Abstracts of Invited Lectures
Poster Abstracts

Falk Symposium 159

IBD 2007 – ACHIEVEMENT IN RESEARCH AND CLINICAL PRACTICE

Istanbul (Turkey)
May 4 - 5, 2007

Scientific Organization:
Ü. Dağlı, Ankara (Turkey)
G.J. Mantzaris, Athens (Greece)
J. Schölmerich, Regensburg (Germany)
N. Tözün, Istanbul (Turkey)
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119. Evaluation of 100 Crohn's disease patients according to the Vienna and Montreal classifications
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120. Granulomatous cheilitis in a patient with Crohn's disease: A pictorial follow-up description
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121. Beneficial effect of a polymeric feed, rich in TGF-β on adult patients with active Crohn's disease: A pilot study
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124. Ulcerative colitis and viral hepatitis
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125. Cytokines in children with inflammatory bowel diseases
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126. Correlation between endoscopic severity and the histologic activity index in inflammatory bowel disease

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129. Evaluation of our Crohn's disease patients with upper gastrointestinal tract involvement  
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130. Location of our ulcerative colitis patients according to Montreal classification: Is there any change by the years?  

131. Evaluation of our operated ulcerative colitis patients  

132. Clinical activity and disease progress according to Montreal classification in ulcerative colitis  
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Session I

Epidemiology, risk factors and genetics
Inflammatory bowel disease in Turkey

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Inflammatory bowel disease (IBD) comprising primarily of Crohn’s disease (CD) and ulcerative colitis (UC) is increasingly prevalent in racial and ethnic minorities.

In order to estimate the IBD prevalence in Turkey a study is commenced by the Turkish IBD Society in September 2004. All records of patients admitted and treated in the hospitals by gastroenterology specialists were prospectively written to the web page of IBD society. The distribution of CD and UC was analyzed as well as sex, age, and smoking habit at the time of diagnosis, familial aggregation, appendicectomy rate, localization of disease and extraintestinal manifestations. Until September 2006, 2398 IBD (1729 UC, 623 CD, 46 IC) patients were recorded. The prevalence rates were 4.54/10⁵ for IBD, 3.27/10⁵ for UC and 1.18/10⁵ for CD. The highest prevalence rate was observed in the age group of 50-59 years for UC, and 40-49 years of age group for CD. The prevalence of IBD was higher in the urban (6.05/10⁵) than the rural (1.75/10⁵) population. The male to female ratio was 1.30 for UC and 1.25 for CD.

A family history of IBD, smoking and extraintestinal manifestation was more common in CD than in UC. Previous appendicectomy was reported in 1.8% of patients with UC, and 13% with CD.

The predominant form of UC was distal colitis, which affected almost 37.6%, of the studied population. Pancolitis and left sided colitis was present in 36.2% and 25.6, respectively. An ileocolonic location was observed in 52.7% of patients, pure colonic in 24.3% and pure small bowel in 22.3%.

In Turkey, investigations of IBD genetic markers are still scarce. There are two studies associated with polymorphism in the NOD2/CARD15 gene. In one of the studies, the polymorphisms in the NOD2/CARD15, NOD1/CARD4, and ICAM-1 genes was investigated in Turkish patients with IBD and healthy control groups. In this study, the three previously described Crohn’s disease predisposing variants were not found to be associated with UC or CD (1). In the second study, the CARD15/NOD2 mutation was investigated in 56 CD patients and 100 healthy controls. Among the three NOD2/CARD15 mutations only G908R variant allele was found to be associated with disease (8% in CD, 0% in controls) (2). In the other study, cytokine gene polymorphisms (TNFalpha, IL-1B, IL-1RN, IL-10) was investigated and these polymorphisms were not important risk factors in the susceptibility to IBD in Turkish patients (3).

Although the true epidemiologic profile of IBD in Turkey is still unknown. Our study revealed low prevalence rates.
References:


Inflammatory bowel disease in Greece

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It has been suggested that some of the clinicoepidemiological parameters of inflammatory bowel disease (IBD), (ulcerative colitis – UC and Crohn’s disease – CD) differ in some degree in different parts of the world. These differences could be attributed either to environmental and/or genetic differences. In this presentation the clinical characteristics, course and prognosis of IBD in Greece, are analyzed based on a series of papers published in the international literature. The most significant findings could be summarized as follows:

**Ulcerative colitis:** The epidemiological features of UC in Greece are similar to most of the developed countries of the world. The disease affects men in a higher proportion compared to women. Positive family history could also be obtained in Greek patients although in a smaller proportion compared to other European countries, probably reflecting genetic and/or environmental differences. Age at onset of the disease, extent of the disease, and number and proportion of extraintestinal manifestations do not differ compared to other parts of the world. However the need for surgical intervention as well as the development of colorectal cancer during the course of UC is quite smaller compared to other European and North America countries. Mortality seems to be generally low and does not seem to be related, at least in a great degree, to the underlying enteropathy.

**Crohn’s disease:** Again, most of the clinicoepidemiological characteristics of patients with Crohn’s disease in Greece are similar to those reported from the developed countries of Europe, North America and the neighbouring Mediterranean countries. However, other parameters, such as the higher incidence of the disease in males, the relatively lower incidence of familial clustering and the milder course of perianal disease, all underline the importance of environmental, genetic and other factors in the pathogenesis and course of the disease in different parts of the world.
IBD in Southern Europe

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Crohn’s disease and ulcerative colitis are two major forms of idiopathic IBD. They share many epidemiological and clinical characteristics. Major problems in the epidemiological studies of IBD are: 1. lack of diagnostic gold standard criteria and complexity and expense of diagnostic work-up all cause problems in reporting incidence of this diseases, particularly in less developed countries; 2. most epidemiological studies come from the large referral centers and may be, therefore, biased toward reporting more advanced forms of disease, underestimating its true incidence; 3. frequent misclassification of IBD phenotypes might be due either to the true natural course of disease (reassignment of a diagnosis may be as high as 10% in the first 2 years after diagnosis) or due to the methodological problems; 4. differences in health systems in various countries.

However, inspite of these methodological limitations, distinct temporal and geographic trends in incidence have been observed. The pattern of sharp rise in the incidence of CD observed from the mid-1950s to the early 1970s followed by stabilization of the rate since 1980s in developed countries of northern Europe is now repeating itself with time delay in southern Europe. The same hold true for UC. Higher incidence rates have been generally observed in more northern latitudes, but the north-south gradient is increasingly disappearing in Europe due to the stabilization of incidence rates in the north and increasing rates in the south (1, 2, 3, 5, 6, 11, 12).

This paper will review the epidemiological data from southern Europe, particularly from 4 countries: Greece, Croatia, Italy and Spain. The data on ulcerative colitis are shown in tables 1-4 and on Crohn’s disease in tables 5-8.

Table 1. Ulcerative colitis – Greece (2, 3)

<table>
<thead>
<tr>
<th>Location</th>
<th>Incidence</th>
<th>Period</th>
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</thead>
<tbody>
<tr>
<td>Ioannina</td>
<td>4.0</td>
<td>1982-91</td>
</tr>
<tr>
<td>Central Greece</td>
<td>11.2</td>
<td>1990-94</td>
</tr>
<tr>
<td>Heraklion</td>
<td>9.4</td>
<td>1990-94</td>
</tr>
</tbody>
</table>

Table 2. Ulcerative colitis – Croatia (4, 5)

<table>
<thead>
<tr>
<th>Location</th>
<th>Incidence</th>
<th>Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zagreb</td>
<td>0.9</td>
<td>1980</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>1989</td>
</tr>
<tr>
<td>Rijeka</td>
<td>2.7</td>
<td>1995</td>
</tr>
<tr>
<td></td>
<td>4.3</td>
<td>2000-04</td>
</tr>
<tr>
<td>Table 3. Ulcerative colitis – Italy (6)</td>
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<tr>
<td>--------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Florence</td>
<td>4.0</td>
<td>1978-87</td>
</tr>
<tr>
<td></td>
<td>9.6</td>
<td>1990-92</td>
</tr>
<tr>
<td>Bologna</td>
<td>5.0</td>
<td>1986-89</td>
</tr>
<tr>
<td>Lombardia</td>
<td>7.0</td>
<td>1990-94</td>
</tr>
<tr>
<td><strong>Italy</strong></td>
<td>3.4-10.5</td>
<td>1999</td>
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</table>

<table>
<thead>
<tr>
<th>Table 4. Ulcerative colitis – Iberian peninsula (7, 8, 9, 10, 11, 12)</th>
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</thead>
<tbody>
<tr>
<td><strong>Spain</strong></td>
</tr>
<tr>
<td>Catalonia</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Barcelona</td>
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<tr>
<td>Granada</td>
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<tr>
<td>Central Spain</td>
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<tr>
<td>Madrid</td>
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<tr>
<td>Pamplona</td>
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<tr>
<td>Soria</td>
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<tr>
<td>Sabadell</td>
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<tr>
<td>Aragon</td>
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<td></td>
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<tr>
<td>Asturias</td>
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<tr>
<td>Castellon</td>
</tr>
<tr>
<td><strong>Spain 06,-8 median 3.8 2001</strong></td>
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<td>Huelva</td>
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<tr>
<td>Oviedo</td>
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<tr>
<td><strong>Portugal</strong></td>
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<td>Almada</td>
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<table>
<thead>
<tr>
<th>Table 5. Crohn's disease - Greece (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heraklion</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Ioannina</td>
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<table>
<thead>
<tr>
<th>Table 6. Crohn's disease – Croatia (5, 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zagreb</td>
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<tr>
<td>Rijeka</td>
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</table>
Table 7. Crohn’s disease – Italy (6)

<table>
<thead>
<tr>
<th>City</th>
<th>Rate</th>
<th>Years</th>
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</thead>
<tbody>
<tr>
<td>Florence</td>
<td>1.5</td>
<td>1978-87</td>
</tr>
<tr>
<td></td>
<td>3.4</td>
<td>1990-92</td>
</tr>
<tr>
<td>Bologna</td>
<td>2.7</td>
<td>1986-89</td>
</tr>
<tr>
<td>Lombardia</td>
<td>3.4</td>
<td>1990-94</td>
</tr>
<tr>
<td>Palermo</td>
<td>2.7</td>
<td>1987-89</td>
</tr>
<tr>
<td><strong>Italy</strong></td>
<td>1.9-6.6</td>
<td>1999</td>
</tr>
</tbody>
</table>

Table 8. Crohn’s disease – Spain (7, 8, 9, 10, 11, 12)

<table>
<thead>
<tr>
<th>Region</th>
<th>Rate</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asturias</td>
<td>0.8</td>
<td>1975-79</td>
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<tr>
<td></td>
<td>6.1</td>
<td>1994-97</td>
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<tr>
<td>Aragon</td>
<td>0.8</td>
<td>1975-79</td>
</tr>
<tr>
<td></td>
<td>3.3</td>
<td>1990-92</td>
</tr>
<tr>
<td></td>
<td>3.9</td>
<td>1992-95</td>
</tr>
<tr>
<td>Galicia</td>
<td>0.8</td>
<td>1976-82</td>
</tr>
<tr>
<td>Barcelona</td>
<td>0.4</td>
<td>1978-87</td>
</tr>
<tr>
<td>Catalonia</td>
<td>0.2</td>
<td>1978</td>
</tr>
<tr>
<td></td>
<td>0.7</td>
<td>1987</td>
</tr>
<tr>
<td>Granada</td>
<td>0.9</td>
<td>1979-88</td>
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<tr>
<td>Central Spain</td>
<td>1.6</td>
<td>1981-84</td>
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<tr>
<td>Soria</td>
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<td>1981-90</td>
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<td>1.3</td>
<td>1983-88</td>
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<tr>
<td></td>
<td>3.3</td>
<td>1983-93</td>
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<tr>
<td>Castellon</td>
<td>1.9</td>
<td>1992-96</td>
</tr>
<tr>
<td><strong>Spain</strong></td>
<td>0.4-5.5</td>
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<td>Huelva</td>
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<td>Oviedo</td>
<td>7.5</td>
<td>2001-03</td>
</tr>
</tbody>
</table>

The available data indicate that the incidence rates of IBD, and particularly of CD, in southern Europe have in many areas reached the level of observed rates in western and northern Europe, indicating rapid changes in the environmental factors relevant for IBD.

References:


Comparison to North and Central Europe

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The incidence and prevalence of ulcerative colitis (UC) and Crohn’s disease (CD) is varying across Europe.

A marked increase has been reported for CD up to nine-fold over 40 years and a more gradual increase for UC.

The causes for this increase have not been elucidated. The increase is probably caused by external factors since genetic factors cannot account for the increase.

However, genetics have been the focus of research for the last five to 10 years and the gene CARD-15 located on chromosome 16 has repeatedly been shown to be associated with CD. The presence of a mutation in CARD-15 increases the risk of developing CD by up to 20-fold depending of the numbers of alleles involved.

In a European study (EC-IBD) the prevalence of mutations varied across Europe with significantly lower prevalence in Scandinavia compared to Southern Europe. No correlation was found between the incidence of CD and the prevalence of mutations in CARD-15.

Disease presentation at diagnosis was found to be comparable across Europe.

Cumulative relapse rates in UC were fairly even across Europe. However, the highest relapse rate was found in Denmark compared to Greece.

Surgery rates were varying across Europe and were significantly higher in Northern Europe compared to Southern Europe.
Session II

Bacterial and viral infections mimicking IBD
Tuberculosis of the colon: A diagnostic challenge

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Gastroenterologists working in the developing world face a number of challenges in the field of inflammatory bowel disease (IBD). A high burden of enteric infections, limited access to endoscopy and poorly developed healthcare infrastructure make the diagnosis of IBD difficult.

Worldwide there is a resurgence of tuberculosis (TB) and it is estimated that a third of the world’s population is infected. Furthermore 80% percent of all new cases in 2004 occurred in Africa, South-East Asia and Western Pacific regions

A complex relationship exists between Crohn’s disease (CD) and intestinal TB. Both are chronic granulomatous inflammatory conditions which share similar pathogenic and morphological characteristics. Clinically it is difficult to differentiate between CD and ileocolonic TB. In the developing world both diseases affect young and middle-aged people and present with similar symptoms. Fistulisation, extra-intestinal manifestations, smoking and thromboembolic disease are associated with both diseases.

Colonoscopy with intubation of the terminal ileum and endoscopic mucosal biopsy play a crucial role in the diagnosis of ileo-colonic TB. The majority of intestinal TB cases will involve the ileocaecum with varying degrees of contiguous colonic involvement. Endoscopic features of colonic TB include circumferential ulcers, pseudoplyps, nodules, a patulous ileocaecal valve and fibrous bands forming pseudoshelves. A combination of these features have a PPV of 88.9% for colonic TB.

Confirming a diagnosis of colonic TB on endoscopic mucosal biopsy is difficult due to the submucosal nature of the disease. The pathognomonic features of caseating granulomatous inflammation and acid fast bacilli are present in only a minority of cases. Retrospective studies from Southern India and South Africa have identified a number of features, other than caseous necrosis and acid fast bacilli, that appear helpful in distinguishing CD from colon TB in colonoscopic biopsies. These include confluent granulomas, multiple granulomas in a given biopsy site, large granuloma size, bands of epithelioid histiocytes lining ulcers, submucosal granulomas and disproportionate submucosal inflammation.

A diagnosis of colon TB depends on careful clinical evaluation combined with systematic assessment of colonoscopy and histological findings.
References:


Parasites in IBD

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Infections caused by the protozoa Entamoeba histolytica (E. histolytica) are common especially in the developing world. It is estimated that 10% of the population is infected with this parasite and is the third most common cause of parasite related mortality after malaria and schistomiasis. It is important to distinguish E. histolytica from E. dispar which is 10 times more prevalent but non-pathogenic.

E. histolytica infection can imitate IBD, may cause a relapse of the underlying IBD, or can present with IBD simultaneously. Focal masses (ameboma), perforation and toxic megacolon have been described. Corticosteroids can exacerbate amibic activity and precipitate fulminant colitis, therefore it is very important to document the presence or absence of amebae especially in patients requiring corticosteroids. Amebea can be eradicated by drug therapy.

Stool microscopy, histology, stool antigen tests and serology are the most commonly used diagnostic tools. Even in the presence of the disease stool studies may be negative. Results of the serological investigations may compromised by corticosteroids. Therefore, it is important to maintain a high index of suspicion and start concomitant treatment both for ameba and IBD especially in rapidly deteriorating patients.

The frequency of amibiasis in IBD patients varies according to the geographic region. In a recent study it has been reported 22% in UC and 10.9% in Crohn’s disease in Turkey.
Bacterial and viral infections mimicking inflammatory bowel diseases

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Inflammatory bowel disease (IBD) is a group of chronic diseases involving the gastrointestinal system, characterized by inflammation in bowel and sometimes associated with extra-intestinal features. Ulcerative colitis and Crohn's disease are two common disorders in this group. The commonest presentation for Crohn's disease is abdominal pain, diarrhea and weight loss; whereas, the most common clinical feature is bloody diarrhea in ulcerative colitis. There are number of bacterial and viral infections mimicking clinical presentation of IBD. Because of wide spread use of immunosuppressive medications in either ulcerative colitis or Crohn's disease, such mimicking infections should be excluded in these clinical settings. The most common infections mimicking IBD are cytomegalovirus (CMV), mycobacterium tuberculosis, clostridium difficile, Ebstein Barr virus and Yersinia enterocolitica infections. Clinical presentation of CMV colitis is almost identical with severe ulcerative colitis. Tuberculosis became an increasing concern in patients with IBD, especially in whom anti-TNF regimens are considered to be the choice of treatment. Interestingly, intestinal tuberculosis and Crohn's disease are clinically and radiologically similar diseases. The histological differential diagnosis of Crohn's disease and intestinal tuberculosis can be very challenging, as both are chronic granulomatous disorders with overlapping histological features. Clostridium difficile is an opportunistic pathogen that causes a spectrum of disease ranging from antibiotic-associated diarrhea to pseudomembranous colitis. Symptoms seen in these patients are similar to those in IBD. Thus, distinguishing the two conditions can be challenging. Furthermore, in recent years number of studies has shown increased prevalence of Clostridium difficile in patients with IBD. In summary, presence of these infections mimicking IBD should not be neglected and great care must be taken in differential diagnosis in patients suspected IBD. Furthermore, superinfections with such organisms should be considered in patients on immunosuppressive medications with refractory and severe disease.
Viral hepatitis, HIV and IBD

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Head, Dept. of Gastroenterology, University Hospital, P.O. Box 1352, Heraklion, Crete, Greece

Existence of viral infection with Hepatitis B virus (HBV), Hepatitis C virus (HCV) and Human immunodeficiency virus (HIV) in patients with Inflammatory bowel disease (IBD), may cause problems in treatment. Moreover either HIV colitis or HIV associated infections may mimic IBD and make a firm diagnosis difficult.

A. HBV and IBD. Crohn’s disease patients are possibly at increased risk of HBV infection (and also HCV), due to surgical and endoscopic procedures. Treatment with corticosteroids may be dangerous. As early as 1980, corticosteroids were shown to increase viral replication a fact confirmed and recently reviewed (1). HBV contains a glucocorticosteroid responsive element that stimulates viral replication and transcriotional activity. Flares of HBV hepatitis with increased aminotransferases have been described at steroids withdrawal, sometimes leading to hepatic decompensation. Early antiviral treatment with lamivudine as the drug of choice are mandatory in these patients, while pre-emptive treatment may be effective but controlled trials are not available. Evidence with azathioprine is conflicting with case studies reporting either no effect on HBV liver disease or flares of disease activity. Data on infliximab therapy are mostly coming from patients with rheumatoid arthritis. There is evidence that TNFα synergizes with interferon, in suppressing HBV viral replication and is essential for clearance of HBV virus (2). There are several recent case studies showing no effect of infliximab treatment on HBV liver disease. However, there are also reports of disease exacerbations in Crohn’s disease patients and therefore the current recommendation by most investigators is the pre-emptive treatment with lamivudine, before starting infliximab (3).

B. HCV and IBD. Prevalence of HCV infection is higher in IBD patients in Europe compared to blood donors. Corticosteroids increase HCV viremia and bolus administration although does not affect viral load in renal transplantation, is associated with higher histological activity index. Azathioprine has no effect on either viral replication or liver disease and may even have in vitro antiviral activity. Cyclosporine inhibits HCV replication in a dose dependent manner and shows additive effect to interferon (4). TNFα has a different effect on HCV virus, compared to HBV. It may lead to inflammatory and possibly fibrosis, therefore the use of its antagonists may be beneficial.
In fact, all published series, recently reviewed (3), agree that infliximab (or etanercept) have no effect on either viral replication of HCV related liver disease and therefore their use is absolutely safe in IBD patients with concomitant HCV infection.

C. HIV and IBD. Diarrhea and abdominal pain are usual in HIV infection and idiopathic ulcers of the esophagus and rectum due to HIV are common, making differential diagnosis with Crohn’s disease difficult. HIV associated cytomegalovirus colitis and Salmonella, Campylobacter or Shigella ileitis may also mimic IBD. Corticosteroids may induce Kaposi’s sarcoma, or alternatively Kaposi’s sarcoma may be associated with ulcerative colitis usually due to HHV-8 virus (5). Elevated TNFα is found in all stages of HIV. There have been 3 controlled trials of anti-TNFα in HIV. In all, the reduction of TNFα levels was not associated with either changes in plasma HIV RNA levels or numbers of CD4 cells. This is in agreement with recent evidence indicating that infliximab does not activate replication of many lymphotropic herpesviruses commonly associated with HIV (6). Interestingly, thalidomide, a drug successfully employed in the treatment of aphthous ulcers and HIV associated wasting, has been tested in two open-label trials of refractory fistulizing Crohn’s disease with very encouraging results (7).

References:

Inflammatory bowel disease (IBD) is comprised of two separate entities: Crohn’s disease (CD) and ulcerative colitis (UC). Susceptibility to IBD is determined by numerous environmental, genetic, and immunological factors. Recent advances in our understanding of specific immune deficits as they pertain to both CD and UC have enabled therapeutic breakthroughs using a variety of novel reagents targeting components of the immune system (cytokines, receptors, transcription factors) with monoclonal antibodies, receptor antagonists and small peptides.

Genetics clearly contribute to the etiology of IBD. The concordance rate in monozygotic twins is about 40% to 60% for CD and about 5% to 20% for UC. In addition, having a first-degree relative with IBD increases risk about 15-fold. Genome-wide screening has identified 7 loci, named IBD1-7, that are linked to IBD. The best characterized of these genes, NOD2/CARD15, falls within the IBD1 locus on chromosome 16. Three different loss-of-function mutations in NOD2/CARD15 increase the risk of IBD significantly. These mutations, which fall in a region involved in peptidoglycan recognition (muramyl dipeptide), may affect innate immunity by decreasing the ability of intestinal epithelial cells and macrophages to clear intracellular bacteria.

Other genes in the IBD loci are still being studied. IBD3 on chromosome 6 contains the MHC region, and IBD5 on chromosome 5 contains the organic cation transporter (OCTN) gene cluster; mutations in both have been linked to increased risk of CD. Mutations in the chromosome 10 gene DLG5 appears to increase the risk of both CD and UC possibly because of its role in epithelial integrity.

Several environmental risk factors have been proposed in IBD. Cigarette smoking has divergent effects on CD and UC. Smoking is associated with a higher risk of developing CD and more rapid disease progression. Conversely, cigarette smokers are less likely to develop UC. Prior appendectomy appears to protect against the development of UC. Other environmental factors, such as breast-feeding, diet, measles vaccination, oral contraceptives, and various infectious agents, including mycobacteria paratuberculosis, have been tested, but none has been conclusively shown to effect the development or course of IBD. Luminal flora, however, clearly play a role in IBD. None of the 30-plus animal models of IBD develops disease when reared in a germ-free environment, and patients with CD lose tolerance to their own flora.

Whether primed by genetics or environmental factors, subsequent immunological deficits in the gut appear to lead to IBD. The normal intestine exists in a state of tightly controlled, physiologic inflammation. Innate and regulated adaptive immunity
allow for an effective immune response to pathogens with an equally rapid return to physiologic inflammation when the threat is neutralized. In IBD, however, the immune response is dysregulated. The key factor in disease pathogenesis appears to be the CD4+ T cell. Those found in the lamina propria have an enhanced activation status and secrete high levels of cytokines.19-21 In contrast to normal intestinal T cells, these cells persist after activation because of a defect in apoptosis.22 The type of dysregulated T cell is different in CD versus UC. CD appears to be mainly a helper T cell 1 (Th1)-mediated disease, while UC appears to be a mixed T cell response with components of both a Th2 (IL-5 and IL-13) and Th1 (IFNγ) response. Recent studies suggest that a distinct lymphoid population, NK-T cells, may be the source of the increased IL-13 seen in UC tissues.

More recently attention has turned to other members of the IL-12 family. Specifically in a number of animal models as well as in CD patients IL-23 has been shown to be playing a role in the inflammatory process. IL-23 shares its p40 subunit with IL-12. Thus antibodies directed against p40 would effectively neutralize both cytokines. IL-23 stimulates a novel set of T cells called TH17 or ThIL-17 cells. IL-17 is a potently inflammatory cytokine and is part of a larger IL-17 family. Like IL-23, the level of IL-17 has been shown to be increased in tissues from patients with CD. How much of a role this molecule plays in driving the inflammatory process in CD remains to be determined. Another IL-12 family member may be involved in the pathogenesis of UC. EBI3, one component of IL-27, is found at increased levels in UC tissues.

The newfound knowledge of specific immune deficits in both CD and UC has led to an explosion of targeted biologic therapies. Current goals in biologic therapy are to prompt T cell apoptosis, to inhibit Th1 activation, to inhibit the production and neutralize function of inflammatory cytokines, and to inhibit T cell recruitment to the lamina propria from blood vessels. Responses to these biologics have been encouraging in achieving and maintaining patient remission, yet they have also revealed new insights into the immune system in IBD that will enable the development of further biologic therapies.

References:


Session III

Diagnostic standards and developments in imaging
Endoscopic and histologic grading in IBD

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One of the most important factors to be taken into consideration when a therapy for IBD is instituted is the severity of disease activity. Decisions should in most cases not exclusively be based on symptom severity only, but on the combination of symptoms and laboratory findings, endoscopic appearance and histological findings.

Although a large number of parameters have been used routinely in the assessment of inflammatory bowel diseases (trips to the bathroom, abdominal pain, general well-being,…), it remains often unclear what exactly these terms mean (and what not), how reproducible they are and what their significance with regard to disease severity really is. Endoscopic descriptors were addressed in a study by Baron and colleagues, the first attempt to classify the severity of ulcerative colitis endoscopically. In a cross-sectional study the interobserver variability in describing the appearance of the rectosigmoid mucosa using a rigid proctoscope in patients with UC was evaluated. The endoscopic disease activity was rated using a 4 point scale (0-4) that was mainly based on the severity of bleeding. Notably, ulceration was not assessed. Interobserver variation was calculated for all variables and was the highest for ‘graded’ variables such as ‘redness’. However, the best agreement was reached for ‘friability’ (bleeding to light touch). Since then, several modifications to this score have been used in clinical trials. It is now generally accepted that ‘inactive’ UC represents absence of bleeding and friability.

In Crohn’s disease the situation is more complicated given the presence of lesions in other parts of the GI tract besides the colon and the discontinuous nature of the inflammation. Moreover, strictures may create problems to assess the whole colon/terminal ileum. This means that an ‘endoscopic score’ can be spuriously low if the disease is mainly located in the small bowel and this should be taken into account in clinical trials. The same is true for histological scores in Crohn’s disease, where the place of sampling can determine the type and severity of inflammation (e.g. in the edge or further away from ulcers). Despite all these problems, several reproducible scores have been developed and validated both for endoscopic and histological grading of Crohn’s disease. Since endoscopic endpoints are becoming essential in the era of biological therapies, more work in this area is definitely needed.

In conclusion, it needs to be said that an ideal scoring system for IBD is not available yet. We need to rely on the combination of clinical parameters, endoscopic appearance, histological lesions and biochemical findings. Novel scores that assess the impact of treatments on the natural history of the disease and the ‘burden’ of IBD need to be developed.
Conventional imaging

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Between 1994 and 2006, we performed 4000 conventional enteroclysis (CE) to achieve primary radiological diagnosis of different neoplastic or non-neoplastic small bowel diseases. In our series, 340 (34%) of last 1000 pathologic cases were inflammatory bowel disease (IBD). After the cases of partial intestinal obstructions by adhesions, it was a second largest pathologic group. Crohn’s disease (CD) was the must common IBD.

The indication of the CE was decided by abdominal surgeon or by gastroenterologist. Range of age was very large; from 7 to 68 years. We performed CE by standard technique descripted by Herlinger. 12F catheter was used for transnasal intubation. Tip of the catheter was positioned distal to the ligament of Treitz. All the procedure was navigated under fluoroscopic control. During the fluoroscopy, peristaltic activity of the small bowel which give valuable information in the evaluation of IBD, was examined. A total of 150-250 ml 70% W/V barium suspension was infused by an infusion pump. To achieve the double contrast phase, 1500-2000 ml of 0.5% methylcellulose solution in water was given. Infusion rate was modified according to the peristalsis. Images were obtained by a C-armed digital device. In 4000 CE examinations no complications related to the procedure were observed. We believe that CE performed with adequate technique was less invasive.

The common CE findings of CD were aphthous, linear or spiculated ulcerations, ulceronodular pattern, fold thickening, skip areas, strictures and fistulas. Staging of the CD were defined by CE findings based on its degree and anatomic extent. Stage 1 consisted of early lesions, with fold thickening, aphthous ulcerations, and mucosal granularity. Stage 2 consisted of intermediate lesions, with nodular pattern, linear ulcerations, mesenteric border rigidity with scalloping of the antimesenteric border, and a moderately thickened bowel wall. Stage 3 consisted of advanced lesions, with an ulceronodular pattern, deep ulcerations, and marked thickening of the bowel wall.

Endoscopic or radiologic all diagnostic modalities have their own advantages or disadvantages. Small bowel because of his length and anatomic location limits the extent of endoscopic examinations. Double contrast, long standing and homogenous optimal distension of the small bowel are essential for correct radiological interpretation, CE provide these essential conditions. As a result, properly performed CE demonstrates not only intermediate or advanced findings of IBD, but also early pathological mucosal findings to achieve an early diagnosis or reasonable differential diagnosis. This is especially important since the second majority of the small bowel diseases in our series consist of IBD.
Novel imaging

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Technical advances in cross sectional imaging, including rapid acquisition of high resolution images, in both static and dynamic mode, direct multiplanar imaging, utilization of novel contrast media and rich soft tissue contrast, have created a new imaging environment and imaging standards for assessing IBD.

In the current clinical routine, cross sectional imaging should demonstrate the transmural extent of inflammation, depict abnormalities beyond severe luminal narrowing, characterize individual lesions, identify intraperitoneal extension or extraintestinal complications of the disease process, present three-dimensional data, provide vascular information and confer to clinical management decisions.

An increasing role has been established for computed tomography in evaluating mural and extramural lesions and in assessing mesenteric involvement and ancillary intraabdominal findings associated with IBD.

CT enteroclysis and CT enterography have been proposed for a detailed assessment of the small bowel. CT enteroclysis combines the advantages of enteral volume challenge with the ability of cross sectional imaging and reformatting to depict mural and extramural manifestations of the disease. On CT, the thickened bowel wall may have a homogeneous or stratified appearance. Mural stratification is often seen in active lesions, particularly after intravenous contrast administration. Transmural inflammation of the small bowel in Crohn usually involves the adjacent mesentery. Fibrofatty proliferation of the mesentery, manifested as increased CT attenuation, is the most common cause of bowel loops separation in Crohn. Associated findings include mild reactive lymphadenopathy and mesenteric hypervascularity.

Recent reports are suggestive that MR Imaging of the small bowel can be successfully employed for the evaluation of IBD. MR enteroclysis is a novel imaging technique that combines morphologic and dynamic information. It provides three-dimensional imaging capabilities, excellent soft tissue contrast in breath-hold acquisition times and absence of radiation exposure.

MRE is equal to conventional enteroclysis in detecting, localizing and estimating the length of all involved small bowel segments. The characteristic discrete, longitudinal or transverse ulcers of Crohn disease can be easily disclosed, following optimal distention and homogeneous luminal opacification. Bowel wall thickness and length of involved segment can be measured accurately on MRE images. Using bowel wall enhancement patterns after i.v. contrast administration and/or dynamic imaging utilizing a cine-true FISP sequence, inflammatory type of stenotic lesions can be differentiated from fibrostenotic strictures.

Exoenteric manifestations of IBD, like fistulae, phlegmons or abscesses are demonstrated in detail, due to high contrast generated from the bright mesenteric fat. Disease activity can be additionally appreciated on MRE. Bowel wall thickness in excess of 7 mm, enhancing mesenteric lymph nodes after i.v. contrast administration, regardless their size, and presence of discrete ulceration have found to correlate favourably with active disease. Accurate individual lesion detection, provided by MRE, may successfully address clinical questions related to classification of Crohn disease subtypes.
Session IV

Cases and controversies
Case 1: Dominant pain in suspected CD
Case presentation

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UB; 68-year-old male, retired police officer
Date place: Mersin
Living in Istanbul
Weight: 60 kg height: 170 cm

Chief complaint: Abdominal pain, abdominal distension, diarrhea
Past medical history: Benign prostate hyperplasia (1999)
                Crohn’s disease (Diagnosed at year 2001)
                Cholecystectomy (1992)
                Appendectomy (1992)
                Depression (Diagnosis 2005)
Family history: Mother died from liver cirrhosis
                Father died due to urinary bladder carcinoma
Drugs: 5-ASA 3 g/day
         AZA 2.5 mg/kg/day
         Clomipramine hydrochloride 1 x 1 tab/day for depression
Social habits: Ex-smoker (35 pack-years)
               Quitted smoking 8 years ago
               Alcohol: social drinker

• Patients presented to the Emergency Unit with the complaints of severe abdominal pain, abdominal distension and a constipation since 4 days. He had a long history of abdominal pain around the umbilicus with 3 attacks of subileus which responded to medical therapies. He also lost 20 kg during the last 5 months with diarrhea more than 10 times/day with mucus.
• ESR: 60 mm/h, WBC: 9800/mm³, Hb: 10.7 g/dl, Plt: 337,000/mm³ Alb: 2.6 g/dl T.prot: 6.2 g/dl, CRP: 24.3. Stool exam for ova and parasites and stool culture were negative. Abdominal USG and esophagastroduodenoscopy were normal.
• Colonoscopy: Ulcers and nodular lesions at the terminal ileal mucosa Histopathology: Ileitis with ulcers: inflammatory exudates, crypt distortion, inflammatory cell infiltration, no granulomas detected.
Colonic biopsies characterized with ulcers, edema and crypt regeneration, no granulomas
• Enteroclysis: Significant dilatations on small bowel segments and mucosal ulceration.
• Attacks of subileus responded to medical therapy including IV steroids
• Steroid tapered and stopped within 3 months and the patient continued to AZA 2.5 mg/kg/day and 5-ASA 3 g/day.
• Patient’s diarrhea improved and his CRP levels declined after 4 months but his abdominal pain subsisted.
• Enteroclysis at 8th month of therapy showed edema and segmentation at almost entire ileum with significant narrowing in terminal ileum. IV steroids were added to treatment. He also received fluids and electrolyte replacement, TPN, ciprofloxacin 400 bid and metronidazole 500 mg bid. But he responded only partially to treatment.
• Repeated colonoscopy reconfirmed ulcers and nodular lesions in the terminal ileum with fibrotic stricture that prevented the passage of colonoscope.
• Pelvic MR revealed a concentric 3-4 cm long narrowed segment at the terminal ileum level and thickening of the walls of ileal loops jejunal segments were found to be normal.
• Patient refused operation or endoscopic balloon dilatation at this point.
• One month later he presented with abdominal pain, distension, nausea and vomiting. Multiple air-fluid levels seen on plain abdominal X-ray. Sedimentation rate: 105 mm/h, CRP: 44.9, Hb: 12.2 g/dl, MCV: 78, Wbc: 8700 mm^3, PLT: 286,000/mm^3, Alb: 3.5 g/dl, T.prot: 7.2 g/dl
• He accepted surgery and an ileocecal resection was performed Pathology of the resected segment confirmed the diagnosis of CD with granulomas.
• Methylprednisone was tapered within 2 months and the patient was kept on AZA 2.5 mg/kg/day in addition to 5-ASA 3 g/day
• He is still in remission at the present time
Case 2: Dominant diarrhea in suspected Crohn’s disease

Case presentation

S. Disibeyaz
Turkiye Yüksek, Ihtisas Hospital, Gastroenterology Division, Ankara, Turkey

Case Presentation

Mrs. H.O
38-year-old female, office worker, Ankara

Past Medical History

- Subtotal thyroidectomy for multinoduler goitre with thyrotoxicosis in 1990
- 2 pregnancies, 2 children, no abortion, no miscarriage

Social Habits

- Smoker for 20 years (10 cigarettes/day)
- Social drinker

Family history

- No family history for IBD

Medical History

In 1986, she suffered from diarrhea for the first time which immediately started following an antibiotic therapy for an acute upper respiratory system infection and had not ceased for almost 4 months. She had had at least 20 defecation in a day, without blood and mucus and she lost 10 kg at that time. After an antibiotic therapy which was given intravenously, her symptoms resolved in time.

