroids are used in the treatment of inflammatory bowel disease (IBD) and a part of IBD patients show steroid dependence or/and resistance, the role of MDR proteins could be straightforward in these cases. Farrell and al. previously published data about the correlation of steroid response of IBD patients and immunohistochemical detection of MDR-expression on lymphocytes, and Hirano et al. published similar data on MDR1 mRNA using RT-PCR technique, although very few clinical data was obtained with functional investigation of MDR-proteins. Previous studies of Schwab et al revealed highly elevated CD8+/MRP1 activity in IBD patient with corticosteroid resistance.

Patients & Methods: We present a single case report to show a possible way of using the functional investigation of MDR-proteins in the future in clinical practice. We developed a clinical follow up of the functional MDR-activity of IBD patients in cooperation. After informed consent and ethical approval we took peripheral blood samples from the patient before and after the modification of therapy. After separation of mononuclear cells on Histopaque we investigated CD3, CD4, CD8, CD14 and CD19 positive mononuclear cells. Determination and calculation of functional MDR1- and MRP1-activity was performed with Calcein-assay by FACS following the original description: http://www.solvobiotech.com.

Results: In our current case report we present the follow up of both the clinical and MDR1/MRP1 activity data of a 27 years old woman with Crohn's disease (CD), never treated with steroids before. Due to the activity of her disease (CRP: 38,57, CDAI score: 221) parenteral steroid treatment became necessary. Before the beginning of steroid therapy her lymphocytes showed strongly elevated MDR functional activity, especially in the CD8 positive group, which increased further upon steroid treatment. After temporary amelioration of symptoms, beside the reduction of the steroid dose and the installation of azathioprine the patient's state worsened, a palpable mass occurred and finally surgical resection was needed.

Conclusion: The highly elevated MDR1/MRP1 functional activity of PBLs might predict steroid therapy failure in IBD patients, thus the follow up of the functional MDR-activity might be useful in predicting steroid resistance and also in avoiding side-effects of insufficient steroid therapy. We are currently following up more patients to confirm the probability of this correlation.
Determination of the MDR1 and MRP1 functional activity of peripheral and infiltrating intraepithelial lymphocytes of IBD patients

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Introduction: Previous studies showed possible correlation between MDR-expression of peripheral blood lymphocytes (PBL) and steroid resistance/treatment of IBD patients. Few results are available about MDR-expression of intraepithelial lymphocytes (IEL) compared with of PBLs. We developed a clinical protocol and thus aimed to determine and follow-up the functional activity of MDR1 and MRP1 proteins in PBL and IEL from endoscopic and/or surgical samples of IBD patients and to investigate results in connection with each other and clinical data.

Methods: Peripheral blood and biopsy and/or surgical samples from IBD patients were collected in parallel after informed consent and ethical approval only during the necessary and scheduled investigations according to the patients state. Up to now 12 tissue samples were collected and brought afterwards to one cell suspension by collagenase treatment. Functional MDR1- and MRP1-activity of PBLs and IELs were determined by the functional Calcein-assay (http://www.solvobiotech.com).

Results: Surgical specimens usually and bigger endoscopic samples provided cells enough for determination of functional MDR-activity of both lymphocytes. In 9/12 samples the calculation of MDR-activities could be performed and in cases suitable for comparison we found correlation of functional MDR-activity of PBL-s and IELs.

Discussion/Conclusion: We could develop a sampling protocol for determining functional MDR-activity of PBL-s and IELs of IBD patients. Our initial results found similar MDR1 and MRP1 functional activity in investigated cells. More investigation might confirm the possibility of monitoring the functional MDR-activity of IELs in IBD by PBLs and thus it might be helpful in predicting steroid resistance in IBD-treatment.
Determination of MDR1 and MRP1 expression of peripheral blood lymphocytes (PBL) before and after corticosteroid treatment of inflammatory bowel disease (IBD) patients

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Introduction: Our aim was to determine the activity of MDR1 and MRP1 proteins in mononuclear cells isolated from peripheral blood samples of IBD patients, to investigate their connection with the treatment and the clinical symptoms and to develop a clinical protocol for MDR-follow up in IBD.

Methods: We investigated 8 patients (5 women, 3 men) with active IBD (ulcerative colitis: 2, Crohn's disease: 6) treated with corticosteroids. After informed consent and ethical approval we took peripheral blood samples before and after the modification of therapy and during the clinical follow up from each patient. Determination and calculation of functional MDR1- and MRP1-activity was performed with Calcein-assay method following the original description: http://www.solvobiotech.com. We investigated the mononuclear cell subgroups by labeling with anti-human CD3, CD4, CD8, CD14 and CD19 antibodies.

Results: We compared the MDR activity of PBL before and after corticosteroid therapy in patients with active IBD. Although very few cases could have been investigated up to now, data of the clinical follow up showed that MDR1 or MRP1 activity increased in connection with steroid administration, especially in CD 8 positive lymphocytes. The study is in progress to obtain more clinical evidence to validate these data.

Discussion/Conclusion: During the study we succeeded in developing a protocol for the clinical follow up of MDR-activity in IBD patients. We began to monitor the influence of treatment on the activity of MDR1/MRP1 proteins. The few cases analyzed up to now showed that corticosteroid treatment upregulates the MDR1 or MRP1 activity of PBL (especially CD 8 positive lymphocytes). This correlation have to be confirmed on higher number of cases to obtain a noninvasive diagnostic method to determine steroid-resistance probability of IBD patients.
Evidence of monoclonal origins of dysplasia in ulcerative colitis

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Introduction: Ulcerative colitis (UC) associated colorectal cancers develop from areas of dysplasia. Loss of heterozygosity (LOH) of tumour suppressor genes such as Adenomatous polyposis coli (APC), deleted in colon cancer (DCC) and SMAD4 occur in UC dysplastic tissue. LOH analysis is used as a reliable marker of clonality. This study aimed to use LOH at 3 loci for assessment of clonality within dysplastic UC tissue.

Methods: Tissue was categorised histologically. Laser capture microdissection was used to isolate individual crypts. DNA was amplified for microsatellite markers close to the loci of APC (5q21.1), DCC (18q21) and SMAD4 (18q21.1). PCR product was analysed with ABI 3100 sequencer and genotyper software and abnormal tissue allelic areas were compared with normal tissue allelic areas as a ratio.

Results: LOH for microsatellite markers was found in chronic inflammation in 1 patient at a low frequency (1 marker, 50% of crypts). LOH of the same microsatellite marker was seen in low grade dysplasia at a low frequency (44%) but at a very high frequency across multiple high grade dysplastic patches in different patients (up to 100%). LOH of multiple markers was seen in some patients.

Discussion/Conclusion: Lower LOH frequency in inflamed and low grade dysplasia compared to high grade dysplasia suggests which marker is lost first, and the earliest lost marker can be used a clonal marker. 'Across the patch' loss of the same allele in high grade dysplasia suggests monoclonal derivation. Increased crypt fission is likely to be responsible for mutation spread.
Bone marrow transplantation induces remission in Crohn's disease: Where do the cells go?

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Introduction: Recent studies show that bone marrow (BM) transplantation induces remission in Crohn's disease. We used a mouse model of Crohn's colitis to elucidate the mechanism of action of BM transplantation. BM forms myofibroblasts in inflamed colons, which we now show can produce collagen. BM also forms multiple vascular lineages and contributes to both angiogenesis and neovasculogenesis.

Methods: Female mice were lethally irradiated and rescued by a BM transplant from male donors. After 6 weeks, colitis was induced by injection of trinitrobenzene sulphonic acid (TNBS), and colons analysed 1-14 days later. In situ hybridisation for Y chromosome was combined with immunohistochemistry for specific antigens to determine cell phenotype. A novel triple staining method combined in situ hybridisation and immunohistochemistry with autoradiography for collagen mRNA.

Results: Cells derived from BM (Y chromosome-expressing) were abundant in inflamed colons and associated vasculature; vascular smooth muscle lining cells (VSMLCs) expressed alpha-smooth muscle actin (SMA); endothelial cells expressed ICAM1 and vWF; myofibroblasts expressed SMA and collagen mRNA. Inflammatory cell infiltration was ruled-out. BM contributed to 57% of myofibroblasts, which produced collagen. BM-derived endothelial cells, pericytes and VSMLCs were frequent in blood vessels, with 27% of VSMLCs of BM origin in inflamed colons. BM contributes to both angiogenesis and neovasculogenesis, confirmed by vessels composed entirely of BM-derived cells.