In 1990, she had a subtotal thyrodectomy for multinoduler goitre with thyrotoxicosis then Propycil and a nonselective beta blocker were added to her medications after the operation.

She had no symptom until 1994 when she was hospitalized for the severe diarrhea which had been present since about 4 months. She had more than 30 watery defecation in a day without blood but some mucus and she had lost 12 kg before being admitted to the hospital. After the first evaluation, a total colonoscopy was carried out and showed a diffuse colitis involving the entire colon and a normal ileum; she was diagnosed as Ulcerative Colitis according to the histopathological findings.

Initially, Salofalk® tablets 3 mg/day were administered but she did no respond to 5-ASA treatment alone and 2 weeks later prednisolone at a dose of 40 mg/day was added. Her symptoms abated with prednisolone and she gained some weight. Prednisolone was subsequently tapered and discontinued and she was discharged with a maintenance dose of 5-ASA. She didn’t come back for her follow up visits for 10 years and she quitted all her medications (including Propycil) two and a half years later following the diagnosis. She denied any symptom during that time.
In September 2005, she complained of pain on her heels and was examined by an orthopaedic surgeon who diagnosed bilateral heel spurs. A watery diarrhea in increasing severity which was in a frequency of 7-8 stools/day at the beginning restarted while she was taking an NSAID prescribed by her physician. She discontinued the NSAID after she had diarrhea, but refrained to visit a doctor for almost 1 year.

When she was admitted to our clinic, she had a stool frequency of up to 30 times a day and she had lost 10 kg within a year. She also suffered from fever, arthralgia and mild abdominal pain which was relieved after defeation. She immediately underwent a total colonoscopy including ileal intubation which revealed a diffuse colitis involving the entire colon from rectum to the caecum in a continuous pattern with mucosal edema, loss of vasculary, increased mucus in the lumen in addition to mucosal ulcers, some being longitudinal and some aphtous in appearence. Ileocaecal valve and ileum were normal.

In biopsy specimens taken from the colon, histopathological findings revealed an intact surface epithelium with luminal irregularity and increased lymphoplasmocytic cells in lamina propria of the colonic mucosa. There was also a granuloma which was formed by epitheloid histiocytes and giant cells in a field. Distortion, dilatation and inflammation but no abcess formation were seen in crypts. Biopsies taken from ileum revealed a histologically normal ileal mucosa.

Barium series of the small intestine also showed a normal ileum and jejunum. An abdominal ultrasound examination revealed a wall thickness up to 8 mm along the entire colon.

Laboratory findings were as follows:

Hb: 10.1 g/dl, Htc: 30%, WBC: 10,000/mm³, Plt: 560,000/mm³, CRP: 16 mg/dl, Fibrinogen: 650 mg/dl, ESR: 72 mm/h, Blood sugar, urea, creatinine, LFTs and serum amylase were normal. Free T₃: 2.48 (2.5-3.9), FreeT₄: 0.51 (0.58-1.64). Microscopic examination of stool for E. histolytica and stool tests for EH antigen were negative.

Although some endoscopic findings were atypical (continuous involvement of the colon including rectum without skipped areas), histopathological findings including granuloma formation; some other endoscopic findings like longitudinal or aphtous ulcers along with some clinical symptoms (no blood and mucus in the stool), suggested Crohn’s disease (CD) and we accepted the case as a CD case located in the colon. Considering to relieve her arthralgias, salazopyrin tablets 4 g/day were given and azathioprine was added at an initial dosis of 50 mg/day which was further increased to 100 mg/day in 2 weeks.

Her first visit was 4 weeks later following the final diagnosis and when this presentation was written, her stool frequency had decreased to 5 in a day and she gained 4 kg. Her joint pain subsided and the laboratory markers showing the activity of the disease had improved.
Case 3: Refractory diarrhea in UC
Case presentation

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S-C, 24-year-old man

He was diagnosed with ulcerative pancolitis (UC) in 2003. Remission was obtained with steroid treatment. He was subsequently initiated azathioprine and mesalazine because of corticosteroid dependent UC. A year after the diagnosis was made, he had an episode of right dural sinus thrombosis owing to homozygous factor V Leiden mutation. Oral anticoagulant therapy was added to his treatment. Three months later he was admitted with watery diarrhea (6-7 times/day, without blood or mucus), bloating, malaise, weight loss, edema of the legs, and contraction of the arms and legs.

Physical examination revealed paleness, blood pressure of 80/60 mmHg, pulse rate of 110/min, 2/6 systolic murmur in all heart zones, decreased chest sounds on left basal zone, dullness to percussion on left costophrenic sinus, ascites under the umbilicus and bilateral pitting edema of the legs.

Laboratory analyses were as follows: Erythrocyte sedimentation rate: 6 mm/h, C-reactive protein: 64.7 mg/l, hemoglobin: 8.7 g/dl, white blood count: 5800/mm³, platelet count: 471,000/mm³, glucose: 98 mg/dl, lactic dehydrogenase: 568 U/l, creatinin: 0.2 mg/dl, sodium: 133 mEq/l, potassium: 2.7 mEq/l, calcium: 4.4 mg/dl, phosphorus: 3.1 mg/dl, total protein: 2.7 g/dl, albumin: 0.7 g/dl, gamma globulin: 0.6 g/dl, triglyceride: 98 mg/dl, cholesterol: 109 mg/dl, urinary analysis: normal, serum ascites albumin gradient: 0.7 g/dl, ascites total white blood count: 200/mm³, ascites glucose: 92 mg/dl, ascites lactic dehydrogenase: 28 U/l, and anti HIV and p-ANCA-negative.

Stool analysis revealed no erythrocyte, leukocyte, protozoon, protozoon cyst, helminth or helminth egg. There was abundant fatty acid and starch on stool analysis. Gastroscopy revealed cardia insufficiency, erythematous gastritis and duodenitis. Biopsy of duodenum showed chronic duodenitis; staining for amyloid was negative. No organism grew from culture of jejunal aspirate. IgA endomysial antibody was negative. All total serum immunoglobulin concentrations were low. Aeromonas hydrophila was detected by stool culture.

The patient was given fluids, albumin and calcium intravenously, and ciprofloxacin was started 500 mg bid orally according to antibiogram results. Upon this treatment, diarrhea began to resolve in a few days. Edema, ascites and pleural effusion disappeared with one week therapy. Control stool culture after the treatment was negative. Control laboratory results were as follows; calcium: 8.1 mg/dl, albumin: 2.5 g/dl, gamma globulin: 1.9 g/dl. Multivitamin was added to his treatment and he was discharged. On follow-up 1 month later, he was symptom free; his physical examination was normal. Laboratory analysis revealed erythrocyte sedimentation
rate: 6 mm/h, C-reactive protein: 3.1 mg/l, hemoglobin: 11.7 g/dl, white blood cells: 5800/mm$^3$, platelet count: 359,000/mm$^3$, albumin: 4.2 g/dl, gamma globulin: 1.9 g/dl. The patient is still being followed up from our outpatient clinic. He is symptom free and on remission.
What is the role of surgery in IBD?

Prof. Neil J. Mortensen, M.D., FRCS
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Whilst surgery has a pivotal role in the management of inflammatory bowel disease it cannot cure the disease and is reserved for its complications.

In ulcerative colitis the important indications for surgery are severe acute colitis, pre-cancer and cancer, and failed medical therapy – steroid dependent or steroid resistant. The choice of surgery is between a proctocolectomy or a restorative proctocolectomy with ileoanal pouch.¹

Functional results of the pouch operation seem to be stable with time and there is a 10% failure rate at around ten years.

In Crohn’s disease the situation is more complicated and depends on the anatomical distribution of disease.² Here obstruction and sepsis/fistula are more common indications. For small bowel disease the choice is between strictureplasty and resection. In the colon segmental resection may be possible or colectomy and ileorectal anastomosis where there is rectal sparing.

A defunctioning loop ileostomy can be used for diffuse colonic disease or uncontrolled perianal disease with proctectomy a last resort.

The key to successful management is a combined gastroenterologist/surgeon team with timely referral for surgery after aggressive medical therapy to ensure the patients highest quality of life.

References:


The changing face of IBD over the last decades

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IBD has become a real challenge to health in all developed and many developing countries over the world. Racial differences observed in the past had probably more to do with the risk of exposure to environmental factors causing the disease than with genetics. The highest incidence and prevalence rates of IBD are now observed in Manitoba (Canada) and are the highest among non-Aboriginal persons, persons with high socioeconomic status, persons with the lowest rates of enteric infection and the highest rates of multiple sclerosis (1). Immigrants in to areas with high prevalence have an increasing chance of developing IBD with time. In areas with high prevalence there is a strikingly high occurrence of familial clustering suggesting common exposure or shared susceptibility.

There is compelling evidence now that disturbed innate immunity in the gut predisposes to Crohn’s disease (2). Smoking remains the only environmental factor modulating both Crohn’s disease and ulcerative colitis although in opposite directions. Appendicectomy has been found to protect against ulcerative colitis (3). Although no single pathogen causing IBD has been identified molecular studies of the fecal flora show quantitative changes of the different species and loss of diversity. The course of IBD seems more aggressive in areas with high prevalence than in areas with low prevalence. Population based studies have shown that glucocorticosteroids do not change the outcome of the disease and have a deleterious effect long-term (4). Although immunosuppression is used more widely in the past decade this use has not decreased the need for surgery (5). The greatest breakthrough in therapy has been the introduction of the monoclonal antibody to TNF. This therapy has greatly improved the impact of our treatments on the quality of life of IBD patients and the need for corticosteroid use has decreased greatly. Moreover the need for surgery is decreased with these treatments (6, 7). Surgery in Crohn’s disease has become more conservative. Extensive resections have been replaced by short segmental resection and stricture plasties. There are much less intestinal cripples in the Crohn’s disease population.

The impact of better therapy for UC or need for surgery is not yet visible and we are awaiting the results of longitudinal studies.

It may be expected that therapy will greatly improve further in the coming years.
References:


Session V

Laboratory markers and other tools
Antibodies: Useful tools or pathophysiology markers?

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The IBD serologic panel is rapidly expanding. Anti-neutrophil cytoplasmic antibodies (ANCA) and anti-Saccharomyces cerevisiae mannan antibodies (ASCA) have remained the most widely studied markers but immune reactivity against a new group of bacterial antigens such as I2, OmpC and flagellin has been described in Crohn’s disease. Recently, anti laminaribioside carbohydrate (ALCA) and anti chitobioside carbohydrate (ACCA) were discovered using a glycan array. Several clinical avenues have been explored such as the usefulness of serologic markers as screening tools for IBD and in accelerating a diagnosis in patients with indeterminate colitis. Another area of interest is in disease stratification. Emerging data suggest there is a diversity of qualitative and quantitative responses to environmental antigens that differs among groups of IBD patients which may be associated with different clinical behaviors. As a result it may be possible to tailor therapy on the basis of serological responses. Prospective studies are needed before translating this concept in clinical practice. Clustering of IBD patients into more homogeneous subgroups based on antibody responses may help to unravel the pathophysiology of subsets of IBD. Genotype-serotype correlations between antibodies levels and variations in innate immunity genes associated with Crohn’s disease were demonstrated. Of note, the antibodies associated with Crohn’s disease are all directed against bacterial and fungal antigens. Candida albicans is one of several potential immunogens for ASCA and may be at the origin of an aberrant immune response in Crohn’s disease. Further understanding the genetic and environmental factors leading to antibody formation may offer some new clues regarding the origin of IBD.
Gastrointestinal Behçet’s disease

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Behçet disease (BD) is an inflammatory condition and mostly presents with oral aphths, genital ulcers. However, ocular, vascular, articular, nervous system and gastrointestinal involvements are also common. In contrast to high prevalence of BD in Turkey, Middle Asia, Japan and Korea, it’s rare in Europe and US. Gastrointestinal involvement is uncommon, encountered in even less than 1%, both in Turkey and western world. When compared to Turkey, which is an endemic country for BD and having relatively higher prevalence of inflammatory bowel disease (IBD) than Asia, much higher prevalence of Gastrointestinal Behçet’s Disease (GI-BD) in Asia, may need further evaluation. As it is in Crohn’s disease (CD) and intestinal tuberculosis (IT), GI-BD most commonly seen in ileo-cecal area of the intestine. Furthermore, macroscopic and microscopic details of gastrointestinal involvement are not specific for GI-BD, and easily confused with other IBDs’ like CD, Ulcerative colitis (UC), IT and some potential inflammatory reasons like NSAIDs use. Except relatively common hepatic venous vascular occlusion by thrombosis, call Budd-Chiari syndrome, other intestinal and extra intestinal involvements are rare. For reliable treatment data, controlled studies are lacking, and we mostly have to rely on the results of small or case based studies. In resistant cases, there are some limited supportive evidences about the promising effects of immunosuppressive and biologic agents. Surgical treatment may be considered for complications like perforation, bleeding, obstruction and stubborn fistula formation. Since flare ups are frequent even under medical treatment, if necessary, surgical treatment should be done conservatively, sparing as much small intestine as possible.
Molecular and biological markers for treatment decisions

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Crohn’s disease and ulcerative colitis are relapsing inflammatory disorders that require life-long therapeutic concepts. As many of the newer trials have focussed on therapy refractory disease most investigations have concentrated on this field. The following therapeutic scenarios could involve biomarkers: (i) Many therapeutic interventions induce remission (or maintain remission, respectively) in only a subgroup of patients. Therefore decision making for the choice of therapies is important. (ii) A loss of response in a therapy that was initially successful results in the clinical problem to redirect/change therapies. (iii) A third group of problems include the occurrence (and possible prediction) of toxicity.

(i) A particular problem in drug development is an excessive response to placebo. Analysis of placebo responses in trials with biological therapies (e. g. anti-TNF therapy) has revealed that in particular those patients who have low disease activity are prone to produce a placebo response. It has been therefore concluded that patients without objective (i. e. biochemical or endoscopic) parameters of inflammation should be re-evaluated before a biological therapy is initiated. Interestingly, only little prediction of response is possible in patients receiving the biological therapy. Here CRP is not overly helpful and the evaluation of genetic markers has not conclusively revealed alleles that would predict responses to anti-TNF therapy.

(ii) The loss of response to a previously successful biological therapy (i. e. anti-TNF therapy) in an ongoing maintenance program, is often related to the induction of anti-drug antibodies. The assessment of antibodies against the biological drug is often complicated by interference with drug levels in the circulation and lack of availability of laboratory tests. However, the detection of effective drug levels (that would be reduced in the presence of antibodies) is helpful to make the decision to change the drug.

(iii) The side-effect profile of some immunosuppressants is critically dependant on the activity of inactivating enzymes. Most important is thiopurine-methyltransferase (TPMT) that inactivates azathiorprine. Genetic testing for TPMT variants may identify incapacitated individuals but does not result in a comprehensive prediction of toxicity. The biochemical assessment of TPMT activity predicts a broader range of complications but does not result in a comprehensive prediction of all side-effects, too.

The use of biomarkers to guide therapeutic decisions is still based on incomplete datasets. The contribution to clinical therapy is limited.

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Stool tests: Are they useful?

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With the advent and popularity of panendoscopy many doctors have forgotten the limitations that endo-, entero and colonoscopy have including the associated inconvenience, discomfort and at times morbidity.

The seventies and eighties saw the introduction of a number of radioisotopic techniques to assess gastrointestinal function. This allowed accurate quantitation of protein loss ($^{51}$Cr-labelled albumen), blood loss ($^{51}$Cr-labelled red blood cells, bile acid absorption ($^{75}$SeSECAT), iron absorption ($^{58}$ and $^{59}$Fe), intestinal permeability ($^{51}$CrEDTA), $^{111}$Indium white cells scanning and faecal excretion. These set the standards for all subsequent tests, but the cost of these tests, the need for multiple patient visits, specialised labelling facilities and radiation meant that they never gained widespread use in clinical practice (as opposed to research). However the potential value of these tests if they could be simplified was realised.

A particularly good example of this was the development of non-radioisotopic methods for assessing intestinal inflammation. Conventionally this had been achieved by microscopy of stool, but the method lacks sensitivity. Stool TNF levels were tried but the problem of marker degradability was a problem. This was solved with the discovery of calprotectin which is a protein selectively localised to neutrophils and is not degraded by intestinal bacteria. The quantitative measure of calprotectin in faeces (ELISA) was shown to correlate significantly with the golden standards ($^{111}$Indium white cell faecal excretion and histopathological indices of inflammation). Extensive studies show that the main areas where the test is clinically useful

1. As a diagnostic screening test: enabling patients with the Irritable Bowel Syndrome (normal calprotectin) to be distinguished from patients with inflammatory bowel disease (raised calprotectin)
2. It is currently the most specific and sensitive indicator of disease activity in IBD
3. It is the most sensitive and specific test available for predicting imminent clinical relapse of quiescent IBD.
4. As an indicator of therapeutic response.

It has been suggested that the calprotectin test is suitable as a screening test for colorectal cancer. Numerous studies suggest that the test is abnormal in over 90% of patients with established colorectal cancer and about 50% of patients with colorectal polyps. It outperforms faecal occult bloods in this respect, but it is far less specific. Other markers of intestinal inflammation are in development such as faecal lactoferrin. It is possible that markers specific to other cells such as mast cells, lymphocytes, etc. will be developed. If used in conjunction with neutrophil marker analyses this will allow a greater discriminatory diagnosis yield.

Other faecal markers that are being developed use molecular biological methods to characterize DNA fragments and products of cancer cells. As yet these lack the sensitivity that is required for non-invasive screening tests, but their specificity is often excellent.
Session IV

Features of drugs used in IBD
5-Aminosalicylic acid

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Different drugs are in use for the treatment of IBD and among them 5-aminosalicylic acid (5-ASA; mesalazine) is most commonly prescribed. 5-ASA (1.5-4.8 g/day) is a drug of first choice in the treatment of mild to moderately active UC and maintenance of remission. The benefits of 5-ASA for the management of CD are controversially discussed [1-4].

As in IBD local inflammatory processes in the intestinal mucosa are involved, the therapeutic principles should be targeted to the affected areas. Therefore modified release formulations, suppositories, enemas and foam of 5-ASA have been developed [5]. Following oral or rectal administration of 5-ASA, the released active agent is taken up by the epithelial cells of the gut. During absorption of 5-ASA, intestinal acetylation to the inactive major metabolite Ac-5-ASA starts. Subsequently, 5-ASA is presystemically acetylated in the liver. Ac-5-ASA is eliminated by glomerular filtration and active tubular secretion [5].

The selection among the various formulations should be guided by the proximal extent of the disease. Enemas distribute 5-ASA from the rectum and sigma up to the transverse colon (absorption about 25% of the dose). 5-ASA from foam will reach the proximal sigmoid colon. When given as suppositories 5-ASA will be delivered only to the recto-sigmoid region (absorption about 13%). Combining rectal and oral administration of 5-ASA will achieve several-fold higher target levels in the colon and rectum than oral therapy alone. Thus, an increase in the clinical efficacy of 5-ASA can be expected [6, 7].

The intestinal release pattern of the various 5-ASA preparations has been extensively studied by pharmacokinetic and scintigraphic approaches. In general, the median systemic exposure to 5-ASA ranging from about 20 to 45% is comparable for all oral formulations [8] and inflammatory sites in the small and large bowel will be reached. Clinical outcome will depend on effective target concentrations in the affected intestinal mucosa which show a large interindividual variability [9]. Various modes of action are discussed for 5-ASA [10] and several studies indicate that it plays also a protective role in the chemoprevention of colorectal cancer [11]. It is evident from many trials that adverse events or withdrawals due to side effects (5-10%) are comparable to those in placebo treated patients [12] and that 5-ASA does not impair renal function [13, 14].

In conclusion, 5-ASA represents a first-line agent for the management of IBD particularly UC. In numerous studies it has proven its clinical efficacy and safety. Its topical action and pharmacological features have been well described.
References:


Glucocorticosteroids

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Treatment with glucocorticosteroids (GCS) induces an array of powerful anti-inflammatory effects, and these compounds remain our mainstay of medical treatment in moderate to severe attacks of inflammatory bowel disease (IBD).

The efficacy of orally given cortisone in moderate and severe attacks of ulcerative colitis (UC) was established in a randomised controlled trial (RCT) already in 1955, and subsequent studies with other GCS-agents such as hydrocortisone, prednisolone and betamethasone, have further confirmed the role of steroid treatment in various topical formulations for active distal UC and proctitis. Large RCTs have also proven the efficacy of GCS in active Crohn's disease (CD). A course of GCSs given parentally in high dose is still the standard treatment regimen for severe attacks of IBD (UC or CD) at most centers,

Clinical response is usually seen within a few days following treatment initiation with GCS, and the majority of patients will experience a profound improvement in bowel symptoms and general well-being. Complete remission, including endoscopic healing, is more often achieved in UC than in CD. However, 20-40% of IBD-patients respond inadequately, or not at all to GCS therapy.

The beneficial effects of GCS may be offset by troublesome and sometimes hazardous and/or irreversible, untoward effects including mood swings, acne, diabetes, and impact on bone metabolism. This has led to the development of improved GCSs with higher topical potency, rapid first-pass metabolism, and thus less systemic exposure in order to reduce the risk of adverse events.

Budesonide is the most widely evaluated and extensively used of the new topical GCS-preparations for IBD. In rectal formulations, budesonide is efficacious for active distal UC/proctitis and for pouchitis, but without causing appreciable impact on adrenal gland function. Oral slow release preparations of budesonide (9 mg/daily) are comparable to standard prednisolone treatment in mild/moderate, active ileocaecal/right colonic CD with a symptomatic remission rate after 8 weeks of 60-70%. However, budesonide causes less suppression of endogenous cortisol levels and fewer/milder GCS-related side-effects. Budesonide may have a role in the medium/long-term management of certain sub-groups of CD-patients, but appears not to be efficacious for postoperative prevention of recurrence.

Oral budesonide is the drug of choice for treatment of diarrhoea in patients with active microscopic (collagenous and lymphocytic) colitis. This particular group of patients may often be well controlled using low doses of budesonide as maintenance treatment (1-3 mg/day).

For active extensive and left-sided UC, several dedicated colonic slow-release preparations of budesonide are under evaluation in RCTs.
Various immunosuppressive and immunomodulatory drugs have been used for therapy of inflammatory bowel diseases (IBD). Azathioprine and its metabolite 6-mercaptopurine (6-MP) are key drugs for therapy of IBD and have been discovered by Elion and Hitchings. Starting with the initial description of Bean in 1962 and the large controlled trial by Present in 1980, numerous studies have addressed the role of 6-MP or azathioprine in IBD. It was found that azathioprine and 6-MP may induce clinical remission in IBD patients and, more importantly, are highly effective in maintaining remission. Mechanistically, Tiede and coworkers showed that azathioprine induces T cell apoptosis in IBD patients by specifically blocking the vav/Rac1 signaling pathway via 6-Thio-GTP. These data provide a rationale for the design of novel therapeutic strategies in IBD in the near future that are based on the specific blockade of the Rac1 pathway. Moreover, 6-Thio-GTP levels may be used to monitor azathioprine therapy in IBD patients.

In addition to azathioprine, other classical immunosuppressive drugs including methotrexate (MTX), cyclosporine, mycophenolate mofetil, leflunomide and others have been used for therapy of IBD. None of these drugs is as effective for maintenance of remission in IBD as azathioprine. One of the key clinical problems with azathioprine consists of its delayed onset of action, however. This suggests that novel drugs should be developed by improving the affinity of azathioprine to its specific target Rac1.
Antibiotics and probiotics in IBD

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Many experimental and clinical observations suggest a potential role for intestinal microflora in the pathogenesis of inflammatory bowel disease. Manipulation of the luminal content using antibiotics and probiotics may represent a potentially effective therapeutic option. The available studies do not support the use of antibiotics in ulcerative colitis. Antibiotics are effective in treating septic complications of Crohn’s disease. The use of antibiotics as primary therapy for Crohn’s disease is more controversial, although this approach is frequently and successfully adopted in clinical practice. Antibiotics are the mainstay of the treatment of pouchitis even if proper controlled trials have been not carried-out.

Probiotics are “living organisms, which upon ingestion in certain numbers, exert health benefits beyond inherent basic nutrition. Several mechanisms have been proposed to account for the action of probiotics. These include antagonistic activity against pathogenic bacteria, either by inhibition of adherence and translocation, or by production of antibacterial substances such as antimicrobial peptides and hydrogen peroxide. Probiotics also stimulate mucosal defence, both at the level of immune and epithelial function. Encouraging results have been obtained with probiotic therapy in experimental colitis. VSL#3, a highly concentrated cocktail of probiotics has been shown to be effective in the prevention of pouchitis onset and relapses. Results on the use of this probiotic in UC are promising, both in terms of the prevention of relapses and the treatment of mild-to-moderate attacks. Results in CD are not yet clear because of conflicting data and the limited number of well-performed studies.
Alternative medications

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Alternative medications are not well defined. In general this term denotes medications used in complementary and alternative medicine (CAM). Although great progress has been made in the development and use of effective drugs for IBD, about 30-50% of patients with IBD in Europe and North America are using unconventional therapies. Such therapies are mostly used complementary to conventional drugs and frequently patients do not inform their treating physicians about the use of CAM. Mostly used are homoeopathy and herbal medicine, making up for about 50% of CAM in IBD. Several surveys suggest that long lasting use of drugs (f.i. cortisone) with limited beneficial effects, serious side effects of conventional therapies and poor quality of the relationship between the patient and his treating physician determine the use of CAM. Despite its wide spread use the evaluation of the efficacy of CAM in IBD is difficult for many reasons, including chronicity and heterogeneity of IBD, different unpredictable and highly variable courses of the disease as well as weak definitions for treatment indications and for therapeutic endpoints.

Homoeopathy so far has not been studied specifically in IBD. A recent meta-analysis, however, comparing placebo controlled trials of homoeopathy and allopathy, including 110 homoeopathy trials and 110 matched conventional-medicine trials, led the authors to conclude, that he clinical effects of homoeopathy are placebo effects. There is no reason to assume, that homoeopathy in IBD will do better.

Contrary to homoeopathy, the effects of dietary fibre from Plantago ovata seeds, fish oil, germinated barley food stuff (a prebiotic), wheat grass juice, oral Aloe vera gel, bovine colostrum enemas, acupoint catgut embedding therapy, and the use of Chinese medicinal herbs f.i. as Jian Pi Ling tablets have been studied prospectively in patients with ulcerative colitis. Furthermore, derivatives of Boswellia serrata (incense), seal oil, curcumin (a natural compound used as food additive) and acupuncture and moxibustion were tested both in patients with ulcerative colitis and with Crohn’s disease.

Comparison of Plantago ovata seeds with mesalazine in patients with ulcerative colitis in remission as maintenance treatment over a period of 1 year showed no difference. Hoewever, the sample size was too small to test the equivalence hypothesis reliably. Boswellia serrata extract H15 reduced the Crohn’s disease activity index in 44 patients with active disease by a similar extent after 8 weeks as the comparator mesalazine in 39 patients, and therefore may be considered equivalent with mesalazine in the setting of this trial.

All other studies report “promising results”, but must be considered as preliminary and inconclusive so far. The fact, that herbal and other CAM treatments are meanwhile in the process of clinical testing is an important step forward, as contrary to general belief, that natural medicines are safe, numerous reports in the literature testify to the contrary, especially with herbal drugs.
Session VII

Treatment algorithms: “The standard patient”
Mild-to-moderate distal ulcerative colitis

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The terms left-sided ulcerative colitis (LSC), ulcerative proctosigmoiditis (UPS) and ulcerative proctitis (UP) apply to disease extending distal to the splenic flexure, or confined to the rectosigmoid colon, or limited to the rectum, respectively. The area of colonic involvement is not stable overtime since extension but also regression have been described. However, defining the extent of disease has several important therapeutic (and prognostic) implications.

Active mild UP is treated initially with 5-ASA suppositories (0.5-1 g daily for one month). Suppositories reach the proximal rectum and are more tolerable than foams or enemas. 5-ASA foams or enemas (1-4 g daily) are reserved for disease unresponsive to 5-ASA suppositories. Steroid suppositories or foams are effective alternative for patients unresponsive to or intolerant of 5-ASA. For moderate UP or if topical treatment fails oral 5-ASA and/or oral steroids are added to the topical therapy. Relief of proximal constipation may be useful for induction of remission before stepping up therapy.

5-ASA suppositories (0.5-1 g daily or every other day) are recommended for maintenance of remission of UP. For more active or frequently relapsing UP combined oral and topical 5-ASA therapy should be given.

Mild UPS is treated initially with rectally administered 5-ASA foams or enemas. Oral 5-ASA alone is less effective than topical 5-ASA. Combined oral (3-5 g/day) and rectal 5-ASA therapy is the treatment of choice for moderate UPS or mild UPS unresponsive to two weeks topical therapy; this may also prevent proximal extension of disease. Oral prednisolone with topical steroids are recommended for patients unresponsive to 5-ASA.

Mild LSC should be treated initially with rectally administered 5-ASA enemas (1-4 g) which can reach the splenic flexure. If the flare has not settled within two weeks steroid enemas or combined oral 5-ASA and 5-ASA enemas are an effective alternative. Oral prednisolone (starting dose 40 mg daily) and 5-ASA or steroid enemas are reserved for patients with moderate LSC or LSC unresponsive to combined oral and topical 5-ASA. As a general rule, UPS or LSC should not be considered refractory to 5-ASA before the optimal oral and local therapy is given. However, care should be taken to avoid prolonging inadequate treatment because this leads onto refractory disease.

Remission of UPS or LSC should be maintained with oral and topical 5-ASA. The frequency of 5-ASA enemas is depended upon the frequency and severity of prior relapses. Frequent relapses of disease (> 2/year) despite maximal oral and topical maintenance therapy should be treated with immunosuppressants.
Mild-to-moderate extensive ulcerative colitis

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There is a consensus to recommend the use of oral 5-ASA (4 g/day) as a first line treatment for patients with mild to moderate acute episodes of UC. The ECCO group also recommends to combine this treatment with local amino-salicylates. Steroids should be used only as second line treatment. We review the literature and discuss the evidence which led to these conclusions.

5-ASA is usually preferred to sulfasalazine for its tolerance and safety profile however sulfasalazine may be chosen first in case of associated arthritis. If the activity of the disease improves in the first 4 weeks and even if full remission is not yet obtained, it is recommended to continue with the same treatment as remission may take more time to be obtained. In fact: improvement of UC with oral 5-ASA is frequent but obtaining remission is usually slow.

A majority of the clinical symptoms relate to disease activity in the distal part of the colon, therefore we designed a study to investigate if adding a 5-ASA enema to oral 5-ASA has additional benefit for patients with extensive mild/moderate active UC. This randomised, double-blind study was performed in 127 ambulatory patients. All of them received 4 g/day (b.i.d. dosing) oral mesalazine for 8 weeks. During the initial 4 weeks, they additionally received an enema at bedtime containing 1 g mesalazine or placebo. Disease activity was assessed using the UCDAI with clinical and endoscopic signs at 4 and 8 weeks. Remission was obtained in 44% of the mesalazine enema group (Me) and 34% of the placebo enema group (Pl) at 4 weeks (p = 0.31) and in 64% Me vs. 43% Pl at 8 weeks (p = 0.03). Improvement was obtained in 89% Me vs. 62% Pl at 4 weeks (p = 0.0008) and in 86% Me vs. 68% Pl at 8 weeks (p = 0.026). A combined oral and local treatment with 5-ASA is therefore more effective than the oral treatment alone.

Systemic corticosteroids are appropriate if a prompt response is required (however this is not well defined in literature and we lack comparative studies in this setting), or if symptoms of active colitis do not respond to the combined treatment with mesalazine within 4 weeks.

Any patient who has an early relapse despite a maintenance treatment with mesalazine can be treated for this active episode with a higher dose of mesalazine and a combined oral and local mesalazine treatment but is also best started on an immunomodulator (in order to better prevent further recurrence).
Mild-to-moderate ileocecal Crohn’s disease

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The European evidence based consensus on the diagnosis and management of Crohn’s disease has stated that the treatment of active Crohn’s disease should be based on the site as well as on the activity and behaviour of the disease. According to this consensus budesonide 9 mg/day is the preferred treatment (EL2a, RG B). The benefit of mesalazine is limited (EL1a, RG B). Antibiotics cannot be recommended (EL1b, RG A). No treatment is an option for some patients with mild symptoms (EL5, RG D). The consensus favoured budesonide because it is superior to placebo (OR 2.85, 95% CI: 1.67-4.87) and 5-ASA 4 g/day (OR 2.8, 95% CI: 1.50-5.20). Budesonide achieves remission in 51-60% over 8-10 weeks. Budesonide is preferred to prednisolone for mildly active Crohn’s disease because it is associated with fewer side effects, although a Cochrane systematic review has shown budesonide to be somewhat less effective (pooled OR 0.69, 95% CI: 0.51-0.95).

Moderately active ileocecal Crohn’s disease should preferably be treated with budesonide 9 mg/day (EL1a, RG A) or with systemic corticosteroids (EL1a, RG A). Antibiotics can be added if septic complications are suspected (EL5, RG D). Prednisolone is associated with a good clinical response (92% remission within 7 weeks at the high dose of 1 mg/kg), but causes more side effects than budesonide. The consensus did not favour sole nutritional therapy, antibiotics (unless septic complications are suspected), Infliximab (until more date are available) or surgery for moderately active ileocecal Crohn’s disease as first line therapy.
Therapy of mild-to-moderate colonic Crohn’s disease

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Crohn’s disease (CD) is an idiopathic, inflammatory disorder of the gastrointestinal tract with various clinical presentations. Management targets of CD are to induce and maintain remission and to keep or improve a patient’s quality of life. The treatment plan for CD depends on the disease location and severity and should be individualized according to a patient’s response and tolerability to medical intervention. There are many drugs which can be successfully used for inducing remission. The choice of maintenance therapy depends on what drugs were used to induce remission. The patients should be educated about the side effects of drugs used and the importance of the adherence to the treatment (1).

There is only one therapeutic measure that should be advised in all CD patients: quit smoking. Treatments currently used for mild to moderate colonic CD are aminosalicylates, antibiotics and budesonide as shown in figure 1 (2). Enteral nutrition, given orally or via tube feeding, can be an alternative treatment. Because of the absence of important side effects and the presence of beneficial effects on nutritional status, the enteral nutrition can be preferred as an alternative treatment especially in pediatric patients and adult patients with malnutrition (3). Treatments for moderate to severe CD are corticosteroids, infliximab and immunomodulators (1,2).

Figure 1. Medical therapeutic approach in ‘inflammatory’ active Crohn’s disease (2)

Aminosalicylates

Aminosalicylates have been used for over three decades to treat mild to moderate CD (4). Sulfasalazine and 5-aminosalicylic acid (meselamine) are the commonly used aminosalicylates. Sulfasalazine contains a sulfonamide antibiotic (sulfapyridine) linked by an azo band to an anti-inflammatory salicylate (meselamine) (1). Two large and several smaller studies have shown that sulfasalazine is modestly effective in
inducing remission in CD, especially in colonic CD (5). It requires colonic bacteria to release the active moiety of the drug - meselamine. Since sulfapyridine is responsible for most of the side effects, meselamine formulations were developed. Although data derived from clinical trials of meselazine in CD do not show clear evidence of efficacy, meselazine has been accepted as first line treatment of choice for mild to moderately active CD by the majority of gastroenterologists (6). But Sandborn and Feagan suggested an algorithm which dropped meselazine in favour of sulfasalazine for left-sided colonic CD and budesonide for ileal and right colonic disease in their recent review (7).

**Budesonide**

Although the efficacy of classic steroids are well known for induction of remission of mild to moderate CD, their side effects are also well documented. Budesonide is a useful alternative to systemic steroids when steroid treatment is needed (8). The safety profile of budesonide is better than steroids but its efficacy is limited in patients with colonic disease (5).

**Antibiotics**

Many experimental and clinical observations suggest that intestinal microflora plays a potential role in the pathogenesis of inflammatory bowel disease. Manipulation of luminal contents using antibiotics is a potentially effective therapeutic option. Although antibiotics are used in the septic complications of CD, their use as a primary therapy in CD is more controversial (9).

**Conclusion**

The novel evidence based approach for the treatment of mild to moderate CD suggests sulfasalazine 3-6 g/day for up to 16 weeks for patients where disease is restricted to the colon and budesonide 9 mg /day for 8-16 weeks, followed by a tapering schedule over 2-4 weeks by 3 mg increments for disease located in the terminal ileum and right colon (5, 7). If patients do not respond to sulfasalazine, budesonide or antibiotics, classic steroids, immunomodulators and the new biological therapies should be considered (5).

**References:**


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Thus far all treatments available and most under development aim at inhibiting or modulating the effects of the array of mediators produced by inflammatory cells such as chemokines, cytokines and others. This has led to remarkable success using conventional treatments although neither cure of the disease nor even causal treatment has been achieved. More recently individual cytokines have been inhibited, in particular tumor necrosis factor. The results have somehow been disappointing although a better use of these expensive drugs might improve the outcome. Many other biologicals, for example inhibiting cell adhesion and other pro-inflammatory cytokines, have been developed and are under active investigation. However, thus far none has been shown to be a "magic bullet".

A few alternatives have been discussed, in particular autologous stem cell transplantation, the use of growth factors and hormones as well as completely different approaches using for example antidiabetic drugs and nutritional concepts. It has been in particular found that probably we need a number of different approaches since there is no such thing as Crohn’s disease and even ulcerative colitis which both represent a group of phenotypically and genotypically different disorders probably needing differentiated treatments.

More recently the concept of the defect barrier has achieved prominent attention again. Data from animals and from humans suggest that barrier disturbances including the lack of endogenous antibiotic peptides, erroneous recognition of commensal bacteria and abnormal bacterial epithelial interaction are main causes for these syndromes. Consequently endogenous and exogenous substances influencing luminal contents, in particular bacteria, as well as membrane functions have been tested. In particular probiotics, phosphatidylcholine and even bile acids have been studied, endogenous canabinoids and others will probably be tested as well.

In summary the shift of etiological and pathophysiological thinking from the general principles of inflammation towards more focused barrier concepts leads to novel treatment approaches which need however to be tested in appropriate trials. Pilot results are promising and seem to be more rational than the anticytokines strategies which have been tested in the last 10 years.
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Session VIII

Cases and Controversies
CD with fistula: Case presentation

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Mrs EG, DoB: 13-3-1969 in Piraeus.
She lives in Athens.

No family history of IBD.

Past Medical History: Appendicectomy at 16 years.
No autoimmune diseases.
One abortion. One miscarriage.

Smoker for 16 years (15-20 cigarettes a day).
Social drinker.

- CD was first diagnosed in 1994 when she was 26-year-old. The disease involved the terminal ileum and the entire colon in a discontinuous way.
- In the next 3 years she received repeated courses of oral and rectal steroids and oral sulfasalazine. Finally, in 1997 she underwent an operation in a private hospital for stricturing disease: a stenosed part of the terminal ileum proximal to the ICV (the ICV was preserved) and the sigmoid colon were excised.
- Between 1997 and 2003 she was followed in a private Clinic. She had had at least one annual flare of CD which was treated with oral steroids; mesalazine 1 g tid was given for maintenance treatment.
- In 2003, she was admitted in another private clinic with fever, diarrhea, three perianal fistulae, type I arthritis, and finger clubbing. She received IV steroids for 10 days combined with oral azathioprine (150 mg a day) but azathioprine was stopped 15 days later because of pancreatitis. She was given oral steroids and then long term oral budesonide.
- 9 months later she developed severe type I arthritis and received rofecoxib which led to another flare of disease. She also complained for severe dyspareunia. She then was admitted to our hospital.
- On examination, she was pale and cachectic. Her height was 167 cm and the body weight 45 kg, the pulse rate was 98/min. She was feverish and had mild rebound tenderness in the lower abdomen. There were three actively draining perianal fistulae (one to the buttock), finger clubbing, arthritis (elbows, knees, ankles), and erythema nodosum (tibiae). The CDAI was 320.
- WBC 16,260 (P 73%, L 16%, M 8%, E 3%), Plats 674,000, Hb 9.8 g/dl, Hct 31.2%. Fibrinogen 737 mg/dl (200-400), INR 1.14, ESR 71 mm/h, CRP 18.4 mg/dl. Urinanalysis normal, Urine culture –ve.
- Blood sugar, urea, creatinine, LFTs and serum amylase were normal. HBsAg and anti-HCV were –ve.
- Cholesterol 140 mg/dl, albumin 3.1 g/dl, serum Fe 15 µg/dl, ferritine 8 mg/ml, Vit. B12 184 (160-970 pg/ml)
• Serum Immunoglobulins, electrophoresis, anti-dsDNA, SMA, AMA, LKM-1, anti-TG, anti-TPO, pANCA, cANCA, AGA, EMA, anti-tTG were all –ve. ANA were +ve (1:160).
• Abdominal US: No abnormalities were seen from the liver, gallbladder, bile ducts, pancreas, spleen, kidneys.
• Abdominal CT scan: Diffuse inflammation of the perirectal fat tissue with a fluid collection in the left perirectal area. There is also another fluid collection in the left buttock muscle which is enhanced by the IV contrast medium. A similar lesion is seen in the neighboring subcutaneous fat tissue which communicates to a draining fistulous tract to the overlying skin.
• Enteroclysis: Approximately 10 cm from the ICV there is a cobblestone pattern with stenosis of the lumen (length 15 cm) and deep ulcers. More proximally mild thickening of some bowel loops. The ICV is not stenosed.
• Colposcopy: No fistula was seen.
• Colonoscopy: Severe colitis and terminal ileitis with ulcers of all size and shape and numerous pseudopolyps. The opening of a fistula is seen in the rectum which does not communicate with the vagina. Multiple biopsies were taken which confirmed the diagnosis of Crohn’s ileitis and colitis.
• She received fluids and electrolytes, TPN, ciprofloxacin (400 mg bid IV) and metronidazole (500 mg bid IV). The patient was examined under anesthesia and setons were placed to ensure adequate drainage of fistulae and fluid collections were drained under CT guidance. IV methylprednisolone (60 mg IV in 3 divided doses) was started and the patient was offered infliximab (5 mg/kg) at weeks 0, 2 and 6 and subsequently q8. The patient showed a dramatic improvement with rapid resolution of diarrhea and fever, improvement in her general state of health and well-being and normalization of white blood cell counts, ESR, acute phase reactants, and human albumin.
• Capsule endoscopy was performed after the third infusion of IFX which revealed focal edema, erythema and mild scattered aphthous ulceration. A transient stop of capsule was noticed in two areas of the terminal ileum in the absence of ulceration which probably represent fibrostenotic areas. A colonoscopy showed complete healing of colonic lesions.
• The patient continued on IFX q8, fistula drainage was stopped and setons were removed with complete fistula closure.
• However, two years later she became pregnant. She received the last infusion of IFX during the first trimester of her pregnancy before stopping therapy. She had an uneventful pregnancy and delivered a healthy baby.
• After delivery she was treated with mesalazine 1 g tid and remained in remission for 18 months. She then developed mild diarrhea which progressively worsened, malaise, low grade fever, abdominal and perineal pain and finally a draining fistula in the perineal area. There were no symptoms or signs of intestinal obstruction. Laboratory tests showed a rise in WBC counts, ESR, CRP, and fibrinogen. An abdominal MRI showed a fistulous tract communicating to the anal verge. A colonoscopy revealed moderate active colonic inflammation.
• The patient was started on antibiotics for 14 days and then infusions of IFX (0 and 8 weeks and then q8. However, soon it was realized that she needed higher doses of IFX or shorter infusion intervals to maintain disease remission and fistula closure. By the time this case is presented there will be more information on her long-term outcome.
Fistulizing Crohn’s disease: Conservative approach

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Crohn’s disease (CD) is a chronic inflammatory disorder which affects gastrointestinal tract transmurally and can be complicated by fistula formation. A population based cohort-study reported 33% of cumulative incidence of fistula formation after 10 years and 50% after 20 years of disease. The first step should be define the exact anatomic feature of fistula and rule-out infectious complications like abscess. The only treatment for abscess is surgical drainage. A good collaboration between the gastroenterologist and the surgeon is essential in management. Metronidazole and/or prophylaxis are the first choice in simple fistulizing CD with a modest efficacy. If complex fistula is the case it would be wiser to start with antibiotics and AZA/6-MP together as first line treatment. Antibiotics can be a bridge until AZA-6-MP start to work. Infliximab has clearly proved its efficacy in the short-term treatment of fistulizing Crohn's disease. Complete healing of fistula was reported in 55% of patients compared to in 13% of placebo in the first trial. Further studies reported similar impressive results. It is generally well tolerated and safe, but serious side effects might occur and careful follow-up is mandatory. The ACCENT II maintenance trial showed that at 54 weeks, 46% of patients receiving infliximab continued to respond to treatment, compared with 23% in the placebo group. Concomitant use of immunomodulators with infliximab seems to decrease antibody formation. Duration, intervals and dosage of infusions still need to be determined for longer periods since CD is a life-long disorder. AZA/6-MP seems still the mainstay of long-term treatment of fistulae. Methotrexate is another immunosuppressant drug shown to be superior to placebo both in remission induction and maintenance therapy in CD. But the data on fistulizing CD is very limited. Cyclosporine and tacrolimus could be tried as induction therapy in refractory cases but they have no role in maintenance. Hopefully time will provide us more and accurate data not just for infliximab also for developing new biological therapies.
Fistulizing Crohn’s disease: The aggressive approach

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Careful assessment is required before embarking on a course of medical or surgical therapy for fistula. Perianal fistulas, in particular, may be simple and superficial, or may be deep, traversing the pelvic floor musculature, and complex. Other complicating factors that need to be defined include the presence of anal stricture or abscess. Proper evaluation of perianal abscess starts with physical examination to note the location and number of draining abscesses. Most importantly, the presence of tenderness, and possibly fluctuance should be a clue to underlying inadequately treated abscess. Because of the importance of understanding the course, complexity and complications of perianal fistula, pelvic MRI and/or examination under anesthesia (EUA) should be undertaken. EUA, in the hands of experienced surgeons, will not only define the course of the fistula, but will permit drainage of abscess and placement of a seton, a non-absorbable band threaded through the fistula outer and inner orifices, and through the anal canal and secured into a loop. This ensures that recurrent cycles of abscess and drainage will not occur and facilitates medical therapy.

Medical therapy for simple fistulas may consist solely of antibiotics, typically metronidazole and/or ciprofloxacin. In many cases, these superficial fistulas may heal. Deeper and more complex fistulas may require a more aggressive approach. Observational data suggest that 6-mercaptopurine/azathioprine may be effective in closing fistulas. The effect, however, is slow in onset.

Infliximab has been demonstrated to induce a “fistula response,” meaning a reduction in the number of draining fistulas by 50% or more for an individual patient, in about two-thirds of patients. Maintenance therapy with infliximab can prolong the time to loss of response significantly. Chances of success appear to be higher in patients on concomitant antibiotics, and/or who have had seton placed prior to initiating treatment. Similarly, adalimumab has been shown to induce and maintain closure of fistulas in secondary analyses of a large randomized controlled trial.

Patients who fail to respond to anti-TNF agents may consider treatment with tacrolimus. This agent has been demonstrated to be effective in short term induction of fistula closure. The side effect profile, however, is prohibitive. Patients who fail medical therapy may need permanent diversion and proctectomy, as surgical approaches to fistula, such as mucosal or gracilis flaps, have a high rate of failure.

In summary, the treatment of fistulizing Crohn’s disease remains challenging. Optimal approaches incorporate careful evaluation, and combined medical and surgical therapy.
The surgical approach

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Miss A.K, female, 20-year-old, student.

This patient (pt) was diagnosed to have ulcerative colitis (UC) 3 years ago. Initially the disease was limited to rectum and she was managed on Salofalk® suppositories.

She complained of arthralgias in both elbows and knees and was given rofecoxib after a year and a half. Her colonoscopy 2 weeks after the onset of arthralgias, showed extensive colitis; biopsies confirmed the diagnosis of UC. The patient was given oral and rectal mesalazine in addition to prednisolone 40 mg/day; the dose of prednisolone was tapered by 5 mg per week. She was improved on prednisolone. However, when the dose of prednisolone was reduced to 15 mg/day, symptoms relapsed. She was then given oral azathioprine (2 mg/kg/day) on top of Prednisolone and mesalazine. As many other patients on immunosuppressives she experienced an attack of pneumonia which could have been fatal. The attack was eventually over and a colonoscopy performed a year later showed a near normal colonic mucosa and biopsies revealed quiescent UC.

The next attack was precipitated after a flu shot few days later and this time she did not respond to steroids. Only very high dose of IV steroids offered some improvement but could not be sustained even with additional Remicade®. She eventually underwent emergency subtotal colectomy to save her life.

In essence I disagree with the way she was managed since the beginning. The universal management of UC needs a colorectal surgeon to see the pt immediately after the diagnosis. A young girl diagnosed to have UC at the age of 17 was very likely to survive a difficult life. She spent almost half of her life in hospital since the diagnosis. She is a difficult case that only high dose steroids can temporarily alleviate the picture. As we know from the young transplant patients, most of them experience life threatening infections and even fatal malignant disease secondary to long term immunosuppressive usage. Even if the clinical picture could have been controlled by immunosuppressives and steroids, I would not expect a safe future for her as long as she was under treatment with such drugs. Even if she survived everything and reached to 40s or 50s, it should have been very likely for to develop dysplastic colon by those ages. As we understand from her refusal of CyA, she might have some information about what may happen to her after using such drugs for a long time.

Is it really necessary to be such stubborn to treat this surgically correctable condition, by risky medical drugs. In my clinical experience, I have many youngsters who refused when I or a surgeon honestly informed them about the side effects of medical treatment of UC and also the outcome of surgical management.

The contemporary surgical treatment of UC is restorative proctocolectomy. This procedure includes removal of diseased colon and rectum and formation of an ileal
pouch to join the rectal remnant of a centimeter long. This technique has a very high quality of life scores especially in young patient with negligible mortality and acceptable morbidity. A successfully operated pt needs no further medications, no diet, and no risk of colonic cancer. The timing of surgery is also very important. Elective surgery for this procedure is always with less mortality and morbidity and probably shows a better long term success compared to emergency surgery. Another mistake for the current case was to postpone the surgical intervention to need an emergency operation. A subtotal colectomy is almost always performed without rectal amputation and forming an ileal pouch is not safe to do under emergency conditions. These patients frequently need another session to take the rectum out and form the pouch and diverting ileostomy. A third session will be needed to accomplish the bowel continuity. On the other hand, she could have been operated on elective basis in two and occasionally one session surgery.

In conclusion, this case should have been offered restorative proctocolectomy much earlier than she was offered emergency subtotal colectomy.

Mrs EG

Her past medical history includes an appendicectomy at the age of 16 and smokes 2 cigarettes a day which may be related to her CD. She had 2 surgeries for ileal and sigmoid strictures. She had frequent flare ups and frequently put on steroids to alleviate the clinical situation. She had a discouraging experience with azathioprine which was stopped 2 weeks after start because of pancreatitis. She developed extraintestinal disease including joint and skin involvement and hospitalized for complicated perirectal and probable intraabdominal fistulous disease. Infliximab offered dramatic improvement with rapid resolution of diarrhea and fever, improvement in her general state of health and well-being and normalization of white blood cell counts, ESR, acute phase reactants, and serum albumin level. Complete healing of perianal fistulas followed. Infliximab treatment was suspended after she was pregnant and unfortunately everything came back after a year and a half. She was back on infliximab and needs higher doses and more frequent shots.

This is an extremely difficult case of CD. Surgically there is nothing much to offer at this point. For the strictures of the small bowel repeated stricturoplasties can be performed and the small bowel should be greedily preserved and unnecessary resections must be avoided. However, surgeons can be more liberal in offering a surgical removal of colon and rectum if the general condition and quality of life of the patients are worse with debilitating strictural and/or fistulous disease. Although a stoma interferes with the scores of well being, sometimes surgeons are offered by the patients to take the rectum out for ending the misery.

Generally, partial resections and stricturoplasties can be performed for the small bowel disease, and when the colon and rectum can be removed when the medical efforts are no longer helpful. General quality of life of the patients definitely improved after such resections. In other words, surgical treatment should be reserved for the patients whose quality of lives are extremely impaired by the disease and even living with a stoma is better than living with the disease per se.
Refractory UC: Case presentation

N. Apostelou
Evangelismos Hospital, Gastroenterology Clinic A, Athens, Greece

Mis A.K., female, 20-year-old, student.

PMH:
1. Tonsilectomy at 4 years.
2. Appendicectomy for Right I liac Fossa pain at 9 years. No histology is available.
3. Allergic rhinitis

Social habits
She does not drink
Non-smoker

Family history
1. Father: Coronary artery disease (smoker)
   Hypertension
2. Mother: -ve medical history
3. One older sister: -ve history

Current medical condition

Three years ago, when she was a pupil in last class of the High School, she complained for hard, occasionally bloody, constipated stools and discharge of blood and mucus. She visited a gastroenterologist in Athens and underwent a flexible sigmoidoscopy which revealed disease limited to the rectum. Biopsies taken proximal and distal to the margins of inflammation confirmed the diagnosis of ulcerative proctitis. Laboratory tests were unremarkable. She was treated with mesalazine suppositories 500 mg bid which led to resolution of symptoms.

In the months to follow she had had now and then relapse of the same symptoms which were treated with mesalazine suppositories. However, 18 months after the diagnosis she complained for arthralgias in both elbows and knees and was given rofecoxib and omeprazole for 14 days. Fifteen days later she developed acute bloody diarrhea and abdominal pain but no constitutional symptoms. She contacted her gastroenterologist who suggested treatment with oral mesalazine 3 g daily and rectal mesalazine (4 g daily). She showed no improvement and therefore came to Athens again where she had had a total colonoscopy which showed extensive colitis; biopsies confirmed the diagnosis of UC. Laboratory tests showed mild leucocytosis, an elevated ESR (35 mm/h) and CRP (2.1 mg/dl with ULN 0.6 mg/dl). The patient
was given oral and rectal mesalazine in association with prednisolone 40 mg/day; the
dose of prednisolone was tapered by 5 mg per week.

The patient improved on prednisolone and indices of inflammation were restored to
normal. However, when the dose of prednisolone was reduced to 15 mg/day bloody
diarrhea relapsed. She was admitted to the hospital and offered a short IV steroid
regimen coupled with oral azathioprine (2 mg/kg/day). She was discharged from the
hospital and returned to the island she was living on with oral prednisolone,
mesalazine and azathioprine. There was no information what so ever regarding
instructions related to the safety of azathioprine treatment; however, 2 months later
the patient developed chills and rigor, high fever and dyspnoea. She was admitted to
the local hospital and pneumonia was diagnosed on a chest x-ray. The WBC count
was 1500 with 35% polymorphs. Azathioprine was discontinued, fluids, electrolytes
and antibiotics were given IV and on the second hospital day she was transferred to
the same hospital in Athens. There, she had had a joined consultation by a lung
specialist, a gastroenterologist and a hematologist. In addition to the previous
treatment she received sagramostim daily for a week. Symptoms improved in the
next two weeks and she was discharged from the hospital on oral and rectal
mesalazine, and instructions from the hematologist to receive another weekly course
of sagramostim. The WBC count was 4500 with a normal differential.

The patient stayed in remission on oral mesalazine (3 g/day) and mesalazine
enemas (4 g/week) for 18 months. A partial colonoscopy performed 12 months after
discharge from the hospital showed a near normal colonic mucosa and biopsies
revealed quiescent disease.

Then she had a ‘flu’ vaccine. Fifteen days later she developed up to 3 bloody bowel
motions daily, but no abdominal pain or constitutional symptoms. She had a mild
leucocytosis, and mild elevation of the CRP and ESR. Stool tests for pathogens
(including C. difficile) were negative. LFTs were normal. She contacted us on the
phone and received 20 mg oral prednisolone, rectal mesalazine enemas nocte, oral
calcium and vit. D supplements. Symptoms worsened over the next seven days and
she was instructed to increase the dose of prednisolone to 40 mg/day. Despite that,
symptoms did not improve at all and the patient came to Athens and was admitted in
the hospital to receive IV steroids.

On admission, she was a little tired but otherwise well. BP was 100/70 mmHg, the
pulse rate was 95/min, temperature was 37.5-37.8°C. She had mild abdominal pain
over the LIF relieved by defaecation. She opened her bowel 8-10 times daily and the
stools were anchovy sauce. She was a little pale but otherwise normal. Mild
tenderness was elicited on deep palpation on the LIF. The WBC count was 13,500
with 85% polymorphs, the ESR was 56 mm/h and the CRP was 4.5 mg/dl. An
abdominal x-ray revealed mild small bowel ileus but no fingerprints or colonic
dilatation. However, no stools were seen and there was diffuse colonic edema. An
abdominal US was reported ‘normal’. A chest x-ray was normal and a PPD test was
negative. Stool tests for parasites and common pathogens were negative. A flex-
sigmoid showed severe diffuse colonic inflammation. Random biopsies were taken and
histology confirmed again the diagnosis of severe UC but was negative for the
presence of CMV inclusions. Blood tests for CMV-Ag, IgM anti-CMV antibodies and
PCR for CMV viral load were negative. Serum IgG anti-CMV was positive as were
IgG anti-EBV, -HSV1 and HSV-2. pANCA were positive. Serum ANA, SMA, anti-DNA, AMA, ASCA, EMA and tTG were all negative. Serum immunoglobulins were normal.

She was treated IV methyl-prednisolone (70 mg in 3 divided doses/day), rectal drips of hydrocortisone (100 mg bid), TPN (2400 kcal/day), NPM and IV ciprofloxacin and metronidazole. At the end of day 3 and also 5 of intensive IV steroid regimen she had no constitutional symptoms and signs. However, she was still complaining for abdominal pain, passing 4-6 liquid bowel motions with blood and pus. In addition, no improvement was seen in the sigmoidoscopic appearance or the presence of small bowel ileus on abdominal films. She had still elevated WBC and platelet counts, the ESR was 45 and CRP 4.5 (ULN 0.5 mg/dl). The albumin was 3.3 g/l and LFTs were normal. Serum cholesterol was 140 mg/dl.

The patient did not agree to receive CysA. However, she consented to treatment with infliximab (5 mg/kg). However, on the 8th hospital day (3 days after infusion of IFX) her clinical condition deteriorated and she underwent emergency subtotal colectomy. The continuity of the GI tract was restored with an ileal pouch-anal anastomosis (IPAA).
Refractory ulcerative colitis: The conservative approach

Prof. H. Selwyn Odes, M.D.
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The patient is a 20-year-old female who has had ulcerative colitis (UC) for 3 years, and has now undergone surgery after failure of medical treatment. A severe attack of UC is always life-threatening and requires intensive treatment to induce a remission, and then lifelong maintenance therapy to prevent relapses and perhaps colorectal cancer. Therapeutic choices with traditional medications are limited. Mesalazine (5-ASA) in high doses (up to 6 g/day) is effective in improving acute mild to moderate UC, being twice as good as placebo (OR 0.39; CI: 0.29-0.52), but not better than sulphasalazine. Half the improved case will go on to remission. 5-ASA has been shown also to delay recurrence in UC. A dose of 3 g daily is advised. Side effects may require stopping the drug in up to 15% of patients, but these are mild. Nephrotoxicity is rare, being partly idiosyncratic and partly dose-related. 5-ASA cannot control severe colitis. Corticosteroids however are highly efficient for inducing remission in acute moderate to severe UC. Onset of action is rapid, with a response noted in 2 weeks or less. Toxic effects are predictable. Prednisone in a dose of 1 mg/kg is adequate and the oral route is probably as effective as the IV route. Smaller doses are not effective. However, in severe disease IV steroids in high doses are usually used. Proper attention must be paid to bowel rest, and to the levels of serum electrolytes, haemoglobin and albumin. Patients will not respond readily if these are not corrected. As a rule-of-thumb, 60% of patients will go into remission, 20% will become steroid dependent, and 20% will not respond. Too rapid reduction of the dose will result in relapse. Budesonide as enemas has been used for active distal colitis but has no place in severe extensive UC. Corticosteroids and budesonide are not effective in maintaining remission. The purine antimetabolites azathioprine 1.5-2.5 mg/day or 6-mercaptopurine 0.75-1.5 mg/kg are both effective in maintaining remission in UC. However, they are not effective in controlling acute UC given their perceived long onset of action. Intravenous azathioprine (40 mg/kg i.v. azathioprine as three 8-h infusions over 3 days) appeared to be safe and of clinical benefit in inducing response and avoiding colectomy in severe steroid refractory ulcerative colitis in a small controlled trial, but there are no follow-up studies. In severe UC treated with corticosteroids it is wise to add imuran in the early stages of steroid therapy and continue this drug when the steroids are stopped. Leukopenia is a myelotoxic effect noted in some individuals with low activity of the enzyme thiopurine methyl transferase (TPMT). TPMT levels can be measured, as can the TPMT genotype. Methotrexate was shown to be ineffective in chronic UC and has no place in acute UC. The likely role of bacteria in the pathogenesis of IBD provides the rationale for using antibiotics. While there remains much uncertainty about the optimal use of antibiotics in the treatment of UC, their use in acute UC as an adjuvant therapy is advisable.
Refractory UC: The aggressive approach

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Mayo Clinic, Rochester, MN, USA

Refractory ulcerative colitis includes the outpatient with moderate to severe ulcerative despite oral corticosteroids and azathioprine, and inpatient with moderate to severe symptoms despite intravenous corticosteroids. In the outpatient setting, the treatment of refractory ulcerative colitis requires an agent that is effective for both induction and maintenance of response and remission. The only agent proven effective in this setting is the chimeric monoclonal antibody to tumor necrosis factor (TNF) infliximab. Infliximab is administered as a loading dose induction regimen of 5 mg/kg administered at 0, 2, and 6 weeks, and then as a maintenance regimen of 5 mg/kg every 8 weeks. It is unclear whether concomitant immunosuppressive with azathioprine should be routinely administered to prevent antibodies to infliximab. There is no clear evidence that concomitant azathioprine is required for synergy for efficacy. In the inpatient setting there are 3 treatment options available in clinical practice (cyclosporine, tacrolimus, and infliximab) and one additional investigational agent (visilizumab). Cyclosporine is administered as a continuous intravenous infusion at doses of 2-4 mg/kg/day. Two mg/kg/day appear to have similar efficacy to 4 mg/kg/day and is better tolerated. Cyclosporine can be co-administered with intravenous corticosteroids, or as a monotherapy. Tacrolimus is administered oral at doses adjusted to target blood concentration ranges of 5-10 ng/ml (low dose) or 10-15 ng/ml (high dose). High dose tacrolimus appears to be more effective than low dose tacrolimus but is associated with more frequent side effects. Patients who respond to either intravenous cyclosporine or oral tacrolimus in the inpatient setting should continue the same therapy administered orally in the outpatient setting for approximately 3 months while corticosteroids are tapered and discontinued and maintenance therapy with azathioprine or 6-mercaptopurine is initiated or optimized. An alternative to treatment with cyclosporine or tacrolimus in inpatients with steroid-refractory ulcerative colitis is infliximab. Infliximab is administered a loading dose induction regimen of 5 mg/kg administered at 0, 2, and 6 weeks, and then as a maintenance regimen of 5 mg/kg every 8 weeks. Inpatients who fail to respond to 1-2 induction doses of infliximab will likely require colectomy before the 2nd or 3rd dose of infliximab is administered. Which of these 3 agents is the preferred option for inpatients who fail intravenous corticosteroids is unknown. In addition to these 3 currently available treatment options, phase III trials with visilizumab (anti-CD3 antibody) for steroid-refractory ulcerative colitis are currently underway. The treatment options for patients with refractory ulcerative colitis have increased dramatically in recent years, and further advances in the near future are likely.
Surgical treatment of refractory ulcerative colitis

Sotiris Baratsis  
General Surgeon, Head of 1st Surgical Unit, Evangelismos Hospital, Athens, Greece

Ulcerative colitis is characterized by colonic inflammation and extraintestinal manifestations.

The treatment of the disease depends on the extent and severity of the disease.

Surgical treatment cures completely the colonic component of the disease, controls most of the extraintestinal manifestations and almost eliminates the danger of future development of cancer.

The indications of surgery concern:
1. Treatment of acute colitis refractory to conservative treatment.
2. Treatment of chronic colitis in symptomatic disease when is poorly controlled or because of side effects of conservative therapy.
3. Prophylactically to avoid development of cancer in longstanding symptomatic or asymptomatic disease.

In the acute colitis there are two absolute indications for surgery when medical treatment fails:
1. Severe uncontrollable bleeding.
2. Perforation of the bowel, which is the most fatal complication of the acute colitis with or without megacolon.

Another indication is when optimal medical treatment fails (Criteria, TreuelevK & Witts).

We have to keep in mind that mortality increases when the time between perforation and surgery increases and also that the clinical signs are vague. Persistence with conservative treatment by using "second line" agents may be hazardous.

Surgery in acute colitis consists of subtotal colectomy with mucous fistula or Hartmann procedure, which leaves open the options of proctocolectomy, ileorectal or IPAA.

In chronic ulcerative colitis surgery is required when:
1. The symptoms are inadequately controlled in spite of the intensive medical treatment and the QOL is worsening.
2. There are serious side effects of the drugs used.
3. In spite of adequate disease control, there are dangers from continuing medical treatment.
5. Serious disability from extraintestinal manifestations (which respond to surgery).
The backbone of treatment of chronic disease is the use of immunomodulators azathioprine and G-MP.

These drugs have the disadvantage of taking a minimum of three months to act, require a close cooperation between physician and patient for periodic monitoring.

There are serious side effects of the use of azathioprine (leukopenia, pancreatitis etc.). When treatment stops recurrence develops, while 30% of the patients will have recurrence in 12 months. When using G-MP there is a danger of hepatic fibrosis.

In the long term there is the danger of lymphoma or leukemia, even when the patients are asymptomatic.

We have to remind that in long standing cases of ulcerative colitis there is the danger of cancer.

This necessitates endoscopic surveillance for detection of DALM, HGD or LCD.

This practice is not uniform and differs markedly between gastroenterologists.

Surgical treatment of choice is IPAA, which provides treatment of the intestinal part of the disease. When the operation is performed by experienced surgeons, the complication rate is acceptable and there is a significant improvement of the quality of life of the patients.
## List of Speakers, Moderators and Scientific Organizers

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POSTER ABSTRACTS

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Predictive factors of response and relapse to the azathioprine in patients with Crohn’s disease

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The aim of our study was to determine the predictive factors of response and relapse to azathioprine in patients affected by Crohn’s disease.

Methods: During a 10 year period (January 1996-December 2005), 247 patients were treated for Crohn’s disease in our department. 78 have been put under azathioprine. The assessment of the remission has been made at 6 months of treatment. We consider in remission patients in whom the Crohn's disease activity index less than 150 and relapse patients treated with azathioprine and that required glucocorticosteroids treatment or surgery.

Results: The mean age was 35 years. The mean evolutive period of Crohn’s disease before the beginning of the treatment with azathioprine was 26 months. The main indications for azathioprine therapy were: prevention or treatment of the post-operative recurrence (40%), glucocorticosteroid dependence (23%) and treatment of a severe form of the disease (15%).
The rate of remission at 6 months was 66%. With a mean follow-up of 31 months, 30% of the patients developed a relapse.
The predictive factors of remission were the recent character of the disease (p < 0.001) and the good observance of the treatment (p < 0.0001).
The predictive factors of relapse were a sedimentation rate superior to 20 mm at the first hour (p = 0.02), ileal stenosis (p = 0.03), corticosteroid dependance (p = 0.007) and bad observance of treatment (p < 0.001).

Discussion/Conclusion: The treatment by azathioprine is efficient in Crohn’s disease. However, to increase the chances of a good response, this treatment should be instituted as early as possible after the diagnosis and must be well observed.
Association cyclosporine and azathioprine during the severe acute colitis: Does it avoid the colectomy?

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The aim of our study was to determine the efficiency of the association cyclosporine and azathioprine in the severe acute inflammatory colitis resistant to glucocorticosteroid.

Methods: It is about a descriptive survey including 21 patients affected by severe acute inflammatory colitis (Crohn’s disease 7, ulcerative colitis 13 and idiopathic colitis 1 case) having resisted to the intravenous glucocorticosteroid treatment among 50 patients hospitalized in the Department of Gastroenterology of the Hospital Sahloul of Sousse between 2002 and 2005. The diagnosis of gravity was based on the clinico-biological criterias (modified oxford) and endoscopic criterias. The 21 patients have been put under intravenous cyclosporine to the dose of 2 mg/kg/day relieved by the oral cyclosporine (4 mg/kg/day) and the azathioprine (2 mg/kg/day) in case of good clinical and endoscopic improvement judged on the 7th day of treatment.