Discussion/Conclusion: This is the first observation of BM-mediated neovasculogenesis in colitis. We provide an insight into the regenerative function of BM by highlighting the capacity of BM to engraft within inflamed colons and form multiple, functional lineages.
Inhibition of dipeptidyl peptidase IV like activity fails to enhance jejunal growth in mice with experimentally-induced colitis

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Introduction: Glucagon-like peptide-2 (GLP-2), a potent intestinotrophic growth factor, enhances repair of damaged tissues, however its bioavailability is limited by proteolytic dipeptidyl peptidase IV (DPIV). Preliminary studies revealed DPIV inhibitors increase GLP-2 bioavailability. We investigated DPIV pharmacological inhibition and gene knockout effects in the jejunum of mice with dextran sulfate sodium-induced (DSS) colitis.

Methods: DPIV+/- and DPIV+/+ mice were treated twice-daily with DPIV inhibitor (Isoleucyl-thiazolidine) or saline by oral gavage, whilst consuming 2% DSS for 6 days. Mice were sacrificed on days 0, 9 and 14. Jejunal tissue was sampled, histologically determining crypt depth and villus height. Proliferating cell nuclear antigen (PCNA) immunostaining provided epithelial cell proliferative cell labelling indices (LI).

Results: No significant changes in crypt depth and villus height were observed between DPIV-/- and DPIV+/+ mice administered saline at days 0, 9 and 14. No significant changes in crypt depth and villus height were observed between DPIV-/- and DPIV+/+ mice administered inhibitor at all time points. At day 14 following inhibitor administration, LI was significantly lower (p < 0.05) in DPIV-/- compared to DPIV+/+ mice. At day 14 following saline administration, no statistical significance was evident for LI between DPIV-/- and DPIV+/+ mice. No significant changes in LI were observed when comparing DPIV-/- and DPIV+/+ mice, administered saline at day 9 or administered inhibitor at day 9.

Discussion/Conclusion: We conclude that loss of DPIV activity does not significantly increase jejunal growth in the colitis setting and hypothesise that endogenous GLP-2 levels may be insufficient to promote jejunal intestinotrophic effects.
Real-time PCR quantification of faecal bacteria in C57B16 wild-type and Winnie mice

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Introduction: By using molecular techniques to characterise bacterial 16S rRNA genes, it has been shown that the major mucosal bacteria are similar across the mammalian digestive tract, and are dominated by Bacteroidetes and the Clostridium XIVa cluster (CXIVa). However, total mucosal bacteria (UB) and in particular some bacteria in CXIVa are increased in IBD (manuscript in preparation). In addition, our group have mice (Winnie strain) with a single point mutation in the major secreted intestinal mucin, Muc2 that results in incorrect oligomerisation and processing of Muc2, decreased mucus production and goblet cell stress. Winnie mice do not develop spontaneous colitis but develop very severe colitis in response to dextran sodium sulfate. This study aimed to measure some key bacteria in the colon of Winnie vs C57BL6 wild-type (WT) mice using quantitative real-time PCR: UB, Bacteroides vulgatus (Bv), Bifidobacteria species (Bf), Fusobacterium varium (Fv), Ruminococcus gnavus (Rg), R. torques (Rt) - Rg and Rt are known mucolytic bacteria.

Methods: DNA extracted from faeces of 6 WT and 6 co-habited Winnie were used for real-time PCR analysis.

Results: Bf, Bv, Rg were present in all samples, Rt in 75%; Fv was not detected (Bf>Bv>Rg>Rt). There were trends for more UB and Bf in Winnie.

Discussion/Conclusion: Relative abundances of the different bacteria in mice colon are strikingly similar to what we have measured associated with human colonic mucosa. Unlike IBD mucosa, goblet cell stress and a diminished mucus layer did not increase Rg and Rt.
Role of junctional adhesion molecule C (JAM-C) in the pathophysiology of acute pancreatitis

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Introduction: Junctional adhesion molecule-C (JAM-C) is a tight junction associated transmembrane protein expressed on mammalian endothelial cells. It is involved in leukocyte diapedesis and interacts heterophilically with the leukocyte integrin $\alpha_M\beta_2$. Sequestration of neutrophils is an important early event in acute pancreatitis. The role of JAM-C in the pathogenesis of acute pancreatitis is unknown.