Results: Our survey included 11 women and 10 men of middle age of 37 years affected by severe acute colitis resistant to intravenous glucocorticosteroid treatment. The evolution after 7 days of intravenous cyclosporine was favorable with clinical and endoscopic improvement in 17 cases (81%). Two patients had a partial improvement and two had no answer and underwent a colectomy. The 17 patients who improved have been put under oral cyclosporine and azathioprine. To the term of a middle follow-up of 18 months, 7/17 patients developed a relapse and required a colectomy. The remaining 14 patients (67%) remained in remission.

Discussion/Conclusion: The association cyclosporine and azathioprine is efficient in the glucocorticosteroid resistant severe acute inflammatory colitis. This treatment could avoid long-term colectomy at two third of patients.
Course of Crohn’s disease prior to establishment of the diagnosis - Results of the online-based “DMC-questioning“


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Introduction: The course of Crohn’s disease (CD) from the occurrence of first symptoms until the establishment of the diagnosis is widely unknown. We present first results of an online-based questioning (the DMC-online questioning).

Methods: Patients who were diagnosed with CD less than 12 months before interrogation were included. Data on demography, social status, time span to diagnosis, symptoms, and health care utilization were collected in a retrospective census via the internet (http://www.kks-halle.de/dmc). The patients were contacted in cooperation with a patients’ organization (Deutsche Morbus Crohn/Colitis ulcerosa Vereinigung e.V. (DCCV)). Study participation took place anonymously by use of a transaction number that was provided by the DCCV. The scheduled interim analysis is on hand and is hereby presented.

Results: 104 participants were included and 92 of 104 data sets were apt to be evaluated (age of participants 19 to 61 years; mean 31.7; female 62, male. 30). A vocational qualification was not obtained by 15% of the participants, 37% finished their apprenticeship, 47% achieved general qualification for university entrance, and university or technical college was completed in 21%. The median latency time from the occurrence of first symptoms to establishment of the diagnosis was 12.5 months. A median of 5 doctors were consulted and 1 the participant was admitted to one hospital before the diagnosis was detected. Altogether, the participants underwent 784 diagnostic procedures during the time span investigated. Per patient, 8.5 investigations were done until establishment of the diagnosis: 2.1 stool tests, 2.7 abdominal ultra-sonographies, 1.0 esophageo-gastro-duodenoscopy, 1.6 ileocolonoscopies, 0.5 small bowel radiographies, 0.3 computed tomographies, 0.2 magnetic resonance tomographies, 0.04 capsule endoscopies.

Discussion/Conclusion: This Internet-based questioning offers anonymous participation by use of the transaction number. Repeated access is excluded and bias thereby minimized. Results of the questioning might influence future diagnostic and therapeutic strategies in managing CD.

References:


IGF-I as a marker of disease activity and nutritional status in patients with inflammatory bowel disease

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Introduction: Catabolism is regarded as usual complication in patients affected by inflammatory bowel disease (IBD). Recent research data indicates that the complication is mediated by insulin-like growth factor (IGF). The aim of present study was to determine serum levels of IGF-I and in different stages of IBD, and to evaluate the other markers of inflammation, as well as nutritional status indicators.

Material and method: The study has been carried out on 30 patients in active phase of IBD, whose age range from 21-69 years. All subjects were treated at Clinic for Gastroenterology and Hepatology, Clinical Center of Serbia. Diagnosis of IBD was based on clinical, laboratory, endoscopic and histologic criteria. Level of C-reactive protein (CRP) has been considered as indicator of inflammation, while serum albumin concentration serves as nutrition indicator. Levels of IGF-I, CRP, and albumin were recorded on admission to hospital and after six months of the treatment.

Results: In active phase of the disease, marked elevation of CRP (42.98 ± 39.96 mg/L) and simultaneous decrease of serum albumin (21.63 ± 5.08 g/L) and IGF-I (14.7 ± 8.77 nmol/L) were observed. In follow-up analysis, besides reached clinical improvement and recovery, drop of CRP concentration has been observed (4.28 ± 3.06 mg/L), as well as increase of serum albumin (39.83 ± 7.27 g/L) and IGF-I (26.47 ± 12.85 nmol/L) concentrations. The observed differences of the studied marker concentrations tested by Student t-test were statistically significant (5.490, -12.764, and -4.728, respectively).

Conclusion: The results of our study indicates that IGF-I may be used as indicator for determination of IBD activity, as well as for estimation of nutritional status.
The impact of “BioR” on evolution of ulcerative colitis

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Introduction: BioR is immunomodulator and cell membrane stabilizer, product of spirulina platensis. The aim of this work is to define the influence of BioR on evolution of ulcerative colitis in complex therapy with Salofalk®.

Methods: 12 patients with ulcerative colitis have been under observation. 8 of them had moderate activity and 4 – light. The diagnosis was made relying on the clinical data and colonoscopy. The patients were divided into two groups. The first group – 5 patients received BioR 1 ml i/m and Salofalk® 1.5 g per day and. The second group – 5 patients received Salofalk® 1.5 g per day. The course of the BioR therapy lasted 10 days and Salofalk® – 5 weeks.

Results: The first group – abdominal pain, bloody stools, fever, diarrhea, rectal involvement has disappeared in 6 patients (100%). The decrease of hyperemia and edema of colon mucosa at colonoscopy and normalization of Hb, RSE – in 5 patients (83.3%). The changes at the second group are analogical but they are less expressed in terms of quantity. Bloody stools, fever, abdominal pain, diarrhea, rectal involvement has disappeared in 5 patients (83.3%). The decrease of hyperemia and edema of colon mucosa and normalization of Hb, RSE – in 4 patients (66.6%).

Conclusion: The use of BioR with Salofalk® in the complex therapy of patients with ulcerative colitis leads to achievement of positive results during shorter period of time and for a greater number of patients than the use of therapeutically schemes of treatment with Salofalk®. This is due to the expressed cell membrane stabilization and immunoregulatory action of BioR.
The anemic syndrome in inflammatory bowel disease

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Introduction: The pathogenesis of the anemic syndrome in inflammatory bowel disease (IBD) is complex. It can be generated by the chronic inflammation, by the repeated blood loss, by the malabsorption of the folic acid and B₁₂ vitamin. Besides, the anemia may preexist at the debut of the intestinal disease.

Methods: We have evaluated a number of 42 patients with IBD during a period of 5 years, out of which 26 were diagnosed with ulcerative colitis (UC) and 16 with the Crohn’s disease (CD). It was determined the Ht value, Hb erythrocytes indices, the number of reticulocytes, the total capacity of iron bounding (CTLF), the latent capacity of iron bounding (CLLF), the transferrin saturation (TS), the ferritin and reactive C protein.

Results: Out of these ones, 12 of the patients with UC and 6 with CB presented anemia (Hb under 13.5 g/dl in men and under 11.5 g/dl in women). The medium Hb value in the lot of patients with anemia was of 8.3 ± 1.6 and Ht value was of 28 ± 3.5. In 11 of 18 anemic patients (Chi² = 3.51, p < 0.055), the intestinal disease was active. In 5 of 7 patients with anemia without active disease, the investigations and the epidemiologic study suggests an associated cause of the anemia (iron deficiency). In one case, the erythrocytes indices suggest macrocytosis and anemia is remitted after treatment with folic acid and B₁₂ vitamin.

Discussion/Conclusion: The anemia follows frequently IBD in 37.75% percentage. The increased prevalence of the anemia in IBD may be justified in a way by the local socio-economic conditions. The anemia is also correlated with the activity degree of the disease.
Inflammatory bowel disease associated with essential thrombocytemia (case study)

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Z.C. female sex. Debut at the age of 22 years with persistent stool modifications: diagnosis = inflammatory bowel disease (IBD) with mainly symptomatic therapy and intermittent sulfasalazine.

At the age of 26 years, the persistent thrombocytosis is over 600,000/mm³, VSH 20/35 mm, fibrinogen 520 mg/dl, PCR 4.6 µg/ml. The bone marrow aspirate is normo-cellular without significant modifications on eritroid and granulocytic series, the moderate increase of the megakaryocytic percentage and lymphocytary infiltrated 4-5% without elements suggesting a chronic myeloproliferation. The thrombocytosis is considered secondary to IBD and it is not initiated specific therapy.

At the age of 28 years she presented resistant migraine headache, considered to be due to a hormonal dysfunction and to a gallbladder lithiasis, the thrombocytosis maintains between 600,000-800,000/mm³.

At the age of 32, she presents diffuse abdominal pains, changes of transit and fecal materials, abdominal distension, the thrombocytosis is 850,000/mm³. Abdominal echographically reveal splenomegaly 13 cm and Doppler ECHO significant thrombosis of port vena. It is initiated treatment with Hidrea 1 g/day, low dose aspirin (75 mg/day) plus endovenous and per os anticoagulant therapy. The symptomatology ameliorates but the thrombosis of portal vein echographically persists. Later it is administrated INF 3 MU every 2 days with the stabilization of the platelets number about 400,000 mm³. BM aspirate show the large megakaryocytes, sometimes gigantic with hyperlobulated nucleus with mature cytoplasm, dispersed by chance or weak grouped in a normal cellular bone marrow.

At the age of 40, clinically, the hematological disease is stable, IBD with undulant evolution but without major complication, thrombosis of portal vein with portal hypertension and presence of esophageal varices of 2 degree. She need continuous myelosuppression therapy.
The thrombocytosis and inflammatory bowel disease

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Introduction: The hematological anomalies in inflammatory bowel disease (IBD) do not refer only to anemia, but to the increase of the sanguine platelets number. The pathogenesis of thrombocytosis is complex and consists in mechanisms connected with the chronic inflammation, but also with the blood loss at the level of the digestive tract.

Methods: We studied a lot of 42 patients with IBD (26 patients with ulcerative colitis (UC) and 16 with Crohn’s disease (CD) during a period of 5 years.

Results: The thrombocytosis is present in a percentage of 30.95% from the whole lot (31.25% patients with CD and 30.76%). Patients with CD presented higher values of the platelets number. The thrombocytosis is correlated with the CRP value (Chi² = 3.35, p < 0.05) and less with the fibrinogen value (Chi² = 3.20, p < 0.056) and with the state activity of the disease (Chi² = 3.42, p < 0.05). A patient was initially considered as having reactive thrombocytosis, in time being developed manifestations and suggestive complications for the essential thrombocytethemia. The values of this one being much higher in CD and are correlated with state of disease. The reactive C protein (CRP) is increased in all cases of thrombocytosis, correlating in a way with this one’s degree.

Discussion/Conclusion: The thrombocytosis is present in approximately 1/3 of the IBD cases. The thrombocytosis values can get to values that can raise problems of differentiated diagnosis, but the presence of the digestive disease and the evolution presents it.
Extraintestinal manifestations of Crohn’s disease - Case presentation

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An 82-year old male patient, with infrequently diarrhea stools in the past medical history, was referred to our endoscopic department from the dermatology department. He was addressing the dermatology department for an ulcerated, painful lesion situated in the intergluteal fold, on the right side. The lesion had a two-month history. The clinical skin examination revealed a round-shaped, erythematos-violaceous aphthous ulceration, 2/2 cm in diameter. Histopathological exam of the lesion described a acanthotic, ulcerated epidermis, the presence of numerous blood vessels with ballooning of the endothelial cells in the superficial dermis, and neutrophilic infiltrate present around the blood vessels. These findings raised the suspicion of cutaneous Crohn’s disease (CD). Laboratory tests revealed an elevated ESR and CRP levels and a slight anemia (Hb of 11.3 g/dl).

Ileo-colonoscopy performed in our endoscopy department revealed 2-3 ulcerations in the terminal ileum. The pathology confirmed the diagnosis of CD, (presence of the ulcers, polymorphonuclear infiltrate in lamina propria and aggregates of lymphocytes).

Based on clinical data, laboratory findings, endoscopic procedures and histopathology we established the diagnosis of CD with cutaneous manifestations.

The patient was treated with mesalasine (Salofalk®) 4 g per day, which improved both gastrointestinal symptoms and cutaneous ulceration, respectively. After two months of treatment, the ulceration reduced considerably in size and bowel movements were normal.

The case illustrates the diagnosis of CD in an elderly male patient who referred to a dermatology department for a skin lesion and not for the gastrointestinal symptoms, as part of the extraintestinal manifestations of CD.
Osteoporosis as an extraintestinal manifestation in IBD patients

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Introduction: It is known that several IBD patients (pts) have bone density in osteoporotic or even osteopenic range.

Objective of the study: To establish the rate of osteoporosis in IBD pts (with CD and UC) and the risk of fracture.

Material and methods: 47 IBD pts (36 with UC – 14 males, 22 females, 11 with CD – 5 males, 6 females) underwent dual-energy x-ray absorptiometry (DXA) scanning. Pts had a long history of IBD (minimum 8 years), being also treated with corticosteroids during the years. Mean age of the pts: 43 ± 5.5 years. For interpreting the DXA results we used the T-score (number of standard deviations above/below the average peak young-adult bone mineral density).

Results: 28 pts presented a T score between -1 to -2.5 (osteopenia) and 13 pts had a T score below 2.5, suggesting osteoporosis. Only 6 pts presented a normal T score (above -1). The increased risk for fractures was similar in both CD and UC pts, being higher than in normal populations. Females had more frequent a lower T score than males (32 vs. 9).

Conclusions:
1. Besides other risk factors for osteoporosis (smoking, premenopausal status, hypogonadism, etc), IBD pts using corticosteroids are also at increased risk for osteoporosis, either from their active disease, or from the long-term use of the drugs.

2. Therefore, IBD pts, especially elderly ones, using corticosteroids on a long-term basis should undergo a bone density measurement in order to determine the risk of osteoporosis and bone fracture, respectively.
Evolution of epidemiological indices and clinical manifestation in ulcerative colitis in Moldova

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Introduction: The aim of the study was the comparative analysis of epidemiological indices and clinical features at ulcerative colitis (UC) last 20 years.

Methods: Dynamics of epidemiological parameters has been investigated according to official medical statistics. For the comparative analysis of clinical features two groups of patients, which were treated in the specialized department of Republican Clinical Hospital in 1986-1990 (96 patients) and in 2001-2005 (89 patients), have been investigated

Results: Incidence of UC is 0.4-0.5 per 10,000 inhabitants, and prevalence – 2.3-2.6 per 10,000 inhabitants, without the tendency of increase last 10 years.
The localization of pathological process in 1986-1990: total colitis - 35.5% (34), left-side colitis - 46.8% (45) and distal colitis - 17.7% (17). In 2001-2005 extent of colonic involvement has essentially decreased and total colitis has been diagnosed only at 10.1% (9), and distal colitis - at 49.4% (44).
Frequency and severity of acute phases did not differ in analyzed groups. One of the most often complications in 1986-1990 was an intestinal bleeding - 9.4% (9); in 2001-2005 it has been established at 3.4% (3). Toxic dilatation and perforation of the colon have complicated the disease at 3 patients from the first group and have not been diagnosed in the second group.

Discussion/Conclusion: The Republic Moldova is one of the regions with low indices of UC incidence and prevalence; the increase in these parameters is not marked last years. The disease evolution became more favorable in the past years.
Risk factors for steroid dependency and steroid resistance in Crohn’s disease (CD)

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Introduction: Steroid dependency (SD) and steroid resistance (SR) develop frequently in the context of CD patients. Risk factors for the development of SD and SR in CD are unknown.

Aim: We aimed at evaluating whether patients with any of the known risk factors for CD are at risk of developing SD or SR.

Methods: 188 consecutive patients with CD (111 female, mean age 36 years) were included. SD was defined as a relapse within 30 days after the end of steroid treatment or after two attempts of tapering the steroid dose. SR was defined as the absence of respond to steroid therapy for more than 7 days. Gender, tobacco, appendectomy, family history of CD, extraintestinal manifestations, presence of CARD15 mutations (R702W, G908R and 1007fs) and presence of TLR4+299 or the CD14-260 sequences variants were analyzed as potential risk factors for SD and SR. Results are shown as percentages and analyzed by the chi-square test.

Results: Forty patients (21.3%) developed SD, whereas SR was observed in 29 (15.4%). SD was associated to smoking (27.0% vs. 10.4%, p < 0.01) and to the presence of EIM of the disease (34.9% vs. 12.8%, p < 0.01). In addition, although SD was not related to any of the evaluated gene mutations, tended to be more frequent among patients with family history of CD (33.3% vs. 18.0%, p = 0.06). Only previous appendectomy was associated to SR.

Discussion/Conclusion: Tobacco, extraintestinal manifestations and, probably, family history of CD, appear to be associated to SD. Previous appendectomy is related to the development of SR. Genetic variants of CARD15, TLR4 and CD14 play not role in the development of SD and SR.
Age-related changes in the serum dipeptidyl peptidase IV (DPP IV/CD26) activity in patients with inflammatory bowel diseases

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Introduction: The dipeptidyl peptidase IV (DPP IV/CD26) is a membrane-bound multifunctional glycoprotein also present in a soluble form in the plasma. It has been shown that the DPP IV could play a significant role in the pathophysiology of IBD. The aim of this study was to determine the influence of patient's age on the serum DPP IV activity in patients affected with IBD.

Methods: The research was performed on 93 patients, divided in 2 groups: 31 young patients (13.8 ± 1.7 years, 24 with CD, 7 with UC) and 62 adult patients (42.7 ± 14.4 years, 38 with CD, 24 with UC). The control group included 111 healthy blood donors: 46 children (13.8 ± 2.8 years) and 65 adults (41.6 ± 12.1 years). The serum DPP IV activity was measured spectrophotometrically.

Results: The serum DPP IV activities in both young and adult patients with IBD were statistically significantly decreased compared to their healthy controls. The values correlated inversely with the disease severity for both CD and UC. When comparing serum DPP IV activities between young and adult patients with IBD, but even between young and adult healthy controls, it is clear that the serum DPP IV activity decreases statistically significantly with age.

Discussion/Conclusion: The results of this study show that the serum DPP IV could be useful as an available, non-invasive marker in the diagnosis of the disease activity. This research shows that age-related standard values should be established in clinical laboratory practice because of its age-dependent decrease in serum activity.
Effect of budesonide on the quality of life in patients with collagenous colitis

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Introduction: Treatment of collagenous colitis (CC) is largely symptomatic. In previous studies budesonide treatment of CC resulted in improvement of the clinical symptoms. Treatment for 6-8 weeks has been recommended. The aim was to assess quality of life (QoL) with Inflammatory Bowel Disease Questionnaire (IBDQ) in patients with CC before and after treatment for 6 weeks with budesonide.

Methods: Patients with newly diagnosed CC were evaluated to participate. Diagnostic criteria of CC were histological findings of a collagen layer more than 10 µm and inflammatory infiltration in lamina propria.

The patients’ demographic data and medical history were recorded. Registration of the daily stool frequency and the daily stool weight were assessed for three consecutive days.

All patients with significant symptoms (> 3 stools pr. day) were treated with budesonide 9 mg o.d. for 6 weeks.

For each patient QoL was assessed with the IBDQ at baseline and after 6 weeks treatment.

Results: Thirty-nine patients (9 males and 30 females), with a median age of 62 years (range 33-81 years) participated in the study.

All patients reported an increase in QoL. Median IBDQ values increased from 135 at the start to 188 at the end of the study (46%, p < 5 x 10⁻⁹).

Median stool weight was reduced from 419 g/day (range 224-1655) to 160 g/day (range 53-373), and stool frequency was reduced from 5.7/day (range 3-12) to 1.7/day (range 1-4.3).

Discussion/Conclusion: Quality of life in patients with symptomatic collagenous colitis is significantly improved after 6 weeks treatment with budesonide.
GLP-2 induces VEGF release from subepithelial myofibroblasts - Differential effects on intestinal wound repair and mucosal growth in vitro

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Introduction: GLP-2 is a intestinal growth factor. However, the mechanism of GLP-2 action is still unclear. Recent studies revealed the h-GLP-2 receptor on colonic-fibroblasts, which were suggested to release growth factors (e.g. Keratinocyte growth factor - KGF). We sought to investigate the GLP-2 induced intestinal adaptation with an established wound-healing model.

Methods: GLP-2 receptor m-RNA was determined in CCD-18 using (RT-) PCR. Conditioned media (CM) from CCD-18 fibroblasts were obtained following incubation with GLP-2. CM were used to assess proliferation in small intestinal IEC-18 and colonic Caco-2 cells utilizing the MTT-Test. GLP-2 effects on wound healing was determined with an established migration-assay following wounding in IEC-18 and Caco-2 monolayers. The m-RNA levels of TGF-β, VEGF and KGF were assessed following GLP-2 stimulation in fibroblasts using (RT-) PCR. VEGF production after GLP-2 incubation was determined using ELISA.

Results: The GLP-2 receptor m-RNA is expressed in fibroblasts. CM induced proliferation in Caco-2 cells and significantly increased migration following wounding in IEC-18 (p < 0.05). RT-PCR analysis in CCD-18 after GLP-2 stimulation revealed an induction of VEGF and TGF-β m-RNA but not for KGF. Significant and dose dependent VEGF secretion in fibroblasts was found in VEGF-ELISA following GLP-2 stimulation.

Discussion/Conclusion: GLP-2 acts differentially on small and large bowel. While GLP-2 exerts predominantly growth factor action on the colonic epithelium, CM rather stimulated intestinal wound repair in small IEC. We did not identify KGF, but we found VEGF and TGF-β, which could be possibly the mediator of GLP-2 for intestinal repair and wound healing.
Frequency of adenomatous polyps and dysplasia in inflammatory bowel disease

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Aim: The aim of the study is to determine the frequency of adenomatous polyps and dysplasia in patients with inflammatory bowel disease retrospectively.

Method: We retrospectively reviewed the medical records of 897 patients from our outpatient clinic. Of 897 patients, 732 suffered from ulcerative colitis (UC) (438 male, 314 female), 165 from Crohn's disease (100 male, 65 female).

Results: Seventy (9.6%) UC patients had adenomatous polyps (42 men, 28 female). Frequency of polyp occurrence was significantly higher in patients with pancolitis (23/238, 9.6%) and left-sided UC (34/315, 10.7%) compared with patients with proctitis (13/179, 7.2%) (p < 0.05). Of 70 polyps, 61 were in the diseased segment, 9 were in the normal segment. Mean duration of disease was significantly higher in patients with adenomatous polyps. Six percent of the patients (10/165) with Crohn's disease had adenomatous polyps (6 male, 4 female). In patients with Crohn's disease, there were two low-grade dysplasia cases. In the group of UC, low-grade dysplasia was seen in 20, high-grade dysplasia in 4, and adenocarcinoma developed in 3. Proportion of dysplasia and adenocarcinoma was significantly higher in patients with a longer disease duration (> 10 years) compared with < 10-year disease duration (11.6%, 1%, respectively, p < 0.001).

Conclusion: The frequency of adenomatous polyps is higher in UC than Crohn's disease. The incidence of adenomatous polyps is higher in diseased segment, in patients with pancolitis and left-sided UC cases and in patients with a long disease duration. The risk of colorectal carcinoma is increased with disease duration in UC.
Inflammatory bowel disease in children: A single center experience

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Aim: To analyze demographic and clinical features and outcome of the children with IBD.

Methods: File records of the children with IBD were evaluated for the following parameters; demographic features, main symptoms at time of admission, site of the involvement, extra intestinal manifestations, laboratory findings, treatment and outcome.

Results: Totally 32 children (18 female, 14 male) were diagnosed with IBD during 8 year period. Mean age ± SD of the patients were 12.1 ± 3.4 years (range 3-17 years). Twenty-one (65.6%) children were diagnosed as ulcerative colitis (UC), 11 were diagnosed as Crohn's disease (CD). UC were more common in females (66.6% vs. 45.6%, p > 0.05) and associated with older age (13.4 ± 4.2 vs. 11.1 ± 2.3 years, p > 0.05). The duration of the symptoms were 6 ± 1.2 months (1-15 months). The main symptoms were rectal bleeding, diarrhea and weight loss in UC, and abdominal pain, diarrhea and weight loss in CD. Weight and height SD scores were slightly low in children with CD (-1.9 ± 1 vs. -1.7 ± 1.1 and -1.8 ± 1.1 vs. -1.6 ± 1.2, respectively). Ileo-colonic involvement was documented in most CD cases; while left colon or pancolonic involvement were common in UC cases. High sedimentation rate, CRP positivity, increased platelet count, anemia and hypoalbuminemia were found 87.5%, 93.7%, 84.3%, 81.2% and 75% of the cases, respectively; and no significant difference was found between CD and UC cases in terms of frequency of these abnormal laboratory parameters. All the patients were given nutritional support, salofalk and steroid therapy in the active phase, and azathioprine and tapering doses of steroid in the remission. Two patients were received cyclosporine, who was refractor to first line treatment. None of the patient with UC underwent to surgery; while two patients with CD.

Conclusion: Early diagnosis is important especially in children with IBD. Early treatment will prevent the early complications and late complications such as osteoporosis and growth delay.
Tuberculosis infection in patients with inflammatory bowel disease

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Introduction: The clinical characteristics and follow up of the IBD patients with a tuberculosis (tbc) diagnosis is still a major problem in some parts of the world. We report data of our patients who were followed between 1996-2006.

Methods: Patient files of 374 patients with IBD were retrospectively evaluated in terms of tbc diagnosis, treatment and follow-up.

Results: Thirteen patients were found to have a history associated with tbc. All of these patients had diagnosis of Crohn’s disease and were taking immunosuppressive therapy. Five patients had a history of pulmonary tbc. Prophylaxis was given to 3 of these 5 patients. Pulmonary tbc developed in one of that two patients who did not take tbc prophylaxis. On the other hand tbc infection developed in none of the 3 patients who had taken tbc prophylaxis. Three of the 8 patients without a remarkable history of tbc, were found to have a positive PPD before beginning of the IBD treatment. Three of these 3 patients were given tbc prophylaxis. Intestinal tbc was developed in one of them. Remaining two patients did not develop tbc. Tbc prophylaxis was not given to 5 patients that had a negative PPD before the beginning of the IBD treatment. Three of these patients developed pulmonary and 2 other patients developed intestinal tbc. Tbc developed in 1 of 6 patients who had taken tbc prophylaxis. On the other hand among 7 patients who did not take any tbc prophylaxis, diagnosis of was made tbc in 6 of them.

Discussion/Conclusion: Medical history of IBD patients in terms of tbc should be evaluated very carefully before the immunosuppressive treatment with a chest X-Ray and also PPD skin test. Prophylaxis may reduce tbc reactivation significantly. Still tbc reactivation may occur in IBD patients under immunosuppressive therapy even if they are receiving appropriate tbc prophylaxis.
Steroid refractory inflammatory bowel disease: CMV infection - A case report

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Introduction: Cytomegalovirus is detected frequently in patients with inflammatory bowel diseases (IBD). Although it does not cause any infection in immune-competent states, serious CMV infections can occur in immune-deficient patients. CMV infections have been reported in 25-36% of steroid resistant IBD patients.

Case: Thirty-four year old woman was admitted to the hospital with fever, abdominal pain and bloody diarrhea. Laboratory test results were as following; Hgb: 9.1 g/dL, Htc: 28%, CRP: 13.7 (N < 0.03 mg/L), ESR: 20 mm/h. Stool microscopy and serology did not show amebiasis. In colonoscopic examination mucosa was hemorrhagic, fragile and edematous. Deep linear ulcers were present. Systemic corticosteroid treatment was started at a dose of 1 mg/kg. Intravenous cyclosporine was added at 10th day of corticosteroid treatment due to lack of response. Under these medications clinical symptoms did not diminish. Control colonoscopy showed no healing. Histopathological examination of biopsy specimens revealed CMV inclusion particles, besides CMV-DNA levels were 48,000 copies/mL. Immunosuppressive drugs were stopped immediately and IV ganciclovir treatment (5 mg/kg) was initiated. Following 15th day of antiviral therapy, patient did not respond completely and ganciclovir treatment was stopped. However CMV was disappeared in both peripheral blood and colonic samples. Then cyclosporine 200 mg/day, azathioprine 2 mg/kg/day, ciprofloxacin 1000 mg/day and budesonide 9 mg/day were initiated. At 10th day of treatment patient recovered completely and discharged.

Conclusion: In steroid refractory or severe IBD patients, CMV infections should be considered for differential diagnosis. CMV infections should be excluded prior to increasing immunosuppressive dose or adding other immunosuppressive medications.
Magnifying colonoscopy in ulcerative colitis

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Introduction/Aim: Endoscopic examination has an important role in the diagnosis and evaluation of disease activity in ulcerative colitis (UC). But standard endoscopy results generally doesn’t identical with histopathologic results. Magnifying colonoscopy (MC) allows a detailed inspection of the mucosa by 100-fold enlarging the images. The purpose of the study was to evaluate the mucosal and polypoid lesions and inflammation by MC and to compare MC result with histopathology.

Methods: Fifty-three patients with ulcerative colitis were examined. Lesions classified by Matts classification (standard colonoscopy and histopathology) and Saitoh-Fujiya classification (MC) and Matts classification. Indigo carmine used for staining before MC.

Results: We found 135 lesion from 52 patients. Although there wasn’t any correlation between standard colonoscopy and histopathology findings, MC predicted histopathologic staging. 78.5% of normal pit pattern was grade 1,2 (mild). There wasn’t any grade 1 result in villi-like, small yellowish, coral reef-like appearance and polypoid mucosal tag lesions. 40% of coral reef-like and 100% of mucosal tag lesions reported as grade 5. Two dysplasias, 1 adenoma and 1 adenocarcinoma lesion found in coral reef-like and mucosal tag lesions.

Discussion/Conclusion: MC classification of lesions in UC predicted neoplastic and non-neoplastic tissue, although standard colonoscopy didn’t show this detail. Neoplastic lesions have been found only in coral reef-like and mucosal tag lesions.
The effect of caffeic acid phenethyl ester on pancreatic islet hyperplasia in TNBS-induced colitis

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Introduction: Caffeic acid phenethyl ester (CAPE), a phenolic antioxidant derived from the propolis of honeybee hives, is known to be an inhibitor of activation of nuclear transcript factor (NF-κB). NF-κB has a pivotal role in inflammatory bowel disease. The aims of our study were to evaluate the efficacy of CAPE against Pancreatic islet hyperplasia in trinitrobenzene sulfonic acid (TNBS)-induced colitis.

Methods: For that purpose, total 40 Wistar albino rats, colitic (TNBS -induced) and control were studied. Rat colitis was established TNBS (30 mg/rat) and ethanol. Groups of colitic animals were treated with different doses of CAPE (10 or 20 mg/kg/day) or vehicle intraperitoneal, starting after induction of colitis and during 7 days. Every pancreatic tissue embedded paraffin, ten slices different level, and Hematoxylin-eosin stainig. Morphometric analyses were also performed under light microscope. Each slice was counted islet diameters more than 150 micrometer.

Results: After treated with TNBS/ethanol, the extent of colonic mucosal damage and simultaneously the pancreatic islet cell hyperplasia histologically observed (p < 0.05). CAPE 20 mg/kg/day treatment significantly reduced count of pancreatic islet diameter more than 150 micrometer.

Discussion/Conclusion: These mechanisms likely contributed to the attenuation of reduction of inflammation by CAPE.
The effect of caffeic acid phenethyl ester (CAPE) on TNBS-induced colitis

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Introduction: Caffeic acid phenethyl ester (CAPE), a phenolic antioxidant derived from the propolis of honeybee hives, is known to be an inhibitor of activation of nuclear transcript factor (NF-κB). NF-κB has a pivotal role in inflammatory bowel disease.

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Methods: For that purpose, total 40 Wistar albino rats, colitic (TNBS-induced) and control were studied. Rat colitis was established TNBS (30 mg/rat) and ethanol. Groups of colitic animals were treated with different doses of CAPE (10 or 20 mg/kg/day) or vehicle intraperitoneal, starting after induction of colitis and during 7 days. Clinical and pathological markers of colitis severity and apoptotic markers (bax, bcl-2, caspase-3, caspase-8, and TNF-α) with immunohistochemistry in colonic tissue were evaluated.

Results: After treated with TNBS/ethanol, the extent of colonic mucosal damage and apoptotic markers, the levels of malondiadehyde (MDA) and IL-1β were increased. CAPE 20 mg/kg/day treatment was associated with significant reduction in gross colonic injury (p < 0.05), colonic MDA (p < 0.05) and IL-1β levels (p < 0.001). Moreover, bax were significantly reduced in CAPE 20 mg/kg/day -treated rats (p < 0.05).

Discussion/Conclusion: CAPE reduced colonic damage in TNBS-induced colitis. The mechanism of the protection associated with CAPE was due to antioxidant, antiapoptotic and anti-inflammatory effects.
The utility of serum MMP-3 in degree of activity in inflammatory bowel diseases

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Introduction: The matrix metalloproteinases (MMPs) production is increased in the gut of patients with the chronic inflammatory bowel diseases (IBD). The aim of this study was to assess the relationship between serum MMP-3 levels and the degree of activity in IBD.

Methods: Serum samples were obtained from 81 patients with ulcerative colitis (UC) (F/M: 23/58, mean age: 44.2 ± 13.6), 39 patients with Crohn’s disease (CD) (F/M: 13/26, mean age: 41.8 ± 12.4) and 39 healthy controls (F/M: 25/15, mean age: 41.6 ± 12). Determination of MMP-3 was performed with the standardized enzyme-linked immunosorbent assay. Clinical activity in CD was measured by Crohn’s disease activity index (CDAI) and in UC by Truelove-Witts clinical activity index. CDAI higher than 150 was predicted as active disease in CD. UC activity was divided three groups as mild, moderate, and severe. The disease localization was established in patients with UC as distal, left type, or pancolitis and in patients with CD as small bowel, colon, or both.

Results: Serum MMP-3 levels were measured higher in patients with both UC (mean: 32.15 ± 28.62 ng/mL) and CD (mean: 23.44 ± 27.16 ng/mL) than controls (12.01 ± 7.27 ng/mL) (p < 0.01). No significant differences were found in patients with CD who had CDAI > 150 (n: 13, mean: 36.3 ± 44.4 ng/mL) than in patients with CD who had CDAI < 150 (n: 22, mean: 17.3 ± 6.56 ng/mL) (p > 0.05). No significant differences were found among UC patients regarding disease activity. There was no statistically difference regarding disease localization in both diseases.

Discussion/Conclusion: The serum MMP-3 levels increase in patients with IBD but it is not associated with disease activity and localization.
Response to corticosteroid therapy and allelic variants of the multidrug resistance gene (MDR1/ABCB1) in patients with Crohn’s disease

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Introduction: Steroid dependency is an important problem in managing patients (pts) with Crohn’s disease (CD). This study examined the association of single nucleotide polymorphisms in the MDR1 gene of 61 pts with CD with respect to response to corticosteroid therapy.

Methods: According to European evidence based consensus on the diagnosis and management of CD, pts in this study were characterized as steroid-dependent (n = 35) and good responders to corticosteroids (n = 26). Analysis of G2677T polymorphisms in exon 21 and C3435T in exon 26 of MDR1 gene was performed by PCR-RFLP method.

Results: Genotype frequencies of the 2677GG, 2677GT and 2677TT MDR1 exon 21 in the sample were 20, 32 and 9, respectively and of the 3435CC, 3435CT and 3435TT of MDR1 exon 26 genotypes were 12, 31 and 18, respectively. There were no difference in either allele, genotype and haplotypes distributions among different gender and age groups.

No significant deviations from the expected Hardy-Weinberg proportions were observed in the sample, in good response-group and dependent-response group. Pair-wise comparisons of the allele and genotype frequency between different groups of responders revealed no statistical differences for both loci. Likewise, no statistical differences were found in distributions of the estimated haplotypes between those groups.

Discussion/Conclusion: Results in this study indicate that G2677T polymorphisms in exon 21 and C3435T in exon 26 of MDR1 gene don’t have significant influence on development of steroid-dependent CD.
Malignant transformation in ulcerative colitis – Experiences in a Hungarian clinical center

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During a 2 years period we performed 73 screening colonoscopies in patients suffering in ulcerative colitis. The average age of the patients were 43 years, the mean duration of the disease was 10.5 years. In 53 cases we found active inflammation, in 17 cases the whole colon was affected. Biopsies were performed in every case. The macroscopic findings revealed the possibility of malignancy in 6 patients. In 2 cases the biopsies proved adenocarcinoma and in 3 cases mild dysplasia. In 1 case a long-known stenosis suggested the presence of a malignancy. All patients were on 5-ASA treatment. Surgical treatment was performed in 4 cases, 1 total proctocolectomy, 1 ileostomy and palliative chemotherapy due to peritoneal carcinomatosis, 1 sigmoid resection and 1 left-sided hemicolecotomy.

Our results underline the need of endoscopic follow up in patients suffering in ulcerative colitis. Biopsies are necessary despite of the evolving possibilities in chemoprevention. Although the international guidelines suggest performing proctocolectomy in the case of dysplasia or possible malignancy, in individual cases we are forced - because of the circumstances - to choose other solutions. The frequency of adenocarcinoma in our experience was in line with the international data.
Steroid use is not the only cause of osteoporosis in inflammatory bowel disease

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Objectives: Patients with inflammatory bowel disease are at risk of osteoporosis due to many risk factors: steroid use, low BMI, malabsorption, multiple surgical resections. Guidelines suggest that only those patients with risk factors should be assessed for osteoporosis. Our study was designed to elucidate if patients with inflammatory bowel disease per se (without risk factors) are at risk for osteoporosis.

Materials and methods: 40 patients (25 females and 15 males) with newly diagnosed inflammatory bowel disease following gastroenterological investigations were recruited. The inclusion criteria for this study included untreated patients aged between 18-40 who had been diagnosed histologically with either Crohn’s disease or ulcerative colitis. They had no previous exposure to steroids, were non-smokers and with no history of surgical resections. Bone densimetry scanning was performed on each patient.

Results: Thirteen of the forty patients with inflammatory bowel disease had osteopenia or osteoporosis (32%). There was a correlation between T-score, BMI and extent of disease. There was a statistically significant difference in T score between patients with disease duration > 6 months and those less than 6 months (p < 0.02). There was no difference between T score and age of patient or between the type of inflammatory bowel disease – Crohn’s disease or ulcerative colitis.

Conclusions: At present gastroenterologists are only screening those patients with inflammatory bowel disease who have risk factors. Our data suggest that all patients with inflammatory bowel disease should have assessment of osteoporosis via bone densimetry scanning. More research needs to be done to investigate this further.
Efficacy and safety of three doses of infliximab in therapy of Crohn’s disease in children

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Introduction: Infliximab is used in children with Crohn’s disease (CD) who do not respond for conventional therapy and/or suffer from fistulizing disease. The aim of the study was to assess efficacy and safety of three doses of infliximab in CD therapy in children.

Methods: 10 patients non-responding for conventional therapy (4 F, 6 M, mean age 16.1; mean age of disease’s onset 12.3) were included in the study. 4 had history of gut surgery and 2 active fistulas. Patients received infliximab (5 mg/kg) in three repeated infusions at 0, 2, 6 weeks. 6-8 weeks later patients had endoscopical and clinical evaluation that were compared to baseline. Adverse events monitoring had been conducting.

Results: 1 (10%) patient achieved complete response, 6 patients (60%) partial response and 3 patients (30%) had no response. One patient had his fistula closed whereas in the other one it remained active. We found significant increase in patients’ body weight [kg] (52; 38; 54.9 vs. 53.5; 40; 58 [median; lower quartile; upper quartile]) and BMI (18.71; 17.84; 19.25 vs. 19.32; 18.59; 20.91) and decrease in laboratory indices of inflammation: WBC (9.24; 6.61; 9.53 vs. 6.82; 5.5; 8.05), platelets (363; 309; 410 vs. 306; 249; 364), CRP (0.5; 0.3; 1.4 vs. 0.2; 0.2; 0.2). No infusion-related or non-related AE was observed during the study.

Discussion/Conclusion: 1) Infliximab therapy is effective in about 70% of children with CD non responding for conventional therapy. 2) Infliximab therapy improves body weight in these patients. 3) Short time surveillance indicates that infliximab infusions are safe.
Rectorrhagia and inflammatory bowel diseases

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Introduction: Rectorrhagia is a frequent indication for colonoscopy, and this investigation is essential for the etiological diagnosis. The aim of this study is to evaluate the etiology of rectorrhagia in two patients age groups.

Methods: We included 121 patients admitted in our hospital between January 2005 and December 2005 who performed colonoscopy for diagnosis, due to rectorrhagia. We analysed the demographical and etiological data on two different age groups, the cut off value being 50 yrs, as a limit age for colonoscopy screening indication.

Results: The majority of the patients (57.85%) were above 50 yrs. No difference by sex between the two groups was observed. The median age for the first group was 40 ± 7.8 yrs, in comparison with the second 63 ± 9 yrs.
The etiology of rectorrhagia was as follows: hemorrhoids (40.5%), inflammatory bowel diseases (26.45%), colorectal cancer (12.39%), diverticulosis/diverticulitis (8.26%), anal fissures (3.31%), postpolypectomy (3.31%), angiodysplasia (2.48%), ischemic (1.64%) and irradiation (1.64%) colitis.
According age, rectorrhagia due to inflammatory bowel diseases was more frequent in the young group (18.18% vs. 8.26%, p = 0.022) and the colorectal cancer has an increased frequency in the second group (9.92% vs. 2.48%, p = 0.016). For other etiologies no significant differences were recorded between the two age groups.

Discussion/Conclusion: The colonoscopy has an essential role in etiological diagnosis of rectorrhagia.
Inflammatory bowel diseases is more common in young adults hospitalised for rectorrhagia and the colorectal cancer has an increased frequency in adults after 50 yrs, with different impact in patients survival.
Predictive factors of chronic pouchitis after ileal pouch-anal anastomosis for ulcerative colitis

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The aim of our study was to determine the predictive factors of pouchitis after ileal pouch-anal anastomosis in ulcerative colitis.

Methods: Our retrospective study concerned 61 patients treated for ulcerative colitis in our department. 12 developed a chronic pouchitis. We analyze different factors that predispose to pouchitis: age, treatment of the ulcerative colitis before surgery, complications after surgery, stenosis of the anastomosis and Crohn’s disease.

Results: Ileal pouch-anal anastomosis was performed in 61 patients for ulcerative colitis at the University Hospital Sahloul between 1993 and 2004. Operative technique included total proctocolectomy with either distal rectal mucosectomy followed by hand-sewn ileal J pouch-anal anastomosis or stapled ileal pouch-rectal anastomosis. A temporary diverting loop ileostomy was used in all patients. Radiographic contrast examination of the pelvic pouch was routinely performed before ileostomy closure.

Follow-up ranged from 1-10 years (median, 4 years). Twelve patients (20%) experienced chronic pouchitis (9 female, 3 male). All chronic pouchitis patients had at least one pouch endoscopy, and biopsy with histological evidence of pouch inflammation. Pouch biopsy specimens showed the typical findings of lymphocyte infiltration. In three cases, the pouchitis was due to Crohn’s disease. All patients with pouchitis were treated with immunosuppressive or corticosteroid therapy. Improvement was seen in 9 cases. 3 patients underwent a definitive ileostomy. From the different factors included in the univariate study, Crohn’s disease and ileoanal stenosis are the predictive factors of pouchitis.

Discussion/Conclusion: Chronic pouchitis after ileal pouch-anal anastomosis for ulcerative colitis is however frequent and affects the quality of life of patients. The predictive factors of pouchitis are mainly Crohn’s disease diagnosed initially as ulcerative colitis and complications after surgery. However, our study concerns a short number of patients and we need more patients to have significant statistical results.
Predictive factors of glucocorticosteroid treatment failure in severe acute idiopathic colitis

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Introduction: The purpose of our study was to determine clinical, biological or endoscopic factors that predict glucocorticosteroid treatment failure in acute colitis

Methods: Fifty-four Tunisian Caucasian patients with acute idiopathic colitis (ulcerative colitis in 53 patients, Crohn’s colitis in one patient) have been evaluated. Non therapeutic response was defined as over 6 bowel movements per day, blood visible to the naked eye in stools on the fifth day after admission or the development of a complication including a resort of surgery. Predictive factors were assessed using bivariate and multivariate analysis.

Results: Thirty-nine patients (72.2\%) had no medical response. In univariate analysis, predictive factors of therapeutic failure were: male sex, tobacco, previous history of colitis attacks, bowel movements per day over seven at admission and on day three, and pulse rate over 90/mn, temperature over 38°C, systolic blood pressure below 11 on day 3 and on day 5 after admission. In multivariate analysis, bowel movements over seven per day on day 3 of hospitalization and male sex independently predicted a failure of glucocorticosteroid treatment.

Discussion/Conclusion: Bowel movements per day over seven on day 3 of hospitalization and male sex were the independently predictive factors of failure of glucocorticosteroid treatment.
Effect of glutamine-enriched total parenteral nutrition on inflammatory bowel disease

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Introduction: Glutamine has been reported to modulate function of immune cells and gastrointestinal tract. The aim of this study was to assess the effect of glutamine-supplemented total parenteral feeding on clinical and nutritional states in severe IBD. The aim of this study was to assess the effect of glutamine-supplemented total parenteral feeding on clinical and nutritional states in severe IBD.

Methods: 27 patients with severe IBD were qualified to total parenteral feeding with or without glutamine. The clinical, metabolic and nutritional improvement have been analyzed after 14-day treatment.

Results: Thought, we were able to notice some improvements in hemoglobin and transferrin concentration as well as nitrogen balance this still can not be strongly concluded that observation was related on glutamine supplementation. There were any beneficial effect of glutamine on immunological, biochemical and anthropometric parameters of nutritional status.

Discussion/Conclusion: On the basis of currently available clinical data, it seems to be inappropriate to recommend glutamine for therapeutic use in any condition. Moreover, the limited data concerning the supplementation of glutamine suggest that there is not strict evidence of its therapeutic role in IBD. Further studies are required to evaluate the effect of disease location and duration as well as on different formulations of nutritional therapy.
The glycosylation patterns of selected acute phase proteins in ulcerative colitis

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Introduction: In ulcerative colitis acute phase proteins (APPs) play a major but not completely understood pathological role. Changes in glycosylation of APPs may alter its chemical and proinflammatory properties. The aim of the study was to estimate serum alfa1-antichymotrypsin (ACT) and alfa1-acid glycoprotein (AGP) concentrations and evaluate microheterogeneity of those acute phase proteins in patients with ulcerative colitis.

Methods: 25 patients suffering from ulcerative colitis (UC) and 17 healthy control subjects were studied. Patients were categorised as severe (n = 9), moderately severe (n = 8) and mild (n = 8) using True love and Witts’ classification of ulcerative colitis. Microheterogeneity of ACT and AGP was analysed by crossed immunoaffinity electrophoresis (CIAE) with Concanavalin A. In all sera samples standard electrophoresis of serum proteins, cell blood count and CRP were measured.

Results: Our patients suffering from ulcerative colitis had significantly higher serum ACT and AGP concentrations in comparison to healthy subjects. These changes strongly correspond to activity of the inflammatory process. The alterations in glycosylation patterns of those APPs were not strictly related to inflammatory status. However, we were able to observe the correlations between AGP concentration, especially W1-AGP glycoform and platelet count.

Discussion/Conclusion: The glycosylation patterns of AGP and ACT obtained from patients suffering from ulcerative colitis did not differ according to the activity index of ulcerative colitis, even though the serum ACT and AGP concentrations were significantly higher comparing to healthy subjects.
Comparison of 5-ASA treatment modalities for the maintenance of remission in left-sided ulcerative colitis: A long-term follow-up study

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Introduction: Whether orally or topically, 5-ASA is effective and safe in the treatment of left-sided ulcerative colitis. Even though, it was reported that the latter one is superior to the former, it is still not clear the total daily dose and intervals to maintain remission. It has been also not known too much about the natural history of the disease in patients who do not take any treatment during remission except some information obtained from placebo studies. In this study, we compared per oral and topical (both intermittent and continuous) 5-ASA treatment modalities in the maintenance therapy of ulcerative colitis and an option of no treatment in a group of patients.

Methods: A total of 48 patients (32 M, median age 41 ± 11) with left-sided ulcerative colitis under remission for at least 6 months were enrolled into the study. The study group was consisted of thirty-six patients. Remaining 12 which were chosen from the patients who rejected to take any treatment and matching with the study group in terms of age, sex, disease duration and location were approved as the historical control group. Patients were separated into 4 groups as follows: Group I (Oral 5-ASA group, Salofalk® 2 g/daily per oral, n = 12), Group II (Continuous Salofalk® Enema group, Salofalk® Enema 4 g/daily, n = 12), Group III (Intermittent Enema Group, Salofalk® Enema 4 g/twice in a week, n = 12), Group IV (Historical Control Group, n = 12). Groups were first evaluated at the end of treatment period of 12 months and then at the end of follow-up period in terms of relapse rates and mean durations of remission.

Results: For the first 12 months, there were no difference between the groups of treatment arm of study regarding relapse rates and durations of remission (16.7%-11.5 months in Group I, 16.7%-11 months in Group II and 25%-10.1 months in Group III). However, relapse rates were significantly higher and durations of remission were significantly shorter in the historical control group (66%, p < 0.005). In the long-term follow-up period, there were no difference in regard of durations of remission between the groups with the patients who didn’t relapse in first 12 months (Group I: 34.5 ± 21.1 months, Group II: 20.6 ± 11.8 months, Group III: 19.7 ± 6.9 months and Group IV: 15.2 ± 3.7 months, p = 0.1).

Discussion/Conclusion: Intermittent Enema treatment (twice in a week) is as effective as both of continuous enema treatment (every day) and oral treatment. As a natural history of the disease, relapse is seen most frequently in the first 12 months in patients without treatment. After first 12 months, they stay in remission as long as patients who is taken any modalities of 5-ASA treatment.
Retrospective evaluation of results of 1051 colonoscopy patients

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This study aimed to evaluate the results of colonoscopy in a large Turkish population over a 2-year period.

**Methods**: We studied a consecutive series of 1051 patients who had been newly referred for diagnostic colonoscopy from 2004 to 2006. All colonoscopy findings were retrospectively evaluated.

**Results**: The results were shown below. The overall prevalences of ulcerative colitis and Crohn’s disease were 8.94% and 1.52%, respectively. The prevalence of colon Ca was 4.09%. Rectal varices and solitary rectal ulcers were higher in men (p < 0.05). But anal fissures are higher in women (p < 0.001). A positive correlation was found perianal fistulas and Crohn’s disease, with correlation matrix (p < 0.05).

**Conclusions**: It is known that women tend to be affected more commonly than men; we have failed to find a sex difference for occurrence of ulcerative colitis and Crohn’s disease.

<table>
<thead>
<tr>
<th>Results</th>
<th>Total</th>
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<tr>
<td>Number of patients</td>
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<td>534</td>
<td>NS</td>
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<tr>
<td>Normal colonoscopy</td>
<td>254</td>
<td>124</td>
<td>130</td>
<td>NS</td>
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<tr>
<td>Hemorrhoids</td>
<td>548</td>
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<td>271</td>
<td>NS</td>
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<td>42</td>
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<td>P &lt; 0.001</td>
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<td>Polyp in colon</td>
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<td>15</td>
<td>NS</td>
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<tr>
<td>Colon Ca</td>
<td>43</td>
<td>23</td>
<td>20</td>
<td>NS</td>
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<td>NS</td>
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<td>NS</td>
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<td>7</td>
<td>NS</td>
</tr>
<tr>
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<td>2</td>
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Outcomes of gravidity in 44 IBD patients - A single center experience

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Introduction: Gastroenterologists are aware of possible interrelationship between the gravidity and behavior of inflammatory bowel disease (IBD) in female patients. It is recommended therefore that all pregnant IBD patients have a special care in both IBD and pregnancy centers.

Aim and methods: We performed a retrospective assessment in a group of 44 female IBD patients, who became pregnant within the years 2000-2005 in our tertiary center. There were 31 patients with Crohn’s disease (CD) and 13 subjects with ulcerative colitis (UC). In this survey we looked at the activity of IBD at the time of conception, risk of relapse and medical treatment during pregnancy, duration of pregnancy (or time of delivery), and frequency of malformations in newborns. Medical records from both gastroenterology and pregnancy departments were used for data collection.

Results: Most patients (39 pts) were in remission at the time of conception, but in 5 of them moderate disease activity could be detected. Among patients with active disease, only two of them achieved remission at 10th and 12th week of gravidity, with normal subsequent course of both IBD and pregnancy. Two (40%) out of 5 patients with active disease at the time of conception experienced an unfavourable course of pregnancy: one abortion at 10th week in patient with high activity of CD, and one case of urgent surgery due to massive large bowel bleeding in active CD at 12th week of gravidity were observed. This later patient fully recovered after bowel resection, with normal course of pregnancy and delivery thereafter. On the other hand, 4 pts (10% out of subjects with quiescent disease) had a flare of IBD during pregnancy (3 UC and 1 CD patient). Among those 4 patients, one miscarriage at 20th week occurred. Another patient developed relapse of UC during puerperium. No malformation was observed in any of 44 newborns. As far as the medication, 89% were taking mesalazine (mean dose 2 g/daily), while 48% were treated with azathioprine (mean dose 1.8 mg/kg/day). No adverse event related to the medication was seen during all pregnancies.

Conclusions: Our results confirm the importance of absence of disease activity at the time of conception for uneventful course of gravidity in IBD patients. In our group, UC was associated with a higher risk of relapse than CD during pregnancy. On the whole however, neither the course of pregnancy, nor the time of delivery were negatively influenced by the presence of IBD. Both mesalazine and azathioprine were well tolerated, and did not cause any adverse event in our pregnant patients.
Influence of MDR1 polymorphisms on short-term and long-term response to infliximab

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Introduction: Polymorphisms in the MDR1 gene might be crucial for response to drug therapy in patients with IBD.

Aim of the study: We evaluated the most frequently involved polymorphisms of MDR1 gene (C3435T and G2677T/A) as a predictor for therapeutic response in CD pts treated by infliximab.

Patients and methods: Two candidate polymorphic sites with known functional significance were studied in 31 patients treated with standard dose of infliximab (5 mg/kg in three infusions). Short-term clinical response to the therapy was evaluated using CDAI after 30 days since 1st infliximab infusion, and long-term efficacy 1 year after 1st infusion. MDR1 gene polymorphisms were detected by PCR-RFLP method from peripheral DNA. Chi-square test was used to compare allelic distribution in the groups of patients.

Results: We did not observe significant difference in frequencies of either polymorphism between patients classified as long-term responders or non-responders (p = 0.89). We have classified 9 patients as early-responders in the wild-type group for C3435T, while none of them was resistant to therapy. Among pts with C3435T polymorphism, 17 responded to the therapy and 3 didn’t (p = 0.22).

Conclusions: Polymorphism of MDR1 C3435T may have predictive significance for short-term response to infliximab, but long-term response was not influenced.
Clinical and pathogenic peculiarities of indeterminate colitis

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In patients with inflammatory bowel diseases (IBD) frequency of overlap Crohn's disease (CD) and ulcerative colitis (UC) symptoms were increased. These patients detected as indeterminate colitis (IC). At the same time, pathogenic and clinical peculiarities of IC are still unclear.

Aim of study was to investigate clinical, endoscopical, histological and cytokines regulation peculiarities in IC patients.

232 patients with IBD were examined. Among them 180 patients were with UC and 52 patients with CD. Diagnosis of IC was made in patients with overlap of CD and UC clinical symptoms. In all patients colonoscopy with colon biopsy were done and levels of IL-1, -2, -4, -6, -8, -10 and TNF-alfa were studied.

Among IBD in 13 (5.6%) patients IC were detected. In 7 (3.9%) UC patients and 6 (11.5%) CD patients IC were diagnosed. IC more often was diagnosed among patients with total UC (8.7%). Among CD patients IC with stenosis in 13.3% patients, with fistula in 10.0% and without fistula and stenosis in 11.1% patients were found. Clinical symptomatic of IC were characterized by high severity and prolongation of bowel inflammation, extra bowel manifestations. All IC patients had more then one extra bowel manifestations. Endoscopical signs of IC were: combination of CD and UC symptoms, superficial erosions with deep ulcer-fissures, high endoscopical activity of colon inflammation. During histological examination intensive transmural mixed inflammatory cells infiltration in IC patients were found. In all IC patients severe disturbances of slime production were found. In UC and CD patients increasing levels of inflammatory cytokines with decreasing of IL-4 and 10 were found. In CD patients predominant increasing of TNF-alfa, IL-1 and IL-6 with decreasing of IL-10 were observed, but in UC predominantly increasing IL-8 and IL-1 with decreasing on IL-10 and 4 were found. In IC patients predominant increasing of TNF-alfa and IL-1 with decreasing of IL-10 were found.

Thus, IC were found in 5.6% IBD patients, more often among CD patients and characterized by high severity and prolongation bowel inflammation, extra bowel manifestations, intensive transmural cells infiltration and predominant increasing of TNF-alfa and IL-1 levels.
Changes in extent of ulcerative colitis in relation to maintenance remission therapy


Introduction: Although the efficacy of maintenance remission therapy in ulcerative colitis (UC) has been proved in many studies, little is known about its possible effect on the extent of the disease.

Methods: A total of 98 patients, 56 males, 42 females, mean age 52 years, range 22-82 years, from 12 medical centers of Belgium, with actual exacerbation of well-known, endoscopically and histologically proven left-sided UC, were included. The colonic extension was endoscopically determined at the time of the initial diagnosis and at the actual flare-up. The mean duration of UC was 93 ± 72 months, median 84 months, range 3-372 months. The median colonic extension at the time of initial diagnosis was 25 cm, range 2-70 cm from the anal merge. The $\chi^2$-test was used for statistical analysis.

Results: According to our results, 50/98 (51%) patients reported no maintenance therapy during the last three months before the actual exacerbation. The most common maintaining therapy was 5-ASA (43%), while combined therapy was reported by 29.6% of patients. No change in colonic extension was found in 50.7% and 51.7% of patients, respectively with and without maintaining therapy (NS). Some degree of regression was observed in respectively 21.7% and 20.7% (NS), and some degree of extension in respectively 27.5% and 27.6% (NS, p = 0.99). Furthermore, no relationship was found between changes.

Discussion/Conclusion: According to this multicenter study, maintenance remission therapy for left-sided UC was not found to have any statistically significant effect on colonic extension. However, further long-term studies are necessary to confirm these results.
Is re-administration of infliximab (Remicade®) after previous failure in severe Morbus Crohn effective?

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Introduction: Despite the progress in treatment of Crohn’s disease, there are still patients who did not respond to all currently known therapies.

Methods: We report on a 62-year-old male with a known history of Crohn’s colitis since 1999, with severe exacerbations despite all known therapies, including mesalazine, corticosteroids, azathioprine, infliximab (Remicade®), mycophenolate mofetil (Cellcept®) and combinations of them. He also reported serious allergic reactions to azathioprine. Finally, he was operated on twice on 2005 and a subtotal colectomy with ileo-rectal double pouch was performed. However, one-year later he reported continuous serious morbidity with more than 15 bowel movements per day (CDAI > 150). Reactive depression was obvious at that time. Pouchoscopy showed severe ulcerations, mucus and pus. Laboratory examinations showed high CRP levels. Thorax photo was normal and mantoux was negative.

Results: According to clinico-laboratory and endoscopical findings in combination with absence of clear data regarding the therapy of choice in these cases, it was decided to re-treat the patient with infliximab (5 mg/kg IV) at weeks 0, 2, 6 and every 8 weeks thereafter, in combination with mesalazine, budesonide, probiotics, and hydrocortisone foam enemas. He tolerated infliximab infusions well, without severe side effects. Unexpectedly, after second infliximab infusion, his clinical condition was significantly improved and CRP levels were decreased. Three months later he reported almost normal bowel movements for the first time the last years.

Discussion/Conclusion: Re-administration of infliximab in combination with classical therapies are potentially effective in severe cases of morbid Crohn, unresponsive to all current therapies, including surgery.
Could thrombocyte indices be used as disease activity markers in inflammatory bowel diseases?

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Aim: The aim was to observe whether the number of platelets, mean platelet volume (MPV) and platelet distribution width (PDW) do differ between the active and remission phases of inflammatory bowel diseases (IBD).

Material and method: Blood samples were taken prospectively from the patients whom were diagnosed as IBD in our IBD outpatient clinics between the years 2003-2006, in both active and remission phases of their diseases for full blood count analysis. Platelet number, MPV and RDW indices were noted. The patients with IBD, having other concomitant diseases (diabetes mellitus, dyslipidemia, hematological disorders, hypersplenism, valvular heart diseases), taking immunesuppressive drugs or drugs interfering with platelet numbers and functions were not included into the study.

Results: Into the study, 40 patients were included (15 female, 25 male). Platelet numbers, PDW and MPV values of the active versus remissions phases and p values were 404,000 ± 169,000/ml vs. 312,000 ± 105,000/ml, p: 0.004, 11.5 ± 1.67 vs. 14.39 ± 2.31, p: 0.000, 9.70 ± 0.88 vs. 10.05 ± 1.41, p: 0.1.

Discussion: Thrombocytosis is a well known disease activity marker in IBD. The fall in thrombocyte indices like PDW and MPV might also be considered as the markers of disease activity in patients with IBD, as well.
Relationship between serum neopterin levels and inflammatory bowel diseases activity

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Introduction: Neopterin (NP) is produced in monocytes/macrophages primarily upon stimulation with interferon-gamma. The aim of this study is to investigate the role of serum NP levels in Crohn’s disease (CD) and ulcerative colitis (UC) disease activity.

Methods: 61 patients with UC (21 F, 40 M) and 27 patients with CD (9 F, 18 M) who were followed up at Türkiye Yüksek İhtisas Hospital were enrolled into the study. 52 healthy controls (22 F, 30 M) were also enrolled. NP is measured by ELISA. Serum levels above 10 nmol/L are regarded as elevated. Patients with malignancy and systemic infectious diseases were not included into the study. For statistical analysis was used by SPSS 10.01. Significance was established at p < 0.05.

Results: In the UC group 32 (52.5%) patients were active and 29 (47.5%) were inactive. In the CD group 11 (40.7%) patients were active and 16 (59.3%) patients were inactive. The mean age of patients with UC was 42.1 ± 12.9, 42.8 ± 12.8 in CD and 40.1 ± 12.9 in healthy controls. NP levels were significantly increased in patients with active UC compared with remission (p = 0.041). A statistically significant increase was found in three of the clinical activity parameters which are stools with blood and mucus and fever and the endoscopic activity index (p = 0.04, p = 0.023, p = 0.021, p = 0.033, respectively). Similar correlation was not observed in CD group (p = 0.549).

Conclusion: In conclusion we suggest to use serum NP levels as an additional marker to the traditional activity markes in active UC.
SP and CGRP differentially modulate epithelial cell restitution via expression of TGF-beta, TGF-alpha and EGF-receptor RNA in fibroblasts and mast cells in an in vitro wound assay

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Introduction: Substance P (SP) and calcitonin gene related peptide (CGRP) are neurotransmitters of the afferent sensory nervous system. In experimental animal models of colitis, a protective role of SP and CGRP on intestinal mucosa was presumed. The mucosal protection in part depends on a SP and CGRP mediated modulation of mucosal blood flow after injury, but other mechanism seem to add to the protective effect. We demonstrate a mast cell and fibroblast mediated effect of SP and CGRP on epithelial cell restitution in vitro.

Methods: Mast cell and rat kidney fibroblast (NRK-49F) cell-lines were exposed to CGRP or SP in various concentrations. After incubation, the cell culture supernatants were taken from the mast cell or fibroblast cultures and were directly applied to IEC-18 monolayers. While migration and proliferation had been shown in initial experiments, rt-PCR was performed of TGF-beta, TGF-alpha and EGF-receptor at 2 h, 4 h, 6 h, 12 h and 24 h.

Results: CGRP significantly induced epithelial cell migration and proliferation, which is explained by a time dependent TGF-beta, TGF-alpha and EGFR increase, while in vitro stimulation of mast cells had no effect on epithelial cells via stimulation of fibroblasts or when applied directly to epithelial cells. SP significantly induced epithelial cell migration and inhibited epithelial cell proliferation via stimulation of fibroblasts but had no effects via stimulation of mast cells or when applied directly to epithelial cells in vitro. While the results of TGF-beta release over the time course underlined this effect, migration could also be abolished with neutralizing anti-TGF-beta antibody.

Discussion/Conclusion: CGRP and SP modulate epithelial cell restitution in vitro mediated either by mast cells or by fibroblasts. While the epithelial cell migration depends on a TGF-beta release from CGRP stimulated mast cells and SP stimulated fibroblasts the proliferative effects are mediated by TGF-alpha. This observation underlines an important role for the afferent sensory nervous system in mucosal defence and repair and in keeping the mucosal homeostasis.
Colectomy rates after infliximab for refractory ulcerative colitis and predictive factors

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Background & aims: Infliximab (IFX) is efficacious in moderate to severe ulcerative colitis (UC), but follow-up colectomy data are lacking. We studied colectomy rates in our cohort of UC patients.

Methods: The first 117 patients (median age 38 years and 43% female) with moderate to severe steroid-refractory UC treated with 5 mg/kg IFX were studied. At inclusion, 75 patients were on concomitant immunomodulators, 8% were active smokers, 51% never smoked, 59% had CRP ≥ 5 mg/L, 60% had extensive colitis and 51% were pANCA+. Thirty-four percent carried the MDR1 3435TT genotype, and 20% the 2677TT genotype. Short term clinical response was assessed after 4 weeks (single infusion) or 10 weeks (induction). Kaplan-Meier curves were constructed to identify predictors of colectomy.

Results: With a median (IQR) follow-up of 31 (10-42) months, 22 patients (19%) needed colectomy (Figure). Patients who had never smoked (LogRank p = 0.040), with baseline CRP ≥ 5 mg/L (p = 0.039), or carrying the MDR1 3435TT genotype (p = 0.039) came to colectomy faster. Absence of short term clinical response was significantly associated with early colectomy (p < 0.001). Five out of eight patients with severe corticosteroid-refractory UC had a complete clinical response at week 4, 1 significantly improved after a second infusion and 2 needed a colectomy within 2 months.

Discussion: With a median follow-up of 2.5 years, 19% of patients treated with IFX for moderate to severe UC needed colectomy. Never smoking, CRP ≥ 5 mg/L, MDR1 3435TT genotype and absence of short term clinical response were associated with early colectomy.
The ATP-binding cassette transporter ABCG2 (BCRP) and ABCB1 (MDR1) variants are not associated with disease susceptibility, disease phenotype, response to medical therapy or need for surgery in Hungarian patients with inflammatory bowel diseases

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Objective: ABCB1 (MDR-1), a member of the ATP-binding cassette (ABC) transporters, is an attractive candidate gene for the pathogenesis of inflammatory bowel diseases (IBD) and perhaps response to therapy. ABCG2, another important member of the ABC transporters, modulates the absorption, metabolism, cellular efficacy and toxicity of several pharmacological agents, including steroids. Since limited data are available on MDR1 and ABCG2 polymorphisms in East European IBD patients, our aim was to study the ABCG2 and MDR1 variants and patients’ response to medical therapy and/or disease phenotype in Hungarian patients.

Material and methods: 414 unrelated IBD patients (CD: 265, age: 35.2 ± 12.1 years old, duration: 8.7 ± 7.6 years and UC: 149, age: 44.4 ± 15.4 years old, duration: 10.7 ± 8.9 years) and 149 healthy subjects were investigated. ABCG2 G34A, C421A and MDR1 C3435T, G2677T/A SNPs were detected using real-time PCR. Detailed clinical phenotypes were determined by reviewing the medical charts.

Results: The frequency of the ABCG2 and MDR1 SNPs was not significantly different among IBD, CD and UC patients compared to healthy controls. The risk for steroid resistance was not different in CD patients carrying variant ABCG2 (19.6% vs. non-carriers 18.4%, p = NS) or MDR1 3435T (CC: 22.2% vs. CT/TT: 17.6%) alleles. Additionally, the carriage of the variant allele was not associated to familial disease, disease phenotype, presence of extraintestinal manifestations, smoking or response to infliximab therapy or a need for surgery. In UC, the carriage of variant ABCG2 alleles seemed to be prevent arthritis (15.5% vs. 31.7%, OR: 0.39, 95% CI: 0.16-0.98).

Conclusions: MDR1 and ABCG2 SNPs were not associated to disease susceptibility; disease phenotype in Hungarian patients, as well as variant alleles did not predict the response to medical therapy or need for surgery. Further studies are needed to clarify the association between the presence of ABCG2 variants and arthritis in UC.
Quality of life in Crohn’s disease

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**Introduction:** The use of Quality of life (QOL) questionnaires in clinical medicine must be based on instruments that are reliable and valid.

**Methods:** We studied a sample of 84 Crohn’s disease (CD) patients who were classified according to the Montreal classification. Quality of life was assessed by Czech version of the World Health Organization Quality of life Questionnaire (WHOQOL-BREF-CZ) recently validated in Czech Republic and Inflammatory Bowel Disease Questionnaire (IBDQ-CZ). Disease activity was measured by Crohn’s Disease Activity Index (CDAI).

**Results:** 84 CD patients, the mean age was 42.7, 52% were women. 34 patients were active and 50 patients were in remission. In our group we found average global score of WHOQOL-CZ 3.47 (3.82) and the satisfaction with health 2.87 (3.68). Results were compared with Czech standards (value in brackets). Patients with active disease reported lower (inferior) levels in all dimensions global and disease-specific QOL questionnaires than did patients in remission. Mean score IBDQ-CZ was lower in active CD 135.7, than in remission 179.0.

**Discussion/Conclusion:** CD patients with active disease are more impaired than patients in remission. Degree of impairment depends on disease activity. Patients in remission have similar QOL as normal population. The use of combination global and disease specific questionnaire allows a more comprehensive definition of the patient's state of health, identifying features which might be underestimated.
Natural resistance-associated macrophage protein 1 gene polymorphisms in Crohn’s disease

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Introduction: Crohn’s disease (CD) is characterized by chronic activation of macrophages. Natural resistance-associated macrophage protein 1 (NRAMP1) gene regulates antimicrobial activity of macrophages, and has many pleiotropic effects on macrophage functions. Hence NRAMP1 may be involved in the resistance to intracellular pathogens, and this effector of the innate immunity might be involved in the CD pathogenesis. Polymorphic alleles at NRAMP1 have previously been associated with susceptibility to both the putative infectious agents and to autoimmune disorders.

Methods: We therefore investigated its candidacy as a genetic determinant of CD in Greece in an association-based study comparing 200 CD patients with 200 healthy control subjects. The 5'(GT)n promoter polymorphism and 9 single nucleotide or insertion/deletion polymorphisms genotyped across NRAMP1 gene. Semiquantitative RT-PCR was performed in order to investigate the NRAMP1 mRNA levels in RNA isolated from blood of CD patients.