Methods: Acute pancreatitis was induced in mice by administering 3 or 10 hourly intraperitoneal (ip) injections (50 $\mu$g/kg) of cerulein. JAM-C expression was assessed by immunofluorescence on frozen sections and Western Blot at 0 and 10 hours. 300 $\mu$g of the monoclonal rat anti-mouse JAM-C antibody or of a $\gamma$2A isotype matched control were injected ip 30 minutes after the first noxious stimulus. Transgenic mice overexpressing vascular JAM-C and their littermates were administered 10 ip injections of cerulein. The severity of pancreatitis was assessed in both models by measuring serum amylase levels, acinar cell necrosis, edema and leukocyte infiltrate.

Results: JAM-C expression is increased in experimental acute pancreatitis. The monoclonal anti-JAM-C antibody reduced leukocyte infiltrate, serum amylase concentration, edema and acinar cell necrosis significantly. Conversely, leukocyte infiltrate, serum amylase concentration, edema and acinar cell necrosis were significantly increased in JAM-C transgenic mice compared to their littermates.

Conclusion: Early administration of a monoclonal anti-JAM-C antibody significantly reduces the severity of acute pancreatitis in mice. The importance of JAM-C in the pathophysiology of acute pancreatitis is underlined by the fact that cerulein-induced pancreatitis is more severe in transgenic mice overexpressing vascular JAM-C.
Antibody levels to selected bacterial surface antigens are increased in Crohn's disease (CD) but not ulcerative colitis (UC)

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Introduction: Mucosa-associated bacteria are implicated in CD, which on the basis of immunohistochemistry and cultured colonic lymphocytes is believed a TH1 disease, and UC, believed an atypical TH2-mediated inflammation. Previous studies reported increased humoral immune responses to Bacteroides vulgatus surface antigens (SAg) in both CD and UC. The present study compared serum antibody (IgM, IgG, IgA) concentrations to the SAg of four different B.vulgatus strains, Ruminococcus gnavus (a bacterium we find increased in CD and UC) and to F2 (a Clostridium coccoides flagellin which has been linked to increased serum IgG in CD).

Methods: Serum antibody (ELISA) from 40 CD, 40 UC and 40 controls were tested against seven SAg preparations: total faecal bacteria, R. gnavus, B. vulgatus strains and recombinant F2 flagellin.

Results: Serum IgG to all SAg preparations increased in CD but not UC, even though more CD patients (77%) were on immunosuppressives than UC (27%) and controls (0%). Antibody isotype concentrations correlated in each disease group between SAg preparations, except for IgG isotype in CD, possibly indicating a polyclonal response in UC and controls, and to a lesser extent in CD. However, immunoblotting indicated unique reactive antigens as well as common antigens.

Discussion/Conclusion: Preliminary data on F2 flagellin confirm reported increases in IgG with CD. However, increased IgG to the SAg in CD, but not to any SAg in UC or controls, suggests humoral immune responses to these SAg are not involved in UC pathogenesis and are not restricted to specific bacteria in CD.
Detection of *Clostridium coccoides* CBir1 and FlaX flagellin in mucosal biopsies and faeces of IBD patients, and antibodies against it in patient sera

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**Introduction:** *Clostridium coccoides* are a major intestinal subphylum (Wang J, Appl Microbiol 2003; 95: 508) increased in IBD. Flagellin from specific bacteria in *Clostridium coccoides*, CBir1 and FlaX, are dominant antigens in mouse colitis models. Crohn's disease (CD) patients have antibodies against these flagellins (Lodes J Clin Invest 2004; 113: 1296). It is unknown whether CBir1 or FlaX are present in human intestine, and antibody studies are limited.

**Methods:** Pinch biopsies from inflamed and non-inflamed colon from 17 ulcerative colitis (UC) patients, colon of 16 CD patients, 12 controls (NC) and faeces from each patient were collected during colonoscopy. DNA extracted using bead-beating and CBir1 and F2 (FlaX homologue) reagents were used for PCR amplification. Levels of IgM, IgG and IgA antibodies to recombinant F2 were measured in 40 UC, 40 CD, and 40 NC sera using ELISA.

**Results:** All samples were negative for CBir1 flagellin, while 3 UC, 4 CD and 1 NC sample were positive for F2 flagellin. IgM and IgG antibody to F2 were greater in CD sera than both UC and NC, while IgA were not different.

**Discussion/Conclusion:** Unlike mouse colitis models, these flagellin were absent in > 75% IBD colon, however, the presence of F2 flagellin in more IBD than NC samples may indicate that these or similar bacteria are associated with IBD, particularly CD with the greater IgM and IgG responses to F2. However, the humoral immune response against bacterial antigens appears to be greater in CD and that directed towards F2 flagellin may not be specific.
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