Results: Three NRAMP1 polymorphisms [5'(GT)n, D543N and INT4G/C] were significantly associated with CD. Consistent with previous autoimmune disease studies, allele 3 at the functional (GT)n promoter region repeat polymorphism was significantly associated with CD when compared with healthy controls (odds ratio 1.59; 95% CI: 1.20-2.10; p = 0.0011). Interestingly, we observed that CD patients homozygous for the allele 3 expressed 4 times more NRAMP1 mRNA compared to carriers of allele 2.

Discussion/Conclusion: Based on this we can speculate that overrepresentation of allele 3 in CD patients could lead to hyperactivation of bowel wall macrophages that are chronically exposed to LPS and this could subsequently cause the autoimmune-like phenotype characteristic of CD. Collectively, our data indicate that genetic polymorphisms of NRAMP1 might be associated with the susceptibility to CD.
The serum level of TNF-alpha and the incidence of antineutrophil cytoplasmic antibodies (ANCA) in patients with inflammatory bowel disease

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Introduction: The aim of our study was to determine the prevalence of antibodies to neutrophil cytoplasmic antigen (ANCA) and the level of tumor necrosis factor alpha (TNF-alpha) in group of patients with inflammatory bowel disease (IBD).

Methods: We included in this study 42 patients with IBD (28 females/14 males). According to the clinical picture, laboratory examinations, colonoscopy with histopathological examinations, 26 patients had ulcerative colitis (UC) and 16 patients had Crohn’s disease (CD). We determined ANCA by indirect immunofluorescence (IF) and the values of TNF-alpha in serum, by ELISA test, in inflammatory activity and in remission of IBD. Statistical analysis was performed using the Wilcoxon and Anova tests and Person linear correlation.

Results: pANCA was found consistently in patients with UC (69.23%, 18/26 patients) and in a much smaller percentage in patients with CD disease (37.5%, 6/16 patients). TNF-alpha presented serum levels 3 to 4 times higher during the active periods of the disease. TNF-alpha levels was significantly higher in UC than CD patients.
No correlation was observed between the presence of pANCA antibodies and the disease duration, clinical activity, localisation and therapeutic options. All patients was treated with oral mesalazine (Salofalk®, 1.5-3 g/day), while 6 patients with UC and 4 patients with CD followed combinaded therapy: corticosteroids associate with mesalazine or azathioprine.

Discussion/Conclusion: The prevalence of pANCA is high in patients with UC. The highest levels for TNF-alpha was also observed in UC.
The long-term therapy in maintenance of remission in moderate ulcerative colitis

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Introduction: The aim of our studies was to statistically evaluate and compare the efficiency and safety of mesalazine versus azathioprine long-term treatment in maintenance of remission in patients with moderate UC.

Methods: We studied 36 patients with moderate UC, after remission. Initially, the treatment in inducing remission was: mesalazine (Salofalk®) and a short course of systemically active corticosteroids (22 cases) and azathioprine treatment (Imuran®, 1.5–2 mg/kg/day) in 14 cases. A comparative study of maintenance therapy was performed on three groups of patients: A group (20 patients) treated with oral mesalazine (Salofalk, 500 mg x 3/day), B group (9 patients) suffering for distal ulcerative proctitis were treated with Salofalk® suppositories (twice a day for 3 weeks) in addition with long-term oral mesalazine therapy and C group (7 patients) treated with azathioprine (Imuran®, 0.5-1 mg/kg/day). The study of maintenance therapy during 18 months. We evaluated the CDAI, Powell-Tuck index and endoscopic index.

Results: In A group, the remission maintenance rate was 85.0%, in B group was 77.7% and in C group 85.7%. In B group, two cases presented recurence after 6 months and additional therapy were used mesalazine suppositories, for a three weeks follow up period. The frequency of adverse effects was 10.0% in A group (headache, vomiting) and we did not observed side-effects, in B group. Two patients discontinued treatment with azathioprine (and continued with oral mesalazine) due to adverse events: leuco-trombocytopenia and increased aminotransferase levels. The remission maintenance was monitoring at 3, 6, 12 and 18 months with values of CDAI and Powell-Tuck index.

Discussion/Conclusion: The long-term oral mesalazine treatment in association with a short course of mesalazine suppositories still remains the first line in moderate distal UC. Maintenance therapy with mesalazine had therapeutic success and good tolerance.
From a herbal medicine to a save alternative therapy in inflammatory bowel disease. Boswellia serrata - A specific inhibitor of leukotriene biosynthesis

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In the last 30 years, patients were asking for complementary therapeutical approaches beneficial to evidence based medicine to treat inflammatory bowel disease (IBD). One requirement is a reduced level of adverse side-effects. We initiated such a medication with H15-Gufic, a herbal remedy based on boswellic acids as active compound. The substance was provided in tablets produced out of a methanol extract from Boswellia serrata resin. Boswellic acids posses anti-inflammatory activity, e.g., by a concentration of 80 µg/l dependent inhibition of leukotriene B4-formation in stimulated rat peritoneal neutrophil granulocytes and in traditional Ayurvedic medicine. Boswellic acids mediate their beneficial anti inflammatory effect as specific 5-LOX-inhibitor, thus reducing leukotrienes and modifying immunoreactions in autoimmune diseases, like asthma, IBD, multiple sclerosis, psoriasis, similarly as cortisone. No significant side effects or toxicity were reported.

The H15-compound was licensed previously as an effective and save herbal treatment for musculoskeletal disorders in India.

In the first part of our clinical trial, we compared efficacy and safety of H15 together with mesalazine in 102 randomized patients, confirming that therapy with H15 is not inferior to mesalazine. In the second part, we find that the quality of life (SF 36) was significantly improved and stabilized in all eight parameters compared to only three improved parameters in the mesalazine-groop.

We conclude that considering safety, efficacy and quality of life, Boswellia extract H15 appears to be superior over mesalazine in a benefit-risk-evaluation and thus allows to minimize and discontinue therapies with side effects. This suggests H15-monotherapy as an alternative therapy for patients with IBD.
The impact of a 24-hour telephone helpline on the management of patients with inflammatory bowel disease (IBD)

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Introduction: BSG Guidelines recommend that an IBD service should allow ‘rapid access to advice and clinic appointments in the event of a relapse’. We introduced an IBD nurse-led 24-hour telephone helpline in order to improve accessibility to advice and reduce the number of patients requiring urgent outpatient (OP) review.

Aim: We audited the 24-hour telephone helpline on management and OP attendance in a teaching hospital. Patient satisfaction with the service was also evaluated.

Method: We reviewed all calls received by the IBD-helpline over 1-year. Individual calls were documented with outcomes. If treatment change resulted from the telephone consultation, it was considered to have avoided an OP review. To investigate patients’ views on quality of service, 150 questionnaires were randomly sent to the client group studied.

Results: In total 709 patients (ulcerative colitis n = 405) made 2087 calls. Admission as a result of the call was required in 45 (6%) patients. Investigations were arranged in 335 (47%) cases and early review in 84 (12%). Treatment was changed in 285 (40%) patients. Completed questionnaires were returned by 100 (66%) of the 150 patients. 88 patients (88%) said the helpline avoided them seeing their GP and 98 (98%) felt their disease was managed more effectively as a result of the helpline. The quality of care provided by the helpline was considered excellent or good by 95 (95%) of respondents.

Conclusion: A dedicated telephone helpline is an important addition to specialist IBD services. It is valued by patients and the advice and treatment changes suggested can significantly reduce the need for primary care consultation and specialist OP review.
The impact of a nurse led telephone clinic on quality of inflammatory bowel disease care

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Traditional management of patients with inflammatory bowel disease (IBD) consists of regular hospital follow up (FU). The aims of this study were to assess the effectiveness of telephone clinics (TC) on waiting times and failure to attend (DNA).

Methods: Prior to the introduction of TC, routine waiting time and DNA rate for patients attending an IBD clinic were recorded for 3 consecutive months. Criteria for patients suitable for TC were developed (biopsy proven IBD for > 1 year, stable for 6/12 on first line treatment and inactive disease). Suitable patients were invited to participate over a 3 month period and were phoned 1 week before their FU appointment instead of attending. Patients completed a satisfaction questionnaire.

Results: Before introducing TC, 178 patients were reviewed in the IBD clinic. Waiting time for routine FU was 12 weeks and 21 (12%) patients DNA. During the study period 158 patients were booked into clinic. Forty nine 49 (31%) patients met the criteria for TC, all of whom agreed to participate, reducing the waiting time for routine FU to 4 weeks. Seven (6%) patients DNA. More than 90% of respondents were satisfied with TC.

Conclusion: Nurse led TC can reduce the number of IBD patients requiring hospital FU, significantly reducing waiting times and halving the number of patients who DNA.
Endoscopical aspects in the first diagnosis of Crohn’s disease

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Introduction: The aim of this prospective study was to investigate the localisation of endoscopical lesions of Crohn’s disease (CD), in the moment of the first diagnosis of the disease by endoscopy and biopsy.

Methods: We studied 50 patients (33 F, 17 M), consecutively diagnosed with CD. The mean age of the batch was of 38.4 ± 5.3 years (range 14-78). All subjects underwent total colonoscopy + ileoscopy as well as esogastroduodenoscopy with biopsy of all endoscopical lesions.

Results: The distribution of CD lesions was as followed: 22 (44%) ileocecal, 12 (24%) pancolonic + ileal, 5 (10%) right colon, 4 (8%) ileal, 2 (4%) gastric, 2 (4%) duodenal + ileal, 1 (2%) left colon, 1 (2%) esophageal and 1 (2%) gastroduodenal.

Discussion/Conclusion: The distribution of CD lesions in our geographical region is predominantly ileocecal (44%) and pancolonic and ileal (24%). There are also other more atypical localisations like gastric (6%) and esophageal (2%).
Inflammatory bowel disease in Romania: Epidemiological aspects

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Introduction: The aim of this multicenter prospective study was to investigate the epidemiological features of inflammatory bowel disease (IBD) in an adult population investigated in 18 Romanian gastroenterology centres from all geographical regions.

Methods: We investigated all new and old IBD cases referred in these centres 12 months starting from June 2002. We studied epidemiological features, disease characteristics as well as rates of incidence and prevalence of ulcerative colitis (UC) and Crohn’s disease (CD).

Results: During the 12 months of study we included 254 CD patients (85 incident cases) and 407 UC patients (163 incident cases). For UC, the incidence was 0.97/100,000 and the prevalence was 2.42/100,000. For CD, the incidence was 0.50/100,000 and the prevalence was 1.51/100,000. For the incident cases we observed moderate male predominance, wider age distribution and predominant urban residence. Comparing to the literature we noticed lower rates of severe or complicated IBD cases.

Discussion/Conclusion: In our population IBD patients have low rates of severe or complicated diseases, few of them need surgery. Also the incidence and prevalence rates of UC and CD are low. The UC/CD ratio is around 2/1.
Extraintestinal manifestations in ulcerative colitis patients

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Introduction: The aim of our study was to investigate the ulcerative colitis (UC) patients with extraintestinal manifestations correlated with some laboratory investigations.

Methods: There were investigated 25 patients with moderate UC. From venous blood samples were performed: hemoglobin (Hb), hematocrit (Ht), erythrocyte sedimentation rate (ESR), leucocytes count and formula, C-reactive protein (CRP), serum albumin and electrophoresis. Leucocytes phagocytosis was estimated by nitrobluetetrazolium dye reduction test (NBT %).

Results: Clinical examination of the patients with ulcerative colitis showed in 52% of cases extraintestinal manifestations: fever, arthritis, spondilitis and lesions on oral mucosa (stomatitis, aphthae, ulcerative lesions, leukoplakia, granulomatous tongue). Microcytic anemia was found at all patients. There were observed: accelerated ESR (35 ± 5 mm/h), CRP elevated levels (68.5 ± 2.5 mg/L), leucocytosis (12,500 ± 720/microliter), decreased serum albumin (3.2 ± 0.2 g/dl). The phagocytosis NBT test of blood leukocytes was decreased (3.6 ± 0.56%).

The investigation of saliva in UC patients showed the decrease of leukocyte’s number, of the viability of salivary cells (76 ± 4.14%), of the phagocytosis of salivary leukocytes (NBT = 2.6 ± 0.54%), and the increase of epithelial cells number (1340 ± 89.4/microliter).

Discussion/Conclusion: The increase of epithelial cells desquamation was associated with low levels of salivary leukocytes phagocytosis. These can produce the decrease of mucosal defence and can explain the presence and chronic evolution of ulcerative lesions in oral cavity, in UC patients.
Modulation of innate defence in Crohn's disease patients

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Introduction: Crohn's disease (CD) is a chronic segmental inflammation with predilection for the distal segment of the ileum and results in formation of scar tissue in the bowel. The absorption of nutrients, vitamins and minerals may be compromised and multiple deficiencies will be produced.

Aim: to investigate fluctuations of leucocytes phagocytosis in CD patients before and after zinc administration, in vitro.

Methods: Venous blood samples on heparin were collected from 10 CD patients. Phagocytosis assays were performed in vitro in basal conditions and after pre-incubation of blood with zinc sulphate (33 x 10⁻⁴ g/ml). Leucocytes phagocytic capacity was estimated by index of latex particles ingestion in neutrophils (LI %) and by nitrobluetetrazolium dye reduction test (NBT %).

Results: Leucocytes formula was normal in CD patients and leucocytes phagocytosis was decreased in basal conditions (LI = 63.2 ± 3.63%, NBT = 3.4 ± 0.54%). After blood pre-incubation with zinc, the phagocytosis tests were increased with 25-33% (LI = 67.2 ± 1.72% and NBT = 4.6 ± 0.54%) (p < 0.001).

Discussion/Conclusion: Zinc is an important trace element crucial for the body’s immune defences. These data supported the idea that zinc therapy can be useful in Crohn's disease treatment because can reduce their deficiency and activate innate defence.
Treatment of “three week sulphasalazine syndrome” with corticosteroids

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Introduction: Sulphasalazine (SSZ) is widely used in the treatment of inflammatory bowel disease and many rheumatologic disorders. Side effects of this drug are usually dosage dependent and reversible. In few cases systematic and severe reactions may be seen. Here we report a case with ‘three week sulphasalazine syndrome’.

Case report: We report here a 38-year-old woman, who had severe hepatotoxicity with ascites, splenomegaly, lymph node enlargement, and febrile skin eruptions after three weeks of use of SSZ for spondyloarthropathy. Liver enzyme levels were extremely high with prolongation of prothrombin time and decreased albumin level. Hepatitis A, B, C, Ebstein-Barr virus, cytomegalovirus, salmonella, Legionella, autoimmune markers and blood cultures were all negative. Abdominal MRI revealed hepatosplenomegaly, multiple lymphadenopathy and massive ascites. Biopsy of skin eruptions showed dermatitis with lymphocytic infiltration. All symptoms resolved in 4 weeks after drug withdrawal and high dose corticosteroid therapy.

Discussion/Conclusion: The chronology of this case is compatible with so-called "3-week sulphasalazine syndrome". The multi-organ involvement differentiates this entity from other common drug eruptions. Although it is rare potential serious side effects of sulphasalazine should be considered when using this agent.
Refractory infantile Crohn’s disease (CD) partially responsive to infliximab

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Introduction: IBD is rarely seen in infancy and its treatment may be hard.

Methods and results: A girl whose fever and diarrhea started at 1.5 months of age, was diagnosed as CD at 9 months old. She had severe malnutrition, perianal disease with rectovaginal fistulas, and severe anemia. Colonoscopy revealed widespread ulcers and pseudopolyps, histology was consistent with IBD. Prednisolone, metronidazole, mesalazine and TPN were started. As biochemical/clinical remission wasn’t achieved, azathiopurine and cyclosporine were added. Candida and staphylococcus septicemias complicated the course. Repeated colonoscopies after 3rd and 7th months of diagnosis revealed partial improvement. With development of a gluteal abscess and new perianal fistulas while tapering steroids, clinical and biochemical picture worsened. In spite of maximum doses of steroids, antiinflammatory drugs, antibiotics, and bowel rest, bloody diarrhea, high sedimentation, CRP levels, fever and weight loss continued. Infliximab was started when 18 months old as 5 mg/kg iv additionally to other treatments. After the first dose, perianal disease, diarrhea and general condition improved. Repeated doses at 2nd and 8th weeks were well tolerated with further improvement. One year after the start of infliximab, her condition is stable with infusions every 8 weeks. However complete remission could not be achieved in spite of additional use of azathiopurine and steroids.

Discussion/Conclusion: Infantile CD is a rare and severe disease usually refractory to classical IBD treatment. Infliximab is widely used for fistulizing CD, but not in young infants. This case shows it might be efficacious without side effects for this small group of children with severe infantile CD.
Preliminary study on bacterial translocation in serum of patients with inflammatory bowel disease

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Background: The pathogenesis of inflammatory bowel disease (IBD) involves the interaction between genetic susceptibility, mucosal immunity and intestinal bacteria. Bacterial DNA (bactDNA) derived from luminal bacteria may contribute to the perpetuation of chronic intestinal inflammation. Blood microbiological cultures, though, are frequently negative in these patients and bacterial translocation episodes may be put out of sight.

Aims: To evaluate the presence of bacterial translocation in patients with IBD by means of detection of bacterial DNA in blood.

Patients and methods: 23 patients with IBD not treated with antibiotics the month before inclusion were considered in the study and distributed into the following groups: Group I: active Crohn’s disease (CD); Group II: inactive CD; Group III: active ulcerative colitis (UC); and Group IV: inactive UC. A blood sample was collected in endotoxin-free tubes and a broad-range PCR of a highly conserved region of the bacterial 16SrRNA gene was performed using the following primers: 5'-TTCCGGTTGATCCTGCCGGA-3' as forward, and 5'-GGTTACCTTGTTACGACTT-3' as reverse. Bacterial genomic fragments were purified (QIAquick, QIAGen) and identified by automated nucleotide sequencing analysis (ABIPRISM 310, Applied Biosystems). Sequence alignments were carried out with NCBI database (www.ncbi.nih.gov), using the advanced BLAST search tool. Microbiological cultures were carried out among all the patients.

Results: Four patients out of 7 from Group I (57%), 4 out of 7 from Group II (57%), 8 out of 11 from Group III (73%) and none from Group IV showed bactDNA in serum; Bacteria identifications included *E. coli, Enterococcus spp.* and *Staphylococcus spp.* Blood cultures were negative in all cases.

Conclusion: Molecular detection tools in patients with IBD are able to identify a subgroup of patients with presence of circulating bacterial DNA that remain undetected by microbiological culture. The presence of bacterial translocation in patients with inactive CD, the surprising prevalence of bacterial DNA from *Enterococcus spp* in patients with active UC, and the likely existence of immune consequences associated to these facts require new investigations.
<table>
<thead>
<tr>
<th>Group (n)</th>
<th>bactDNA+ n (%)</th>
<th>bactDNA Id</th>
<th>Blood culture n (+/-)</th>
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<tr>
<td>Group I (7)</td>
<td>4 (57%)</td>
<td><em>E. coli</em> (1), <em>Staphylococcus</em> (2)</td>
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</tr>
<tr>
<td>Group II (7)</td>
<td>4 (57%)</td>
<td><em>E. coli</em> (1), <em>Staphylococcus</em> (1), <em>Streptococcus</em> (1)</td>
<td>0/</td>
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<tr>
<td>Group III (11)</td>
<td>8 (73%)</td>
<td><em>E. coli</em> (2), <em>Enterococcus</em> (4)</td>
<td>0/9</td>
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<tr>
<td>Group IV (6)</td>
<td>0 (0.0%)</td>
<td>-</td>
<td>0/4</td>
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Evaluation of Fas/FasL expression in inflammatory bowel diseases

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Recent studies suggest that Fas/FasL mediated apoptosis is involved in the pathogenesis of inflammatory bowel diseases (IBD)

Material and methods: Colon specimens from 15 patients with ulcerative colitis (UC) and 10 patients with Crohn’s disease (CD) were analyzed for expression of Fas and FasL. We performed immunohistochemistry in archival material of formalin-fixed paraffin-embedded tissue using the anti-Fas and anti-FasL antibodies and the streptavidin-biotin-peroxidase method.

Results: The Fas expression was observed in epithelial cells in ulcerative colitis and Crohn’s disease, and in small part in normal subjects. But the FasL was mostly expressed in active lesions of ulcerative colitis, what we have not observed for active Crohn’s disease.
Clinical significance of systolic abdominal murmur in patients with inflammatory bowel disease

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Introduction and aim: Splanchnic hemodynamic changes measured by means of Doppler ultrasonography have been shown to be indicative of the activity state of inflammatory bowel disease (IBD). The aim of this study was to investigate the clinical value of systolic murmur audible over the abdomen of IBD patients in the assessment of disease activity.

Patients and method: 137 patients with ulcerative colitis (UC) and 78 patients with Crohn's disease (CD) were studied between the 1st of March and 31st of December 2006. Activity state of the disease was evaluated and systolic murmur over the abdomen was assessed in all patients. Patients with abdominal murmur were further investigated by means of color Doppler ultrasonography.

Results: In 9 of the 215 patients with IBD (4.2%), a marked systolic murmur was noted over the epigastrium. The murmur more frequently occurred in patients with CD (5 of 78, 6.4%) and in patients with active IBD (8 of 43, 18.6%) than in patients with UC (4 of 137, 2.92%) or in patients with inactive IBD (1 of 172, 0.5%). Duplex Doppler measurements on the superior mesenteric artery and celiac trunk revealed a pathologically high velocity of arterial flow in one or both arteries in all 5 patients with CD and in 2 of the 4 patients with UC.

Conclusions: Systolic murmurs audible over the abdomen and duplex Doppler measurements showed good correlation in our study. Auscultation for a systolic murmur should be a routine examination during the follow-up of cases with IBD. This simple examination may be a useful marker for assessment of disease activity in patients with IBD, especially in CD. The occurrence of a murmur may indicate an active state of IBD with a pathologically accelerated flow in the superior mesenteric artery and/or celiac trunk. The significance of these pathological changes necessitates further investigations.
The neutrophil respiratory burst is generally preserved in Crohn’s disease, but diminished by cigarette smoking

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Introduction: Defective innate immune responses may contribute to the pathogenesis of Crohn’s disease. Previous attempts to examine the neutrophil respiratory burst in this condition have employed indirect measurements of oxygen consumption and non-physiological stimuli.

Methods: We measured neutrophil oxygen utilization directly using an oxygen electrode in 20 healthy controls and 18 Crohn’s patients. Respiratory bursts were induced by the physiological stimulus of normal human faecal flora or PMA, a potent activator of the NADPH oxidase system.

Results: Oxygen consumption in response to either stimulus was not significantly different in Crohn’s disease. The responses to faecal flora and PMA were highly correlated in each individual ($R = 0.82$, $P < 0.001$), except in two Crohn’s patients who manifested potentially dysregulated responses. Cigarette smoking was significantly associated with reduced oxygen consumption in all subjects in response to both faecal flora (90.3 ± 5.8 and 58.9 ± 5.8 nmol/min respectively, $P = 0.004$) or PMA (62.5 ± 5.0 and 31.4 ± 6.9 nmol/min respectively, $P = 0.006$). There was no effect of carriage of $CARD15$ polymorphisms.

Discussion/Conclusion: Neutrophil respiratory burst is generally preserved in Crohn’s disease. The impairment in the process conferred by smoking may nonetheless contribute to impaired acute inflammatory responses in this condition. These results cannot exclude defects in the NADPH oxidase system in a minority of patients.
Src kinase is a key molecule in cell contact-mediated survival signaling in primary human colonic epithelial cells

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Introduction: Apoptosis after the loss of cell anchorage – “anoikis” – plays an important role in the life cycle of adherent cells. Increased rates of epithelial cell apoptosis have been found in Crohn’s disease and ulcerative colitis, potentially contributing to the tissue damage and ulcer formation found in the diseased mucosa. However, little is known about the molecular mechanisms by which signals originating from cell-matrix and cell-cell interactions are coordinated. Src kinase has been shown to associate with structures constituting both cell-matrix and cell-cell adhesion and is therefore likely to be implicated in signal transduction mediated by cell contacts. We therefore investigated the role of Src kinase in cell adhesion-dependent survival signaling in primary human CEC.

Methods: CEC were isolated as intact crypts from the mucosa of surgical specimens. Induction of anoikis was achieved by incubation of crypts in suspension. Reconstitution of cell-cell contacts was obtained by “pelleting” of CEC. Induction of anoikis was demonstrated by caspase-3 activation (Western Blot, DEVD-pNA). Cell lysates were analyzed for phosphorylation of Src and FAK by Western Blot. Src-dependent signaling was blocked by the specific inhibitor PP1.

Results: In the absence of cell-matrix anchorage anoikis could effectively be blocked by the maintenance of cell-cell contacts. In these cells a rapid deactivation of FAK and a partly and delayed dephosphorylation, but no complete deactivation of Src was observed. In contrast, inhibition of Src-dependent signals in CEC with preserved cell-cell contacts resulted in a strong and dose-dependent increase of apoptosis (p = 0.004). The complete loss of cell anchorage induced a rapid and strong increase of Src activation before active caspase-3 could be detected. This Src hyperactivation contributed to transient protection from anoikis in CEC as cells could be “rescued” by reconstitution of their cell-cell contacts by which caspase-3 activity was reduced by up to 50% (p = 0.007). Inhibition of Src in this model reversed the anoikis-blocking effect of reconstituted cell contacts and accelerated apoptosis.

Discussion/Conclusion: Src signaling is of pivotal importance for cell-cell contact-mediated survival in CEC. Hyperactivation of Src significantly contributes to the transient protection from anoikis immediately after loss of cell anchorage in CEC. Our findings indicate that Src kinase is a key regulatory molecule coordinating survival signals mediated by cell adhesion and might therefore be a potential molecular target to strengthen the epithelial barrier in the mucosa of IBD patients.
Colon cancer and IBD: A different case report

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Introduction: It is often difficult to make the distinction between Ulcerative Colitis (UC) and the Crohn’s disease (CD). Special care is required for patients long diagnosed due to the risk of developing malignant transformation.

Aim: The presentation of a colon cancer case, in which the underlying condition was Inflammatory Bowel Disease (IBD) but was diagnosed as CD, while biopsy of the affected large intestine revealed UC.

Material method: A 53-year-old woman was hospitalized due to proctalgia, mucobloody diarrhea and tenesmus, which were persistent for 15 days. She had a diagnosis of CD’s for 20 years, sclerosing cholangitis for 7 years, hepatic impairment Child I, osteoporosis and ankylosing spondylitis. Patient’s last colonoscopy revealed the existence of pseudopolyp at the 5 cm from the anal ring, mild dysplastic alterations and inflammatory bowel disease affecting all large intestine including ileocecal valve but not the terminal ileum.

Results: Rectal examination showed palpable maze at 4-5 cm from the anal ring. Laboratory tests showed hypochromic anemia and elevated CA 19-9. The colonoscopy demonstrated an ulcerative hemorrhagic infiltrative lesion; respective biopsies validated the presence of an adenocarcinoma of the signet ring type and the histological findings from the area of mucosal inflammation demonstrated lesions compatible to active ulcerative colitis.

Conclusions: It is often difficult to discriminate between UC and CD patients, who are for long diagnosed for the disease, have a higher risk of malignant transformation. The frequency of such transformation is much lower for CD than UC for which there is a 3-5% possibility for cancer development.
Anti-inflammatory potential of melanocortin peptides in intestinal inflammation

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Introduction: Recent research has shown a crucial role of mesenchymal cell expressed melanocortin-1-receptor (MC1R) in experimental colitis. The aim of this study was to evaluate therapeutic effects of MC1R's main ligand, alpha-melanocyte-stimulating hormone (alpha-MSH) or its C-terminal tripeptide KPV in intestinal inflammation in vivo and in intestinal epithelial cells in vitro.

Methods: Anti-inflammatory activity of KPV was analyzed in two murine models of inflammatory bowel disease, DSS-colitis and CD45RB<sup>high</sup>-transfer colitis. To further characterize this effect we tested the influence of α-MSH on secretion of IL-8 in various intestinal epithelial cell lines.

Results: In DSS-colitis, treatment with KPV lead to significantly reduced weight loss and tissue myeloperoxidase activity. Histologically, markedly reduced inflammatory infiltrates were seen in colonic tissue. In the CD45RB<sup>high</sup>-transfer colitis model KPV-treated animals regained body weight, while control mice continuously lost weight. In vitro MC1R was found to be expressed by various intestinal epithelial cell lines allowing its ligand α-MSH/KPV to bind to those epithelial cells leading to a marked decrease of cytokine-induced IL-8 secretion in these cells after proinflammatory stimulation.

Discussion/Conclusion: The melanocortin-derived tripeptide KPV showed significant anti-inflammatory effects in two murine models of colitis potentially through downregulation of epithelial expressed chemokines such as IL-8. KPV may therefore be an interesting therapeutic option in the treatment of inflammatory bowel disease.
The incidence of amebiasis in our patients with ulcerative colitis

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Introduction: It is difficult to distinguish inflammatory bowel disease from colitis associated with amebiasis (Entamoeba hystolitica infection) according to both symptomatic and endoscopic appearance of the colon. Sometimes ulcerative colitis can co-exist with amebiasis. This, of course, leads to confusion in the diagnosis and treatment of the disease. We aimed to demonstrate amebiasis in the cases with ulcerative colitis in our gastroenterology clinic.

Methods: 26 patient who were diagnosed as active ulcerative colitis endoscopically and histopathologically between December 2003 and January 2007 were included into the study. Demographical and endoscopic datas were recorded and Entemoeba hystolitica was examined from fresh faeces and biopsy samples.

Results: Male/female ratio of the patients was 0.85 (12 M 14 F, mean age 37.58 ± 16.08), range 16-70 years), 20 (76.9%) were from urban and 6 (23.07%) were from rural area. Entemoeba hystolitica cysts were dedected in 10 (38.5%) patients and Entemoeba hystolitica trophozoite was dedected in only one (3.8%) patient microscopically in samples of fresh faeces. Neither cysts nor trophozoite were dedected in 15 (57.7%) patients. 7/10 patients who were dedected Entemoeba hystolitica cysts in their stool specimens had pancolitis and the other 3/10 patients had distal colitis. Eight out of ten patients (80%) who had cysts in their stool and the patient who was dedected trophozoid in her stool were from urban. Entemoeba hystolitica could not have been shown in endocopic biopsies of any patient by histopathological examination.

Discussion: Although our region is an endemic area for amebiasis we have not seen much active infection in our patients with ulcerative colitis. This may be due to initial excessive drug using, especially metronidazole, for nearly in all patients with chronic diarrhea.
Demographical, clinical, laboratory and endoscopic aspects of patients with ulcerative colitis in our region

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Introduction: The aim of the present study was to assess the demographic, clinical, laboratory and endoscopic pattern of patients with ulcerative colitis in our region.

Methods: Totally 31 ulcerative colitis patients who were diagnosed by colonoscopy and biopsy between October 2003 and December 2006 were evaluated retrospectively.

Results: Male/female ratio of the patients was 1.06 (16 M 15 F, mean age 39.84 ± 15.90, range 16-70 years), 25 (80.6%) were from urban and 6 (19.4%) were from rural area. The mean disease duration was 3.8 ± 3.5 years (0.1-14), 23 (75.19%) of the patients were non-smoker. The distribution of localisation was pancolitis in 18 (58.6%) patients (mean age 35.56 ± 14.6 years), left-sided colitis in 4 (12.9%) patients (mean age 51.75 ± 12.7) and distal colitis in 9 (29.03%) patients (mean age 43.11 ± 17.56). Common complains on admission were bloody diarrhea in 26 patients (83.9%) with a median stool number 3.9/day, abdominal pain in 18 patients (58.06%), diarrhea without blood in 5 patients (16.1%), artralgia in 2 (6.45%) patients. 25/36 (69.4%) patients were with active disease, 5/31 were in partially remission and 1/31 (3.2%) was in remission. Mean levels of CRP, hemoglobin and MCV at acute phase were, 45.38 (range 2.98-191), 11.93 (range 6.1-15.7) and 77.58 (range 59.10-92.90), respectively. Physical examination findings were: fever 12.9% (4/31), tachycardia 16.1% (5/31), anemia 22.7% (7/31), monoarthritis 6.45% (2/31). No cholestatic hepatic disease was founded. Also, no complications such as toxic megacolon, perforation, abscess or perforation have been observed in any patients.

Discussion/Conclusion: Our patients were mostly non-smokers from urban with a male-female ratio of 1.06 and mostly had pancolitis with commonly bloody diarrhea on admission and had a mean duration of disease 3.8 years.
Measurement of intestinal permeability used a lactulose/mannitol test depending on somatometric data

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The gastrointestinal mucosa is a semipermeable barrier to prevent the absorption of harmful agents. Injury of this sensitive system can lead to development of different disorders. The damage of this barrier is characteristic of the inflammatory bowel diseases therefore the measurement of intestinal permeability is important to control of these patients. However, several exogenous and endogenous factors influence the permeability.

Our aim was to study the correlation between the intestinal permeability measured by lactulose/mannitol test (L/M) and the somatometric data. Healthy volunteers (n = 20) consumed standard dose of lactulose/mannitol mixture dissolved in tap water to isoosmolar concentration, then the 6-hours urine production was collected. Lactulose and mannitol amounts were measured in urine by HPLC method.

Results are expressed in percent ratio of ingested doses. The height and weight of volunteers were recorded and the body mass index (BMI) and body surface were calculated. The dependence of lactulose/mannitol ratio and the somatometric data were examined by regression analysis.

Our results suggest that the measurement of intestinal permeability by lactulose/mannitol test are depending on weight, body mass index and body surface. Correlation was found between these parameters: L/M vs. weight (F = 0.003), L/M vs. BMI (F = 0.05), L/M vs. body surface (F = 0.04). These somatometric data can be considered in the measurement of intestinal permeability.

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Prospective registration and validation of possible risk factors of relapse in patients with inflammatory bowel disease (IBD)

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Introduction: Crohn’s disease (CD) and ulcerative colitis (UC) are chronic relapsing diseases. Existing data concerning risk factors for relapse are isolated and obscure.

Methods: Prospective, two-year (9/04-9/06) study of the risk factors responsible for relapse in IBD patients. 95 IBD patients (34 CD and 61 UC), hospitalized due to a disease relapse, answered the following questions: treatment cessation, use of immunosuppressants (IMS) or infliximab (IFX), recent use (last 3 months) of corticosteroids, NSAIDs, antibiotics, recent infection, diagnosis of another disease, surgical procedure, travel abroad, excessive fatigue or stress and change of smoking habits. Also, fecal culture and parasitic examination test for CMV infection and endoscopic findings were assessed. Registration was based on activity indices (CDAI $\geq$ 150 for CD; SCCAI $\geq$ 4 for UC).

Results: 22 patients (23%) ceased off treatment, 16 (16.8%) were taking IMS and 7 (7.3%) IFX, 28 (29.5%) received corticosteroids, 24 (25.3%) NSAIDs, and 19 (20%) various antibiotics, 25 (26.3%) had a recent infection, 8 (8.4%) reported diagnosis of another disease, 3 (3.1%) underwent surgical procedure, 3 (3.1%) travelled abroad, 44 (46.3%) reported excessive fatigue and 33 (34.7%) excessive stress while 11 (11.6%) changed their smoking habits. 9 patients (9.5%) had a positive fecal culture (6 Clostridium difficile), 3 (3.1%) revealed CMV infection and 11 (11.6%) had disease expansion in endoscopy. No difference between UC and CD concerning the frequency of these factors was found.

Discussion/Conclusion: Our results indicate the frequent presence and possible interaction of one or more significant risk factors as possible cause of relapse in IBD.
Multidrug resistance (MDR) gene polymorphisms influence outcome of azathioprine and glucocorticoids in patients with inflammatory bowel disease

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Introduction: We studied single nucleotide polymorphisms (SNPs) in the multidrug resistance 1 (MDR1) gene to look for their effect on therapy outcome regarding azathioprine (AZA) and glucocorticoids (GLCs) in inflammatory bowel disease (IBD).

Methods: A total of 1815 IBD records were reviewed for intake of azathioprine. We recorded patients on AZA, the reasons for AZA discontinuation (disAZA) and the ability of GLC tapering following AZA initiation. Patients were genotyped for MDR1-G2677T/A and C3435T using PCR-RFLP.

Results: We identified 724 IBD patients (403 females, 321 males/551 CD, 168 UC, 5 IC) aged 40.7 ± 13.8 years who previously (n = 295) or currently (n = 429) received AZA/6-MP therapy. Patients who disAZA due to side effects more often carried the 2677T variant compared to patients continuing AZA (46% vs. 39%, p = 0.028, OR 1.59 (95% CI: 1.05-2.41)]. In multivariate analysis, an independent association was found for this SNP with AZA gastrointestinal intolerance [p = 0.009, OR 3.99 (95% CI: 1.33-11.93)]. There were 141 patients started on GLCs together with AZA. Patients with a significant (n = 16) or complete (n = 38) GLC tapering had a lower prevalence of the 3435T allele [46.1% and 46.9% respectively] compared to groups unable (n = 59) or able of only partial (n = 28) tapering (61% and 57.1% respectively) [p = 0.027, OR 0.58 (0.35-0.94)].

Discussion/Conclusion: In this study, we showed associations of MDR gene polymorphisms and outcome of azathioprine and glucocorticoid therapy in patients with IBD. These data further support a role for MDR genetic variants on the functional effect of the P-gp pump function.
Long-term safety of azathioprine treatment in inflammatory bowel disease: Results from a single referral center

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Introduction: To describe the long-term safety in a cohort of IBD patients treated with azathioprine (AZA).

Methods: Retrospective data collection from a database of 1815 IBD patients (1355 Crohn’s [CD], 447 ulcerative colitis [UC], 13 indeterminate colitis [IC]). All patients who previously received or were currently taking AZA were reviewed.

Results: We identified 729 IBD patients previously or currently on AZA (555 CD, 169 UC, 5 IC). Median disease duration was 12 years (interquartile range [IQR] 7-19 years) and follow up on AZA/6-MP was (median, IQR) 7.1 (4.4-9.7) years. Combination therapy with Infliximab (IFX) was administered in 232 patients. Total colectomy was performed in 74 (10.2%) patients. A total of 15 patients [2%] (12 CD, 3 UC/12 females, 3 males) were diagnosed with 17 cancers, all extraintestinal but no lymphoma. Thirteen patients were on concomitant IFX. There was no significant difference in age, gender, duration of disease, and duration of AZA therapy between AZA-cancer and AZA non-cancer patients. In the whole AZA cohort mortality rate was 0.82% (6/729 patients) while all AZA-cancer patients were alive on latest follow up. We identified 88/729 (12%) patients with AZA-related bone marrow toxicity (BMT). Infections were diagnosed in 27 BMT patients (30%), 8 of them were severe and 4/8 were of viral origin.

Discussion/Conclusion: In this large single center cohort of 729 IBD patients treated with AZA, the mortality rate was 0.82% and prevalence of cancer was 2%, all extraintestinal. BMT was associated with infections and half of severe infections were viral.
Crohn’s disease presenting as multiple veins thrombosis

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**Introduction:** Portal vein thrombosis is a rare complication of Crohn’s disease (CD), and its precise cause and appropriate treatment are not known. We describe a patient presenting with extensive portal, hepatic, and superior mesenteric veins thrombosis, and intestinal obstruction.

**Case report:** We report a 54-year-old man presenting with fever, abdominal pain, nausea, vomiting, diarrhea and 20 kg of weight loss for the last three months. Abdominal distention, tenderness and hepatosplenomegaly were found on physical examination. X-ray of the abdomen revealed air-fluid level compatible with small bowel obstruction. In Doppler ultrasonography hepatosplenomegaly, ascites, portal, inferior vena cava, splenic, and mesenteric vein thrombosis were reported. There were no underlying hypercoagulability state. Starting anticoagulation therapy did not improve the clinical features of the patient. Rectum and sigmoid colon were normal except diverticulosis. In small bowel series, luminal stricture in jejuno-ileal junction was reported. Jejunal stricture and ulcers were detected in double balloon endoscopic examination and histopathological examination of biopsy revealed excessive lymphocytic infiltration. Crohn’s disease was diagnosed and IV corticosteroid therapy was started which ameliorated symptoms immediately.

**Discussion/Conclusion:** This is an example of CD diagnosed after presentation with multiple veins thrombosis, and treated successfully with corticosteroid therapy. CD should be considered while evaluating patients with extensive venous thrombosis without underlying cause.
Polyneuropathy and autonomic neuropathy due to high dose 5-ASA

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Introduction: 5-ASA drugs are commonly used in the treatment of ulcerative colitis (UC). Well known side effects of 5-ASA are: gastrointestinal intolerance, skin rash, infertility, interstitial nephritis, elevation of liver enzymes and anemia. Polyneuropathy and autonomic neuropathy due to high dose 5-ASA have not been reported in the literature. We report hereby a case of polyneuropathy and autonomic neuropathy starting after the inadvertent use of high dose 5-aminosalicylic acid (5-ASA).

Case: 46-years-old male patient, presented to our outpatient clinic with abdominal pain and diarrhea of one year duration. UC was diagnosed in colonoscopic examination. Patient’s symptoms resolved with one month of prednisolone and Sulphasalazine (4.5 g/day) treatment. Remission was maintained with SASP (5-ASA + sulfapyridine) but the patient took high dose of SASP with 5 ASA (Salofalk®) for 2 weeks as a result of a misunderstanding. At the 15th day of treatment, vertigo and orthostatic hypotension as 110/70 mmHg in supine and 60/30 mmHg in upright position were observed. Treatment was stopped and folic acid was initiated. All other causes for orthostatic hypotension were excluded including amilodosis by rectal biopsy. Electromyelographic examination revealed polyneuropathy with early stages of axonal degeneration. Cardiovascular tests were compatible with autonomic neuropathy. Within 2 months of follow-up period the patients symptoms improved but the orthostatic hypotension and EMG findings were unchanged.

Conclusion: Polyneuropathy and autonomic neuropathy can be associated with the use of high dose 5-ASA in UC.
NOD2/CARD15 gene mutations in Polish children with IBD - Frequency, distribution and relation to clinical presentation

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Introduction: No data is available regarding the prevalence of NOD2/CARD15 gene mutations in Polish IBD adult and pediatric patients. The aim of the study was to assess the frequency of CARD15 mutations in Polish children and to relate them to clinical presentation.

Methods: 57 children, 28 with ulcerative colitis (UC) and 29 with Crohn’s disease (CD) were enrolled to the study and genotyped for three disease-associated single nucleotide polymorphisms of NOD2/CARD15 gene (SNP13 3020InsC; SNP8 R702W; SNP12 G908W). The SNP presence was correlated to CD phenotype (localization, behavior, extraintestinal presentation, steroid response, surgery performed).

Results: 4 out of 28 (17%) UC patients and 12 out of 29 (41%) CD patients had CARD15 variants detected (p < 0.05). Three 3020InsC variants and one G908W were found in UC patients whereas ten 3020InsC variants and 3 G908W in CD patients (one patient carries two variants). No difference was found in CD phenotype between SNP carriers and non-carriers. The details were as follows: localization (L₁/L₂/L₃): SNP carriers 4/4/4 vs. 3/3/11 in SNP non-carriers; behavior (B₁/B₂/B₃): 11/1/0 vs. 13/3/1; extraintestinal presentation (no/yes): 11/1 vs. 11/6; steroid response (yes/no): 12/0 vs. 14/3; surgery performed (no/yes): 8/4 vs. 12/4, respectively.

Discussion/Conclusion: 1. The NOD2/CARD15 gene mutations are common in polish pediatric CD patients and frequency (41%) is similar to those reported in other countries in middle Europe (Hungary-Bene et al. 52%). 2. The frequency of NOD2/CARD15 gene mutations is higher in pediatric CD than UC patients. 3. The presence of NOD2/CARD15 gene mutations seems not to correlate with CD phenotype.
Salmonella sepsis and HIV infection

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Infection with non-typhoid Salmonella, which usually only causes enteritis in healthy individuals, can lead to severe septicemia in immunocompromised patients. Salmonella septicemia is more common in homosexual men and more apt to relapse in patients with HIV infection. Diarrhea may be absent.

A case report: Here we present a 61-old man, who was admitted to the hospital with presumptive sepsis. He had a past history of recent ischemic insult. On presentation he was febrile, with liver and spleen enlargement and left hemiparesis. Blood and stool culture were positive for Salmonella enteritidis. Intravenous ciprofloxacin was administrated with effect and he was discharged with improvement. A week later his condition deteriorated with progression of hemiparesis and confusion. He was admitted to another infectious diseases department with suspicions of meningitis. Later it was revealed that he was homosexual and ELISA and confirmatory test for HIV were performed with positive result. His condition continued to deteriorate and after a couple of days he died with preautopsy diagnosis visceral candidosis and progressive multifocal leukoencephalopathy.

Conclusion: Salmonella sepsis in adult patient is very suggestive of immunosuppression and test for HIV is strongly recommended.
Early beneficial results of a synbiotic formula (Synbiotic 2000Forte) in Crohn’s disease patients

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Background/Aim: There is increasing evidence to support a role for intestinal bacteria in the pathogenesis of inflammatory bowel disease, since the immune response against commensal flora is believed to drive inflammatory processes associated with the disease. The current study was conducted, in Crohn’s disease patients, to investigate the efficacy of probiotics plus prebiotics to modify the disease state by means of modulating the intestinal microflora.

Material: In an open-label pilot study 7 male adults with uncomplicated active Crohn’s disease (modified CDAI 231 ± 30) referred for anti-TNFα therapy but looking for alternative medicine were encouraged and consented to receive probiotics treatment. Once daily for 30 consecutive days and then once per week for the next 5 mo period they were given a synbiotic formula (Synbiotic 2000Forte, Medipharm, Sweden) consisting of a combination of four probiotics (10^11 CFU each): Pediococcus pentosaceus 5-33:3, Leuconostoc mesenteroides 32-77:1, L. paracasei ssp. paracasei 19; and L. plantarum 2,362; and inulin, oat bran, pectin, and resistant starch as prebiotics. Efficacy was assessed by clinical status, disease activity and CRP values at baseline and at 2, 4, 8, 12 and 24 wks of therapy.

Results: A significant improvement in clinical status and disease activity was evident as early as 2 wks of treatment and was sustained throughout the whole study period. Modified CDAI at 4 wks was 174 ± 22 (p = 0.004) and continue reducing at 8, 12 and 24wks, 94 ± 19, 82 ± 20, 77 ± 14, respectively (p < 0.0001). Similarly, progressive reduction of CRP values confirms cessation of the inflammatory process [56 ± 19 mg/L at baseline vs. 21 ± 9 at 24 wks].

Conclusion: The results of this preliminary study seem to support a role of synbiotics to induce a prolonged remission in Crohn’s disease. However double-blind studies with a longer observation period are necessary, before any final conclusion can be drawn.
Nutritional status and nutritional characteristics of inflammatory bowel disease patients suffering from coincident hepatobiliary disorders

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Introduction: The aims of the study were to assess nutritional status and nutritional characteristics of inflammatory bowel disease patients suffering from coincident hepatobiliary disorders. Furthermore, assessing and evaluating these patients’ practice of consuming formulas, and consumption of drugs, vitamins and minerals.

Methods: Sixty-three patients suffering from inflammatory bowel disease completed an anonymous, voluntary questionnaire in the autumn of 2006. One group consisted of the 12 patients with hepatobiliary disorders. The control group consisted of 51 patients without hepatobiliary disorders. We used $\chi^2$-test to evaluate findings.

Results: Nineteen percent of the patients have been diagnosed also with hepatobiliary disorders, their average BMI was 24.8. Involuntary weight-loss in the past 3-6 months, occurred in 58.3% of the first and 31.4% of the control group. Involuntary weight gain in the past 3-6 months was observable in the first and control group 25% and 35.3%, respectively. Significant difference could be detected between the two groups regarding some regularly taken drugs. Calcium consumption should be mentioned among minerals: 41.7% of the first opposite to 33.3% of the control group. Eating two times a day is not typical for the first group. In the first group, 41.7% regularly consume formulas, while 17.6% in the control group.

Discussion/Conclusion: Medical nutrition therapy is an essential part of Inflammatory Bowel Disease patients’ therapy. Nevertheless evidence could be obtained for indispensability of this in coincident hepatobiliary disorders. This means a continuous dietary counselling and gastroenterological care till the end of life. Dietary counselling is provided mostly by dietitian, gastroenterologist and internist.
New method for determination of bile acid malabsorption in Crohn’s disease

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Introduction: Bile acid malabsorption (BAM) is a common feature of Crohn’s disease (CD) and might lead to complications such as diarrhea, oxalate nephrolithiasis or pigment gallstone formation. Our previous studies on over than 250 inflammatory bowel disease patients indicate that severity of BAM is very difficult to predict on the basis of clinical picture and that a laboratory testing is necessary. This is, however, neglected in diagnostic process, mainly because of lack of generally available methods. Therefore, we improved method for determination of serum levels of 7alpha-hydroxy-4-cholesten-3-one (cholesten), the most promising marker of BAM.

Methods: Cholesten was extracted from serum by chloroform:methanol and purified with hexane:isopropanol on silica solid phase extraction column. After elution with isopropanol, cholesten was dissolved in acetonitrile and separated by high performance liquid chromatography (C18, acetonitrile:water = 95:5 v/v, detection at 241 nm).

Results: This method proved to be accurate, sensitive and linear within a broad range (2 to 500 ng/ml), sufficient for clinical use. Bypassing the complicated extraction at 64°C of original method (Galman, J. Lipid Res. 2003) made this method simple and easy to introduce in a clinical laboratory. As it can be automatized to a considerable extent, good availability can be expected soon.

Discussion/Conclusion: We conclude measuring serum cholesten levels should become an obligatory method for BAM determination in all CD patients. This would lead to more accurate diagnosis, surveillance and might contribute to better targeted therapeutic intervention.
Changes of the expression of the Na\(^+\)/H\(^+\) exchanger NHE3 and the PDZ-adapter proteins PDZK1 and NHERF1 during inflammation in the colon of the interleukin-10-deficient mouse

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**Introduction**: Impaired absorption of salt and water is a crucial factor in the pathogenesis of diarrhea in IBD. The Na\(^+\)/H\(^+\) exchanger NHE3 is the major transport protein for Na\(^+\) and water absorption in ileum and proximal colon. PDZ-domain adapter proteins are central players in targeting, membrane retention and signal complex formation of membrane proteins, including NHE3. We investigated the expression of NHE3 and different PDZ-adapter proteins in the chronic phase of intestinal inflammation.

**Methods**: Total RNA and protein was extracted from colon mucosa of 6-9 months old interleukin-10-deficient (Il10\(^{tm1Cgn}\), Il10\(^{-/-}\)) and wild type (WT) mice on a C57BL/6J background. Gene expression was measured by quantitative RT-PCR and protein expression by Western blot. Tissue sections were examined by light microscopy and immunohistochemically.

**Results**: Il10\(^{-/-}\) mice developed chronic colitis while WT mice remained unaffected. In the inflamed mucosa of the colon, the proinflammatory cytokines IL-1-beta, IL-12, and TNF-alpha were highly expressed on the gene and protein level while IFN-gamma was only slightly increased. Expression of NHE3 was not downregulated in the inflamed colon, though earlier studies have shown that functional activity is severely impaired. Immunostaining of NHE3 confirmed this observation. PDZK1 expression was downregulated in the colon, while NHERF1 expression was not affected.

**Discussion/Conclusion**: The data suggest that in chronic immune-mediated intestinal inflammation, expression of NHE3 is not downregulated, though the absorptive function of the colon is impaired. This functional impairment of the colon may be related to the strong downregulation of PDZK1, which retains NHE3 in the plasma membrane and regulates its transport function.
Galectin-3 inhibits DSS-induced colitis in mice

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Background: We have recently identified galectin-3 (gal-3) as a new and strong fibroblast activator from colonic epithelial cells. Up to now almost no investigations have been performed concerning gal-3 in inflammatory bowel disease (IBD). Our aim was to clarify the role of gal-3 in DSS-induced colitis in a mouse model.

Material and Methods: Female Balb/c mice (Janvier, France) weighting 20-22 g were used for the induction of acute and chronic DSS colitis. Recombinant gal-3 expression was performed by the pET vector system. Gal-3 was purified using avidin affinity chromatography. Mice received a 5 day treatment with PBS as control and gal-3 in concentrations between 100 µg/ml, 50 µg/ml and 10 µg/ml i.p. MPO-activity was measured using BCA-test. The distal third of the colon was used for histologic analysis. Colon length was used as a macroscopic parameter of inflammatory severity. Colonic cytokine expression was determined by quantitative RT-PCR using Light cycler technology (Roche, Molecular Systems, Mannheim, Germany).

Results: Gal-3 treated mice with acute colitis showed a reduced inflammatory reduction of colonic length and a reduced weight loss compared to PBS treated mice. MPO-activity showed no significant differences in control and gal-3 treated mice. In both acute and chronic colitis gal-3 treatment resulted in a significantly reduced colonic TNF, IL-6 and IL-1β expression.

Discussion: Gal-3, a member of the lectin family, significantly suppresses inflammation in acute and- with regard to proinflammatory cytokine secretion- as well in chronic DSS-induced colitis in mice. Treatment with gal-3 may offer a novel therapeutic approach for the therapy of IBD.
Potential role of Mycobacterium avium subspecies paratuberculosis (MAP) in the etiopathogenesis of Crohn’s disease: A case-control study on intestinal tissue

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Introduction: Etiopathogenesis of Crohn’s disease (CD) remains unknown. MAP is the causative agent of Johne’s disease, a chronic granulomatous inflammatory bowel disease of the cattle, similar to human CD.

Aim: To evaluate the potential association between CD and the presence of intestinal MAP infection.

Methods: A case-control study was designed. A total of 41 patients with CD (17 male, mean age 35 years) who required surgical intestinal resection, and 23 controls (no inflamed control intestinal tissue from autopsies), matched by ethnic, sex and age were included. The presence of MAP DNA in surgically obtained intestinal specimens was examined by using desparaffinized tissue. Genomic DNA genotyping was performed by nested polymerase chain reaction. The oligonucleotide primers were derived from the DNA insertion sequence IS900, with is unique to MAP. The primers p89 and p92 were used to amplify a unique 284 bp fragment of IS900 gene. The association of MAP with CD was tested by Fisher exact test and expressed as OR and 95% confidence interval.

Results: IS900 sequence was detected in 2 out of the 41 CD specimens (4.9%) and in none (0%) of the control tissues (OR 2.97, 95% CI: 0.14-64.7). Infected tissues were from two young female patients with ileal stricturing disease (A1, B2, L1 according to Vienna classification) and no genetic predisposition to CD (absence of CARD15 mutations).

Discussion/Conclusion: Presence of MAP infection in intestinal tissue from CD patients is infrequent. Nevertheless, the absence of genetic predisposition to CD in our infected patients could indicate a potential etiopathogenic role in these cases.
Novel anti-carbohydrate autoantibodies in patients with inflammatory bowel disease: Are they useful for clinical practice?

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Purpose of the study: A serology panel including perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) and anti-Saccharomyces cerevisae antibodies (ASCA) is used for the routine diagnostics of inflammatory bowel disease (IBD). IgA and IgG ASCA titers are significantly greater and highly specific for Crohn’s disease (CD), and p-ANCA positivity is highly specific for ulcerative colitis (UC). Unfortunately, this panel has not been shown to have levels of specificity sufficient to distinguish CD from UC in disputable cases. Our current work was prompted by the fact that patients with CD might have elevated serum levels of antibodies specific for certain carbohydrate structures. Tested carbohydrate assays are based on the oligosaccharide chitobioside carbohydrate, laminaribioside carbohydrate and mannobioside carbohydrate.

Summarized description of the project: The aim of this study was to test the diagnostic accuracy of novel anti-carbohydrate assays: anti-chitobioside carbohydrate antibodies (ACCA), anti-laminaribioside carbohydrate antibodies (ALCA) and anti-mannobioside carbohydrate antibodies (AMCA) along with ASCA in patients with UC and CD and in those without IBD. An analysis of serum samples from patients diagnosed of having IBD was performed at the General Faculty Hospital Prague, Czech Republic. The diagnosis of IBD was established according to clinical, radiological, and endoscopic data. Laboratory ASCA, ACCA, ALCA and AMCA markers were recorded, and their accuracy to diagnose UC or CD was assessed. We have tested 83 serum samples: 31 serum samples belonged to patients with CD, 28 serum samples were obtained from patients with UC, and 24 serum samples from healthy blood donors were used as controls. IBDX™ ELISA Glycominds Ltd was used for detection of all mentioned anti-carbohydrate antibodies and ASCA.

Results and conclusions: The prevalence of ASCA in CD patients was 71% in our population, which was in accordance with the reported prevalence of 50-80% in other studies. In UC, 21% samples were ASCA positive. None of the healthy persons had ASCA positivity. The prevalence of ACCA in CD was 48% (much lower value compared to ASCA). A surprisingly high prevalence of ACCA was found in the UC group - 64%; nevertheless the ACCA autoantibody levels in UC were lower compared to CD (p < 0.05). ALCA was characterized by low sensitivity for CD (39% prevalence) and ordinary “false positivity” in UC and healthy persons: 25% and 8%, respectively. Sensitivity of AMCA for CD was also low (42%). Dissatisfactory was also the statement of differences in tested values between the CD and UC sample groups: statistically significant differences were found only in ASCA and ACCA. No significant differences between the CD and UC groups and/or the IBD and non-IBD groups were found in ALCA and AMCA.
Therefore, are novel anti-carbohydrate antibodies useful for clinical practice in patients with IBD? Our answer is: not yet. Raised anti-carbohydrate antibodies are not completely specific for CD so far. It will be useful to analyzed also other patients with chronic inflammatory disorders than IBD – this would be of interest especially to see whether the antibodies to carbohydrates belong to the pool of naturally occurring antibodies.

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Extraintestinal manifestations and complications at patients with inflammatory bowel diseases

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Introduction: Inflammatory bowel diseases (IBD) through the diagnosis and treatment difficulties along with the multitude of extraintestinal manifestations and complications represent a challenge for the medical practice and research.

Methods: The authors have studied a group of 24 patients diagnosed with IBD and hospitalized in Department of Infectious Diseases Timisoara. The positive diagnosis was based on clinical elements (abdominal pain, diarrhea with bleeding, fever, joint pain, perianal lesions, etc.), biological samples (leucocytosis, ESR, CRP, hemoglobin, hematocrit, electrophoresis, fibrinogen, stool culture, etc.) and results of rectoscopy, sigmoidoscopy, ileocolonoscopy. The extraintestinal manifestations and complications that appeared were registered in the individual patient sheet and were diagnosed with the help of specialists.

Results: The following extraintestinal manifestations were registered: fever at 10 patients (41.66%), anemia at 14 patients (58.33%), poliartralg at 15 patients (62.5%), ocular modifications (iritocyclitis, uveitis) at 6 patients (25.00%), pulmonary modifications (alveolitis) at 5 patients (20.83%), weight loss at 12 patients (50.00%) and erythema nodosum at 4 patients (16.66%). We mentions the following extraintestinal complications: liver changes (hepatosteatosis) at 5 patients (20.83%), gallstones at 6 patients (25.00%), kidney stones at 5 patients (20.83%), hypocalcemia at 8 patients (33.33%), hypomagnesemia at 6 patients (25.00%) and vitamin B deficiency at 5 patients (20.83%).

Discussion/Conclusion: The early diagnosis of possible manifestations and complications at patients with IBD permits the applications of adequate therapeutical measures with positive influences on the course and prognosis of these diseases.
Analysis of predicting factors of leukocytapheresis to patients with intractable moderate to severe ulcerative colitis - A multicenter prospective open label study

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Introduction: Leukocytapheresis (LCAP) has been available as a non-pharmacological adjunctive therapy for moderate-severe active ulcerative colitis (UC) in Japan. However, the clinical factors predicting responder to LCAP treatment are still unclear.

Methods: To clarify the predictive factors of response to LCAP, we conducted a multi-center prospective open labelled study. Totally, 112 patients with UC (70 male, average 38.4 years old; 72 pancolitis, 40 left-sided colitis: 21 first attack, 65 relapse-remitting, 26 chronic-continuous patients) were enrolled into the study. LCAP (50 ml/min x 60 min) with Cellsorba EXTM column (Asahi Kasei Medical Co.) was carried out once a week (one to eleven weeks). Clinical response was evaluated by Lightiger’s CAI. When the CAI was decreased to less than five or less than half of the pre-treatment, within three weeks, the patient was considered as a rapid responder.

Results: Mean CAI was significantly decreased from 11.3 to 4.2 with LCAP. Totally, 73.2% of the patients responded and 54.5% was considered as a rapid responder. By multivariate analysis, significant factors correlated to rapid responses were as follows; 1) Severe disease such as CAI > 11 (Yes 64.0%*, No 43.6%); 2) disease duration < one year (Yes 73.1%*, No 46.8%); 3) Steroid-resistant (Yes 73.3%*, No 45.9%); 4) C-reactive protein (CRP) levels before treatment [* , p < 0.05]. Other factors such as duration, disease location, concomitant 5-ASA or immunosuppressants, age, sex or clinical course did not show significant differences.

Discussion/Conclusion: These results suggest that relatively severe UC resistant to steroid with elevated CRP would be a candidate for LCAP.
NOD1 gene E266K (G796A) polymorphism is associated with disease susceptibility but not with disease phenotype or NOD2/CARD15 in Hungarian patients with Crohn’s disease

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Background: NOD1/CARD4, a member of the pattern-recognition receptor (PRR) family, is a perfect candidate as a susceptibility gene for Crohn’s disease (CD). Since only limited and conflicting data are available on G796A polymorphisms in IBD patients, we set out to study the effect of this polymorphism on the susceptibility and course of CD in the Hungarian population.

Methods: 434 unrelated CD patients (age at presentation: 28.6 ± 9.6 years, female/male: 210/224, duration of CD: 8.2 ± 6.9 years) and 200 healthy subjects (blood donors) were investigated. NOD1 G796A was detected by using polymerase chain reaction/restriction fragment length polymorphism. Detailed clinical phenotypes were determined by reviewing the medical charts.

Results: The frequencies of the variant alleles of NOD1 G796A differed significantly between the CD patients and the healthy controls (GG 49.5% vs. 67%; AG 41.5% vs. 28%; and AA 9.0% vs. 5.2%; p = 0.0001). Carriage of the single nucleotide polymorphism of NOD1 G796A proved to be a highly significant risk factor for CD (p = 0.0001, OR: 2.1, 95% CI: 1.5-2.9). Significant associations were not found between the different genotypes and the demographic data on the patients or the clinical characteristics of CD. The different polymorphisms of PRRs (e.g. NOD2/CARD15 SNP8, SNP12 and SNP13 mutations, the TLR4 D299G polymorphism and NOD1 G796A) did not reveal a mutual basis.

Conclusions: Our results suggest that carriage of the NOD1 G796A mutation increases susceptibility for CD in the Hungarian population.
Stricturing esophageal disease complicating glycogen storage disease type 1b (GSB-1b): Case report

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Introduction: GSD-1b is a rare genetic disorder characterized by accumulation of glycogen in tissues and impaired neutrophil function due to a defective G-6-P transporter protein. An association between GSD-1b and Crohn’s disease (CD) has been proposed.

Methods: We report the case of a young girl with GSD-1b who presented with both lower and upper GI tract symptoms. We present the diagnostic approach and evolution of the case.

Results: A 20-year-old woman was admitted for evaluation of episodes of food impaction, chronic diarrhea and abdominal pain. She was diagnosed with GSD-1b at 7 months of age based on the clinical history (hepatosplenomegaly, recurrent upper respiratory tract infections and hypoglycemic episodes) and positive family history (brother) for GSD-1b. Esophagoscopy and upper GI barium studies revealed a long, fibrotic, non-passable stenosis at the upper third of the esophagus, several ulcerative lesions and a non-communicating fistula tract. Colonoscopy showed patchy inflammatory changes more prominent on the proximal colon and around the ileocecal valve. Histology from colon and esophagus was compatible with IBD. CD was diagnosed and prednisolone 40 mg/day started with gradual dose tapering. The treatment resulted in clinical improvement of dysphagia and diarrhea. Nevertheless, repeat barium studies showed no radiological improvement of the esophageal stenosis.

Conclusions: Co-existence of GSD-1b and CD creates therapeutic difficulties, since a patent GI lumen is critical for feeding and prevention of potentially lethal hypoglycemia. The association of CD with GSD-1b, emphasizes the pathogenetic importance of the innate immune system in IBD.
The value of serum TGF-beta1 in degree of activity in inflammatory bowel diseases

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Introduction: Enhanced production of transforming growth factor-beta1 (TGF-beta1) has been demonstrated in patients with inflammatory bowel diseases (IBD). The aim of this study was to assess the relationship between serum TGF-beta1 concentrations and the degree of disease activity in IBD.

Methods: Serum samples were obtained from 79 patients with ulcerative colitis (UC) (F/M: 23/56, mean age: 44.1 ± 13.8), 38 patients with Crohn’s disease (CD) (F/M: 13/25, mean age: 42.4 ± 12.3) and 30 healthy controls (F/M: 19/11, mean age: 40.2 ± 10.5). Determination of TGF-beta1 was performed with the standardized enzyme-linked immunosorbent assay. Clinical activity in CD was measured by Crohn’s disease activity index (CDAI) and in UC by Truelove-Witts clinical activity index. CDAI higher than 150 was predicted as active disease in CD. UC disease activity was divided into three groups as mild, moderate, and severe. The disease localization was established in patients with UC as distal, left type, or pancolitis and in patients with CD as small bowel, colon, or both.

Results: Serum TGF-beta1 levels were measured higher in patients with both ulcerative colitis (mean: 171.8 ± 117.5 ng/mL) and Crohn’s disease (mean: 174.2 ± 104.6 ng/mL) than controls (96.3 ± 87.4 ng/mL) (p < 0.05). No significant differences were found in patients with Crohn’s disease who had CDAI > 150 than in patients with CD who had CDAI < 150. No significant differences were found among UC patients regarding disease activity. There was no statistically difference with respect to disease localization in both diseases.

Discussion/Conclusion: The serum TGF-beta1 levels increase in patients with inflammatory bowel diseases but it is not associated with disease activity and localization.
Diagnostic value of procalcitonin in determining the activity of IBD

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Aim: Crohn's disease (CD) and ulcerative colitis (UC) are idiopathic inflammatory bowel diseases (IBD) generally complicated with systemic or local infections. Procalcitonin (PCT) and C-reactive protein (CRP) are two acute-phase reactants although PCT is more specific marker for bacterial infections. PCT might be helpful to discriminate bacterial infection from inflammatory processes of IBD. The study aimed to compare the diagnostic value of admission serum PCT and CRP concentrations as indicators of disease severity, infection and complications in inflammatory bowel diseases.

Methods: Disease activity, white blood cell count and sedimentation rate were evaluated in 45 IBD (9 CD and 36 UK) patients admitted to the inpatient clinic for active diseases. Serum PCT level was measured by immunoassay on Kryptor based system. Serum C reactive protein (CRP) was determined by nefolometric method. Fifty healthy volunteers were analyzed as a control group.

Results: CD patients with complications had significantly higher PCT and CRP levels than healthy controls (PCT 0.143 ± 0.081 vs. 0.065 ± 0.008 ng/ml, p < 0.05 and CRP 29 ± 7.5 vs. 2.9 ± 0.46, p < 0.001). Active UC patients also have slightly higher PCT levels and significantly higher CRP levels than controls (PCT 0.107 ± 0.042 and CRP 23 ± 5.5). Two IBD patients with severe systemic complications and overt bacteraemia has PCT value above 0.5 ng/ml. Serum PCT levels was highly correlated with serum CRP but no other disease activity parameters.

Conclusion: PCT levels elevated significantly in active CD and UC patients complicated with systemic infections. Although serum CRP is reliable marker for disease activity, our results suggest that PCT could also be used to predict disease activity of CD and bacterial super infections of UC.
Thrombosis in ulcerative colitis

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Through the 1996-2006 period at the clinic of Gastroenterology of Ege University, some 379 patients with ulcerative colitis have been monitored. Vascular complications were found in 4 patients (1.03%); all of them were in active phase.

Vascular complications were manifested as phelobothrombosis of the veins of the lower limbs in two patients who developed pulmonary thromboembolism with exitus lethalis. Brachial vein thrombosis developed in one patient who was exitus after colectomy operation. Cerebral and pulmonary insult was in one patient.

The occurrence of thrombosis in patients with ulcerative colitis is a leading reason for vascular damage with fatal ending in 3 patients of the affected patients.
Safety of infliximab treatment in Crohn’s disease

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Background & aims: The aim of this study was to evaluate the short- and long-term safety of infliximab treatment in patients with Crohn’s disease in clinical practice.

Methods: The medical records of 297 consecutive Crohn’s Disease patients treated with infliximab at the Beth Israel Deaconess Medical Center were reviewed and abstracted for demographic features and adverse events.

Results: The 297 patients received a total of 1794 infusions. Patients had a median of 4 infusions. Forty-four patients (14%) experienced a serious adverse event. The treatment was stopped in 33 (11%) of patients because of serious side effects. Acute infusion reactions occurred in 18 of 297 patients (6%). One patient developed anaphylactic reaction (0.3%) and 10 (3%) had respiratory problems. Serum sickness-like disease occurred in 1 (0.3%) of 297 patients and 3 (1%) patients developed drug-induced lupus. One patient developed new demyelination disorder. Eight patients had a serious infection, one had fatal sepsis. All of the patients with serious infection also were on other immunosuppressive medications. Six (2.1%) patients had a malignant disorder. A total of 4 (1.3%) deaths were observed; two due to gastrointestinal bleeding, one due to sepsis and one due to cardia adenoca. All of the patients who died also were on other immunosuppressive medications.

Conclusions: Although treatment of infliximab is generally well tolerated patients must be followed very carefully for the occurrence of serious side effects.
The coexistancy of microscopic colitis and focal active colitis in patients with irritable bowel syndrome

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Introduction and aim: Aimed to investigate the frequency of possible microscopic colitis and focal active colitis in the histopathological examinations of colon biopsies of the patients with irritable bowel syndrome having normal colonoscopic examination macroscopically.

Material and methods: Seventy-two patients, aged between 15-65 years old who had the diagnosis of irritable bowel syndrome according to ROMA II criteria are included into the study. Colonoscopy were performed to each patient after the informed consent signed. Two biopsies were taken from terminal ileum, caecum, ascending, transverse and sigmoid colons and rectum if no macroscopic lesion is observed. The biopsies were investigated for possible microscopic colitis and/or focal active colitis by the same pathologist twice.

Results: No microscopic colitis is observed where as focal active colitis, nonspecific colitis and eosinophilic colitis were observed in 6 (8.33%), 5 (6.94%) and 1 (1.38%) of the patients, respectively.

Discussion: Microscopic colitis and focal active colitis are rarely seen organic causes underlying the irritable bowel syndrome. Although we did not observe any microscopic colitis, the result of focal active colitis and eosinophilic is similar with the literature.
Gene polymorphisms in Turkish patients with inflammatory bowel disease

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Introduction: Familial aggregations of inflammatory bowel disease (IBD), and ethnic differences in disease prevalence, suggest that IBD may comprise several genetic diseases. The aim of this study was to investigate the polymorphisms that can determine the immune response levels in TNFalpha (-308, -238), IL-1B (-511), IL-1RN (intron 2) and IL-10 (-627, -1082) genes and noncytokine NOD2/CARD15 (R702W, G908R, and 3020insC), NOD1/CARD4 (E266K, D372N), and ICAM-1 (G241R, K469E) genes, which are known to be associated with inflammation, in Turkish patients with inflammatory bowel disease and healthy control groups.

Methods: In this study, the genotypes of 120 patients with UC and 70 patients with CD who were diagnosed either endoscopically or histopathologically and 106 healthy control subjects who stated that they had never had any prior bowel disease history were compared. A polymerase chain reaction/restriction fragment length polymorphism analysis was performed for the polymorphisms of the ICAM-1, NOD2/CARD15, TNFalpha, IL-10, IL-1B genes, and the E266K variant of the NOD1/CARD4 gene, DNA sequencing method for the D372N polymorphism of the NOD1/CARD4 gene and the VNTR method for polymorphism in the intron 2 of the IL-1RN gene were performed.

Results: The three previously described Crohn’s disease predisposing variants of the NOD2/CARD15 gene and the polymorphisms examined in the NOD1/CARD4, ICAM-1, IL-1B, IL-10, TNFalpha and IL-1RN genes were not found to be associated with ulcerative colitis or Crohn’s disease.

Discussion/Conclusion: The results suggest that these polymorphisms are not important risk factors in the susceptibility to Crohn’s disease or ulcerative colitis in Turkey.
Health-related quality of life (HRQOL) in patients with inflammatory bowel disease

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Introduction: IBD has a significant impact on HRQOL because of the chronic course of the disease. The aim of this study is to evaluate HRQOL in patients with IBD, finding its most influenced domains and follow up after six-eight months.

Methods: Forty eight individuals were included, 15 healthy controls and 33 patients with IBD. IBD patients were divided into two groups - 21 in exacerbation and 12 in remission; 16/33 patients were hospitalized for the second time and followed up. HRQOL was measured using two instruments: WHO Quality of Life Instrument - Brief and Inflammatory Bowel Disease Questionnaire, developed by McMaster University - Canada.

Results: HRQOL in more than half of the patients in exacerbation is less than 50% in all domains compared to the control group which has HRQOL more than 80% in all domains. HRQOL in patients in remission is more than 73% in all domains, close to the HRQOL of the controls, excluding the emotional domain where 7/12 patients have HRQOL lower than 55%. In the follow up all patients who underwent clinical improvement also had improvement in their HRQOL and it raised above 70% in each domain, only in emotional health their HRQOL remains between 54 and 64%.

Discussion/Conclusion: The patients in exacerbation have low HRQOL in all domains, but the leading position takes the emotional domain. In patients in remission emotional domain remains with lowest HRQOL. In patients that have improved clinically over time, HRQOL improved too, but still emotional health remains with low HRQOL.
Favorable response to subcutaneous administration of growth factors in experimental colitis in rats

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Introduction: There are indications suggesting that treatments aiming to overcome innate immunity deficiencies could be satisfactory therapeutic alternatives in patients with inflammatory bowel disease. The aim of this experimental study was to investigate the influence of two growth factors i) Colony Stimulating Factor CSF, Lenograstim, Granulocyte and ii) rHu Granulocyte Stimulating Factor, Molgramostim, Mielogen, in experimental colitis in rats.

Methods: Chemical colitis was induced in 62 male Wistar rats using 2,4,6-trinitrobenzensulfonic acid. Animals were divided into 9 groups. Group 1: 10 rats with colitis without treatment (control group). Euthanasia was performed after 15 days. Group 2: 10 animals with colitis without treatment (control group). Euthanasia after 30 days. Group 3: 6 animals with colitis. Immediate treatment with CSF. Euthanasia after 19 days. Group 4: 6 animals with colitis. Treatment started 7 days after the induction of colitis. Animals were kept for 19 days. Group 5: 6 animals with colitis. Treatment started 2 weeks after the induction of colitis. Group 6: 6 animals with colitis. The same as in group 3. Treatment with GSF. Euthanasia after 19 days. Group 7: 6 animals with colitis. The same as in group 4. Treatment with GSF. Group 8: 6 animals with colitis. The same as in group 5. Treatment with GSF. Group 9: 6 animals with colitis. Immediate treatment with prednisolone and euthanasia after 15 days. Growth factors were administered every 2 days at a dose of 10 mcg/kg. The dose of prednizolone was 5.3 x 10^{-3} mmol/kg. Results were analyzed and evaluated using histological score.

Results: The administration of CSF significantly improved the histological score compared to control groups (p < 0.01). Results in group 5 were less impressive compared with groups 3 and 4. The administration of GM-CSF improved significantly the histological score, although in a lesser degree in the group of late administration. When comparing the two growth factors, CSF was superior to GM-CSF especially in the groups with late administration. Differences between CSF and prednisolone were statistically significant in favor of CSF (p < 0.05).

Discussion/Conclusion: The administration of CSF and GM-CSF can significantly improve the histological score in experimentally induced colitis in rats. Early administration produces even better results.
Minor findings in patients subjected to capsule endoscopy for the evaluation of suspected Crohn’s disease. Implications in our therapeutic decision

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Introduction: Wireless capsule endoscopy (WCE) is very useful in diagnosing suspected Crohn’s disease (CD). However in a subset of patients minor findings are seen and their clinical significance is unknown.

Aim: To assess the predictive value of these findings in patients subjected to capsule endoscopy for suspected CD.

Methods: From October 2003 to October 2006, 35 patients (13 men/22 women, mean age 29.23 ± 10.70 years) with suspected CD as assumed by the presence of at least one of the following: iron deficiency anemia, elevated ESR/CRP, chronic diarrhea, hypoalbuminemia or extraintestinal manifestations were subjected to WCE. All patients had been investigated with upper and lower gastrointestinal endoscopy, small bowel barium follow through or enteroclysis without establishing a certain diagnosis. WCE was considered diagnostic of CD if multiple aphthoid ulcers, more than 3 greater ulcers, strictures or extensive mucosal edema, erythema and erosions were identified. WCE was considered inconclusive if isolated ulcers, focal mucosal edema and erythema or a few aphthoid ulcers were identified and negative if no lesions were seen.

Results: The test was diagnostic in 14 patients, inconclusive in 11 and negative in 10. Patients with minor findings (inconclusive test) did not receive any therapy and were followed up for a mean period of 22.12 ± 6.60 months. During that period 6 (55%) deteriorated and a second diagnostic round set the diagnosis of CD; therefore therapy was commenced.

Conclusion: In patients with high clinical suspicion of Crohn’s disease even minor findings in WCE warrant the administration of anti-inflammatory drugs in order to improve outcome.
Azathioprine/6-mercaptopurine (AZA/6-MP) reduces the risk of intestinal re-operation in Crohn’s disease (CD)

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Background/Aim: Despite increased use of immunosuppressive drugs a reduction of intestinal surgery has not been demonstrated recently. As immunosuppressants might be applied too late before first resection we aimed to investigate the influence of AZA/6-MP on the risk of intestinal re-operation in CD.

Methods: The charts of 579 CD patients were reviewed retrospectively with regard to intestinal re-operation and therapy with AZA/6-MP after first intestinal resection. Intestinal surgery was performed in 377 patients (65.1%). In 333 cases data for further analysis were available. Those patients were stratified into no or ≤ 2 months (mo) AZA/6-MP therapy (n = 214), 3-11 mo (n = 23), 12-35 mo (n = 43), ≥ 36 mo (n = 53). Chi-square test, stepwise logistic regression and Kaplan-Meier analysis were performed.

Results: Intestinal re-operation was performed in 132 patients (40%). The rate of re-operation was 49% in patients with no or < 2 mo AZA/6-MP and 24% in patients under AZA/6-MP (p < 0.001). This benefit was observed in patients with stricture as well as in patients with internal fistula as main indications for first surgery (p < 0.001 and p = 0.044 respectively).

The probability to remain free of intestinal re-operation after 5 years of follow up was significantly reduced in patients who were treated with AZA/6-MP ≥ 12 months (log-rank test; 12-35 mo p=0.026, ≥ 36 mo p = 0.003) and after 10 years in those patients who were treated with AZA/6-MP > 36 mo (log-rank test; ≥ 36 mo p < 0.001). Multivariate analysis revealed that no or < 2 mo of AZA/6-MP therapy after first intestinal surgery (OR 3.0; 95% CI: 1.8-4.9) as the only independent risk factor for re-operation.

Conclusion: Immunosuppressive treatment with AZA/6-MP after the first intestinal surgery reduces the risk for re-operation in CD.
Laparoscopic restorative proctocolectomy for colitis ulcerosa

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Restorative proctocolectomy with ileal pouch-anal anastomosis is the operation of choice today for colitis ulcerosa and familiar polyposis. Besides the standard surgical treatment via laparotomy, the restorative proctocolectomy is increasingly performed using minimal invasive surgery. Two technologies are coming in to use, the hand-assisted laparoscopic method (HALS) and the standard laparoscopic technique. After getting experience with segmental laparoscopic colonic resections, we performed a laparoscopic restorative proctocolectomy in a 34-year-old woman with ulcerative colitis. Failed medical treatment and severe dysplasia in different segments of the colon were the indications for surgical intervention.

Method: Five 10 mm trocars were used. First, the left colon was devascularized from the medial direction. Inferior mesenteric vein and artery were closed using „Ligasure”, and the entire left colon was mobilized. Mesorectal excision was performed and the division of the lower rectum (1 cm above the dentate line) was performed through the right low trocar, with an articulated cutting linear stapler (60 mm). Through a 4 cm incision made in this trocar site, after mobilizing and devascularizing the right half of the colon, the entire dissected colon was drawn out. The ileal pouch was made extracorporeally, and the pouch-anal anastomosis was carried out according to the double stapling technique. Protective loop ileostomy was constructed on the right middle port site. The patient healed without abdominal complications. Bowel activity returned on the third postoperative day.

Conclusion: Laparoscopic restorative proctocolectomy is technically feasible. The minimally invasive technique may reduce the chance of complications following long abdominal incisions applied during open surgery.
Severe eosinophilic infiltration in colonic biopsies predicts patients with ulcerative colitis not responding to medical therapy

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Introduction: Increased accumulation of eosinophils in colonic mucosa in ulcerative colitis (UC) is a common event. Eosinophils are potent proinflammatory cells and are involved in the inflammation of the mucosa. We investigated the clinical significance of eosinophilic infiltration in predicting the outcome of medical treatment in a cohort of ulcerative colitis patients with active disease.

Methods: We studied colorectal biopsy specimens from 12 UC patients with disease in long standing remission, 22 patients with active disease who responded to therapy and 10 patients who were non-responders. Baseline and after treatment, demographic, clinical and laboratory data were obtained. We evaluated the following 5 histologic features: mucosal ulceration, mucosal erosions, crypt abscesses, cryptitis and eosinophilic infiltration of the lamina propria. The severity of these lesions was graded as: none or minimal (0), mild (1), moderate (2) and severe (3). Statistical analyses were performed between “responders” and “non-responders” for differences in demographic, clinical, laboratory, endoscopic and histologic parameters.

Results: Laboratory, endoscopic and histologic parameters were significantly improved after treatment only in “responders” group. Analyses of baseline data, before treatment, revealed no significant differences in parameters between “responders” and “non-responders”, except for a less severe eosinophilic infiltration of lamina propria in responders (p < 0.05). Multiple logistic regression analysis showed that severe eosinophilic infiltration in colonic biopsies was the most significant predictor of no response to medical therapy.

Discussion/Conclusion: Assessing the severity of eosinophilic infiltration in the lamina propria of colonic biopsies in patients with ulcerative colitis seems to be a valuable predictive tool of response to medical therapy.
Family history in patients with inflammatory bowel diseases - Potential clinical patterns

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Background and study aim: The clinical patterns for families with inflammatory bowel diseases may be important in the assessment and follow-up of related patients. The aim of our study was to investigate and compare the clinical characteristics of patients belonging to the same family, who were diagnosed with ulcerative colitis or Crohn’s disease.

Patients and method: Out of 100 patients with ulcerative colitis, 5 had affected family members, while out of 37 patients with Crohn’s disease, 2 had another family member who was diagnosed with an inflammatory bowel disease. In each case of family history we took into consideration the patient’s age at the onset of the disease, the type of disease, its location and type of evolution.

Results: In the group of patients with ulcerative colitis there were 4 parent-child pairs (3 mother-child pairs and 1 father-child pair) and 1 pair of siblings. In the group of patients with Crohn’s disease, both pairs of patients were mother-child.
The mean age of onset of the disease was smaller in children than in parents (19.75 vs. 34 in the group of patients with ulcerative colitis, and 16.5 vs. 38 in the group of patients with Crohn’s disease, respectively).
The transmission of the disease was concordant with respect to the type of disease in the pairs with ulcerative colitis. In the case of the patients with Crohn’s disease, the transmission was concordant in 1 case, and discordant in the other (the mother had Crohn’s disease, while the daughter had ulcerative colitis).
In the case of 2 children with ulcerative colitis, the disease spread over the entire colon and had a severe evolution.

Conclusions: The age of onset of the disease in the case of patients with family history is smaller than in the sporadic cases of disease. We encountered more mother-child pairs of patients. With Crohn’s disease, there are cases of discordant transmission. Some cases of ulcerative colitis with family history had a severe evolution of the disease.
**Is endoscopy really helpful in the diagnosis of IBD in children?**


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**Introduction**: The aim-estimation of the usefulness of endoscopic procedures in the diagnosis of IBD in children.

**Methods**: 156 children (65 female, 91 male) mean age 13.2 years (3-21 years) were included into the study. 252 endoscopy were performed (gastroscopy - 50, colonoscopy - 62, rectoscopy - 8, gastro- and colonoscopy - 131). According to final clinical diagnosis children were divided into 3 groups: Crohn’s disease (CD) (n = 62), ulcerative colitis (UC) (n = 58) and indeterminate colitis (IC) (n = 36).

**Results**: Comparisons of selected factors between the groups.

<table>
<thead>
<tr>
<th></th>
<th>age-years (mean)</th>
<th>sex (F/M)</th>
<th>number of affected parts</th>
<th>changes-oesophagus</th>
<th>changes-stomach</th>
<th>changes-duodenum</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD</td>
<td>14.8</td>
<td>25/37</td>
<td>2.1</td>
<td>22%</td>
<td>73%</td>
<td>75%</td>
</tr>
<tr>
<td>UC</td>
<td>13.1</td>
<td>24/34</td>
<td>3.1</td>
<td>11%</td>
<td>61%</td>
<td>42%</td>
</tr>
<tr>
<td>IC</td>
<td>10.5</td>
<td>16/20</td>
<td>2.3</td>
<td>16%</td>
<td>56%</td>
<td>56%</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.01*</td>
<td>n.s.**</td>
<td>0.01*</td>
<td>n.s.**</td>
<td>0.1**</td>
<td>0.02**</td>
</tr>
</tbody>
</table>

* ANOVA, **-chi2-test

Only 34% patients with CD revealed changes below transverse colon. 73% of patients with UC showed changes in the whole colon. Typical findings: in CD was ulceration (in 40%), in UC were mucous fragility (in 35%) and erosions (in 30%).

**Discussion/Conclusion**: Because of a high prevalence of upper digestive tract changes it is necessary to perform panendoscopy in all children with IBD. There are few characteristic colonoscopic futures helpful in differentiating between CD and UC, but pathology is not so strongly evident as in adult patients.
Restorative proctocolectomy as rescue therapy for pediatric patients with ulcerative colitis

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Introduction: Surgery in UC is still noticed as final treatment. Between 1992-2005, 81 children (39 boys) were diagnosed with UC, surgical treatment was successfully performed in 6 children.

Methods/Results: Data was retrospectively collected from 6 post surgery girls (age 11-15, Me: 12.5). Time since diagnosis was: 2-96 months (mean 16.5). Scheduled surgery was performed in one case, the indication was failure to thrive and steroid dependency. In 5 cases operations were performed urgently mainly because of severe rectal bleeding. Clinical activity index (Truelove-Witts scale) ranged from 5 to 7 pt. Most children were undernurished. In all children endoscopic activity (Mayo Endoscopic Score) was maximal. All children were previously treated with 5-ASA, metyprednisolone, azathioprine, one with cyclosporine. In all cases surgery was performed as two-step procedure. The first-step was restorative proctocolectomy with rectal mucosectomy, forming of ileal J pouch, anoilealis anastomosis and ileostomy. The second-step (after 3 to 6 months) was closing of ileostomy. Follow-up time was up to 3 years. No complications were observed except pouchitis in one patient. All patients improved without additional medication.

Discussion/Conclusion: Restorative proctocolectomy in children with severe course of UC, resistent to step-up treatment is rescue therapy. Surgery is also indicated in the case when conservative treatment effects are not enough and time of treatment prolonged. Surgical treatment is safe and ensures fast return to normal life.
Inflammatory bowel disease and scores at the SF36 quality of life questionnaire

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Introduction: Inflammatory bowel disease (IBD) is an invalidating condition leading to impairment of quality of life. There are studies that showed significant differences in quality of life between IBD patients and general population. The aim of our study was to assess health-related quality of life in active IBD.

Methods: A cohort of 57 patients with active IBD, 48 with ulcerative colitis and 9 with Crohn's disease were enrolled in our study. Cases were in-patients referred to tertiary centers. Patients suffering from other chronic diseases were excluded from the study. The patients completed the SF-36 generic quality of life questionnaire in order to assess health-related quality of life. As controls it was used a group of 50 healthy persons that also received the questionnaire. Their socioeconomic status was not different from that of the controls.

Results: Comparisons of the health-related quality of life scores between the two groups were carried out using the Student’s t-test for independent samples, considering the significance level of p < 0.05. The items of the questionnaire had a high answer rate: 93% to 100% in the patients’ group and 100% in the control group. Analysis of data using independent samples t-test shows significant differences between the two groups for every domain of the quality of life questionnaire (p < 0.001).

Discussion/Conclusion: IBD has a negative impact on health-related quality of life. Patients with active disease are more impaired than healthy population.
Terminal ileitis in children with IBD

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Introduction: Terminal ileitis is a distinguishing feature of Crohn's disease. However, in literature you can meet facts about inflammation in terminal pat of ileum.

Methods: 64 children with IBD (20 with Crohn’s disease (CD) and 44 with ulcerative colitis [UC]) underwent colonoscopy with histological examination and videocapsule endoscopy.

Results: Sings of inflammation in terminal ileum were found in 27 children with IBD (43%). Ulcerative inflammation was diagnosed in 12 children (19%), all of them suffered CD. Mild inflammation (hyperemia and swelling of mucosa, blurred vessels patterns, contact hemorrhages) was observed in 15 children (23%). 6 of them suffered CD with other gastrointestinal localization and 9 had UC with total bowel alteration. In these children inflammation had superficial character and spread on 15-20 cm of ileum.

27 children with terminal ileitis underwent videocapsule endoscopy. Intestine was affected in 11 of them (41%). Endoscopic examination showed ulcers, blood and pus in the intestine, inflammati ve polyps, hyperemia and swelling of mucosa, blurred vessels patterns, contact hemmorhages. One child had intestine-bowel fistula. Provided examination lead to changing of diagnosis from UC to CD in 6 children (22%).

Discussion/Conclusion: Though, 90% children with CD had inflammation in terminal ileum. Two third of them had ulcerative inflammation. Reactive ileitis was observed in 21% children with UC. 41% of children with CD have intestinal inflammation. Used videocapsule endoscopy we change diagnosis from UC to CD 22% children.
Relationship between bone mineral density and clinical features in patients with inflammatory bowel disease: A local study in Turkish population

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Introduction: Patients with inflammatory bowel disease are at risk of developing osteoporosis. Most data show no difference in bone mineral density between patients with Crohn's disease (CD) and those with ulcerative colitis (UC).

Aims: a) to compare bone mineral density in patients with CD and UC b) to evaluate possible factors for bone loss in inflammatory bowel disease.

Methods: 44 (24 males) patients with UC and 27 (14 males) with CD were investigated. Both groups had similar demographical features. Lifetime corticosteroid dose was less than 2 g. Bone mineral density (BMD) relative to age standardised mean (Z score) and T scores were measured by dual x-ray absorptiometry (lumbar spine and femoral neck).

Results: There were no significant difference in mean femoral neck and lumbar Z and T scores between CD and UC patients (p > 0.05). In UC, body mass index was of significant importance but not in CD. Femoral neck Z scores were lower both in CD and UC patients with extraintestinal manifestations. Disease activity, localisation, duration, small bowel resection, sex had no influence on bone mineral density in patients with UC and CD.

Conclusions: Extraintestinal manifestation was significant predictor variable for BMD in both groups. Body mass index was only significantly important in patients with UC. Patients with CD and UC should be evaluated separately with further clinical trials.
CD1c+ and CD303+ dendritic cells in patients with ulcerative colitis and Crohn's disease

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Ulcerative colitis (UC) and Crohn’s disease (CD) are the bowel diseases of autoimmune origin, but their etiopathogenesis is still not completely understood. Dendritic cells (DC) as most potent antigen presenting cells could play a pivotal role in the initiating and perpetuating of the inflammatory process.

The aim of our study was to determine the percentages of myeloid (CD1c+) and plasmacytoid (CD303+) dendritic cells from peripheral blood of patients with UC and CD. Peripheral blood was obtained from 42 patients with UC, 24 patients with CD and 35 healthy donors. Myeloid DC were identified as BDCA-1-positive and CD19-negative cells, whereas plasmacytoid DC as BDCA-2 and CD123 double positive cells. Results were expressed as the medians of percentages in PBMC gate. Non parametric tests were applied to statistical comparison. The percentage of CD1c+ DC in peripheral blood was significantly lowered in patients with UC and CD as compared to healthy subjects (p = 0.004 and p = 0.032, respectively). CD303+ DC were also significantly decreased in patients with UC (p = 0.00001), but the myeloid/plasmacytoid DC ration was significantly higher in patients with UC than in controls (p = 0.002). We also found that percentage of CD303+ DC was significantly lower in UC patients than in CD patients (p = 0.01) and myeloid/plasmacytoid ratio was significantly higher (p = 0.004).

Our results could suggest disturbances in percentages of CD1c+ and CD303+ dendritic cells are involved in the pathogenesis of inflammatory bowel disease. Especially the lack of plasmacytoid DC in patients with UC could be responsible for disorders in immune response.
Practicality and feasibility of CT enterography (CT-E) in patients with Crohn’s disease: A community hospital experience

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Introduction: Studies of CT-E for evaluation of Crohn’s disease have thus far focused on university hospital settings. The purpose of this study was to evaluate the feasibility and practicality of CT-E in a community hospital.

Methods: Fifteen patients with Crohn’s and clinically suspected complications underwent CT-E at a 100 bed community hospital in Montreal, Canada. Prior to imaging, patients received large volume negative oral contrast. Breathhold supine multi-slice thin section CT was performed. Comparison with an age and sex matched group was performed with 15 Crohn’s patients with active disease who underwent small bowel follow through (SBFT) and/or conventional CT and/or enteroclysis.

Results: Time to diagnosis using CT-E was 1 hr, comparing favorably with SBFT (mean time 2 hrs), CT/enteroclysis (mean time 1.5 hrs) and CT/SBFT (mean time 2.5 hrs). CT-E was able to determine the length and grade the severity of recurrences. Extraintestinal complications were well demonstrated. In patients with previous surgery, CT-E was able to differentiate disease recurrence from symptoms due to adhesions.

Discussion/Conclusion: CT-E is a relatively rapid, practical and reliable indicator of Crohn’s activity and complications. It is superior to SBFT and enteroclysis for extraintestinal manifestations and superior to conventional CT for mucosal imaging in detecting early recurrences.
Differential effects of anti-TNF antibodies on activated macrophages and dendritic cells in vivo and in vitro

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Background and aims: Anti-TNF antibodies are a potent tool in the treatment of inflammatory bowel disease (IBD). Despite an increased investigatory focus on these drugs over the last years, their methods of action in vivo are not fully understood. However, previous reports hint at an alteration of inflammatory cells, e.g. by inducing apoptosis in monocytes from IBD patients. In this study, we further investigated mechanisms of action of anti-TNF antibodies using a mouse peritonitis model, which provides a huge number of inflammatory monocytes/macrophages and dendritic cells (DC). In addition, murine cell lines and in vitro differentiated human macrophages and dendritic cells were employed to validate in vivo observations.

Methods: Peritonitis was induced by i.p. injection of thioglycollate medium. 72 hours after induction, mice were treated with either infliximab, anti-murine-TNF antibody or IgG control. Inflammatory cells were retrieved by peritoneal lavage the next day. Cells were identified by flow cytometric analysis of a variety of surface markers. Apoptosis induction in these cells and in in vitro differentiated human macrophages and DC was determined by annexin V/PI staining. MAP kinase activation in murine RAW 264.7 and JAWS II cell lines was analyzed by western blotting.

Results: Using different monocyte/macrophage markers, we could determine that anti-TNF treatment in mice leads to a significant reduction of monocytes and macrophages in vivo, which appears to be at least in part related to apoptosis. Conversely, an increased number of activated DC showing no signs of apoptosis could be observed. In accordance with our in vivo findings, in vitro experiments showed that infliximab dose-dependently induces apoptosis in human macrophages, but not in dendritic cells. Agreeing observations could be made in the murine macrophage cell line RAW 264.7, in which anti-TNF treatment reduces the activation of p38 and p42/44, but not in the dendritic cell line JAWS II.

Conclusions: Our data confirm previous results showing that induction of monocyte apoptosis is a major mechanism of anti-TNF treatment. However, while there is a significant reduction in the monocyte/macrophage population, dendritic cells are activated through anti-TNF treatment and do not show any signs of apoptosis both in vivo and in vitro. TNF antibodies therefore appear to exert their anti-inflammatory effects through different mechanisms on various cell populations.
Dual role of endogenous nitric oxide in development of dextran sodium sulfate-induced colitis in rats

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The role of nitric oxide (NO) in the etiology of ulcerative colitis is controversial with reports of the improvement and aggravation of colonic lesions by inducible NO synthase (iNOS) inhibitors.

In the present study, we compared the effect of the selective iNOS inhibitor aminoguanidine and the nonselective NOS inhibitor N(G)-nitro-L-arginine methyl ester (L-NAME) on a dextran sulfate sodium (DSS)-induced model of colitis in rats. Experimental colitis was induced by a 3% DSS-solution added to drinking water for 7 days. Aminoguanidine (5 approximately 20 mg/kg) and L-NAME (10 mg/kg) were administered p.o. twice daily for the first 3 days, the last 3 days or all 6 days of DSS treatment. Body weight and severity of colitis (diarrhea, bloody feces) were observed over a period of 7 days. DSS treatment resulted in severe colonic lesions, accompanied by diarrhea, bloody feces, decrease of body weight and colon shortening. All of the parameters investigated improved significantly with aminoguanidine treatment at 20 mg/kg for 6 days or the last 3 days of DSS-treatment, but L-NAME did not significantly affect the colitis during these periods. When L-NAME or aminoguanidine was given in the first 3 days of DSS treatment, the colonic lesions were slightly aggravated by L-NAME but not affected by aminoguanidine. The expression of iNOS mRNA was observed from the 3rd day of DSS treatment.

These results suggested that endogenous NO exerts a biphasic influence on DSS-induced colitis, depending on the NOS isoenzyme; a beneficial effect of NO derived from constitutive NOS and a detrimental effect of NO produced by iNOS in the development of colitis.
Antiviral treatment in Crohn’s patients with chronic hepatitis C is well tolerated and effective


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Introduction: Due to surgery and/or blood transfusions patients with Crohn’s disease (CD) are at risk to be infected with hepatitis C. The potential side effect profile of antiviral combination therapy in patients with CD is unknown. Therefore hepatitis C is rarely treated in CD.

Aim: Analysis of the efficacy and of tolerability of antiviral combination therapy in CD.

Methods: Nine patients with inactive CD and hepatitis C (genotype 1: 7, 1 with genotype 3:1, 1 unknown) received interferon/peginterferon-α and ribavirin for 24 to 48 weeks. CD specific therapy (mesalazin 4, azathioprin 2, mycophenolate-mofetil 1) was maintained throughout antiviral therapy. CRP, α1-acid glycoprotein and HCV-RNA (PCR) were determined monthly during therapy and for 6 months follow up. End of treatment response (ETR) and sustained virologic response (SVR; undetectable HCV-RNA at 6 month follow up) rates were evaluated.

Results: All 8 patients, who have finished treatment, had an ETR; the remaining patient is still on therapy. So far, 6 patients completed follow up, 4 achieved a SVR, and 2 relapsed. Overall, therapy was well tolerated, but 5 (55%) patients required CD-specific treatment due to increased CD activity (rise of α1-acid glycoprotein:5; diarrhea:4, increased CRP:1). Anemia (Hb ≤ 8.1 mg/dl) due to ribavirin was treated by erythropoetin in four patients. One patient received antibiotics for exacerbation of preexisting fistula. In comparison with baseline there was no significant change after therapy with respect to CD activity.

Conclusion: Hepatitis C treatment is effective and well tolerated in CD patients independent of concomitant immunosuppressives.
Long-term outcome of treatment with infliximab in 440 Crohn’s disease patients: Results from a single center cohort

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Introduction: Although infliximab (IFX) is used in clinical practice for > 7 years, only few data are available on the efficacy long-term.

Aims: To determine efficacy of IFX in Crohn’s disease (CD) long-term.

Methods: In the first 440 out of 562 CD patients treated with IFX for luminal (n = 359) or fistulizing (n = 81) CD, long-term follow-up was completed up to June 2006. Treatment was episodic in 213 (48%), scheduled in 108 (25%) and episodic with switch to maintenance in 119 patients (27%). Concomitant medication was AZA in 228 (52%), MTX in 46 (10.5%) and corticosteroids (CS) in 162 patients (37%). Shortening of the interval between infusions or increase of dose of IFX were considered therapeutic intervention.

Results: A total of 5.029 IFX infusions (median per patient 8, IQR 3-16) were administered over a median of 41 months (IQR 21-69). Median disease duration until 1st IFX was 7.7 years (IQR 3.1-14.7). A long-term benefit to IFX was observed in 60% of patients (n = 262), of whom 42% (n = 186) had a sustained benefit on ongoing IFX and in 17% (n = 76) IFX could be stopped. Of the latter, 91% were still in remission at latest follow-up (n = 46 on AZA, n = 11 on MTX and 12 no therapy). The majority (64%) did not need interventions to maintain continued response, 28% needed 1 or 2 and only 7% needed 3 or more. Once patients started with IFX and responded initially, median duration of continued response was 132 weeks (IQR 57-239). Of all patients on CS at 1st IFX, 73% were weaned completely and did not need retreatment. Only 8% were judged primary non-responders after a maximum of 3 infusions. 40 patients (9%) had to stop IFX definitely due to side effects (19 severe infusion reactions, 20 delayed hypersensitivity, 14 other severe adverse events). In 85 patients (19%), a definitive change in therapy was necessary primarily due to loss of response. Of the 35 primary non-responders, 18 (51%) needed major abdominal surgery, compared to 21% (87/405) of the responders (Odds ratio 3.87 [95% CI 1.91 -7.83], p < 0.001).

Conclusions: This is the largest single center experience on the long-term outcome of IFX in patients with CD. With a median follow-up of 41 months, 60% of patients report a sustained benefit with IFX and 73% could completely stop steroids. Loss of response is usually managed with therapeutic intervention with need for discontinuation in only 19% of patients so far. Almost one third of patients with sustained benefit (29%) were able to discontinue IFX, with sustained disease control for a median of 23.6 months after stop of IFX (IQR 11-44). Primary non-response to IFX was associated with increased risk of abdominal complications needing surgical intervention.
The mRNA expression levels for the NHE3 adapter protein PDZK1 (NHERF3) but not for the Na\(^+\)/H\(^+\) exchanger NHE3 are severely downregulated in the colonic mucosa of patients with active IBD - Implications for the dysregulation of salt and water transport

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**Introduction:** Acute flares of UC (ulcerative colitis) and CD (Crohn’s disease) are often accompanied by severe diarrhea. A major causative factor is the complete loss of sodium absorptive capacity of the inflamed colonic mucosa of patients with acute UC or CD. Intestinal cell lines incubated with TNF-\(\alpha\) and interferon-\(\gamma\) showed downregulation of the major transport protein for intestinal salt absorption, the Na\(^+\)/H\(^+\) exchanger isoform 3 (NHE3) mRNA expression, but surprisingly, we did not find this in the colon of mouse models for IBD. We did find, however, a severe downregulation of the NHE3 adapter protein PDZK1 (NHERF3), which is a major regulator of intestinal NHE3 transport activity (Cinar et al 2006, Lamprecht et al 2006).

**Aim:** To investigate the mRNA expression levels of NHE3, PDZK1, NHERF1 (another NHE3-binding adapter protein), the proinflammatory cytokine TNF-\(\alpha\), the integral brush border membrane protein villin, and several control genes, in colonic mucosa of patients with active UC and CD and healthy controls.

**Methods:** Biopsies were taken from the colon of patients with UC and CD and matched controls. mRNA levels for the respective genes were quantified by real-time PCR. Biopsies from the same area were sent for histology, and the degree of inflammation graded.

**Results:** 1. We found villin to be the optimal internal control for an epithelial-specific gene with minimal changes of expression levels during inflammation. 2. mRNA expression levels for TNF-\(\alpha\) were elevated in mucosa from IBD patients compared to controls. 3. NHE3 mRNA expression was not significantly altered in any part of the inflamed colon and any stage of inflammation. 4. PDZK1 mRNA expression levels were significantly lower in inflamed mucosa in both UC and MC patients, and inversely correlated with the degree of inflammation. 5. The enterocyte expression levels of NHERF1, another PDZ adapter protein of the same family, were not different between inflamed and normal mucosa.

**Discussion/Conclusion:** In the inflamed colonic mucosa of patients with IBD, expression levels for the transport protein for electroneutral salt absorption, NHE3, are not altered, but there is a severe downregulation of the NHE3 adapter protein PDZK1. We speculate that the downregulation of PDZK1 is likely one of the reasons for a dysregulation of intestinal salt absorption during periods of inflammation.
Effects of exopolysaccharide producing probiotic strains on mast cells in experimental colitis

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Purpose: Mast cells are a key cell type, which is actively involved in the pathogenesis of IBD. In the present study, the effect of exopolysaccharide producing probiotics on mucosal mast cell population was evaluated in experimental colitis.

Material and methods: Colitis was induced by intracolonic administration of acetic acid. Then, rats were treated daily with two probiotic strains, *L. delbrueckii* subsp. *bulgaricus* B3 strain (EPS of 211 mg/L - high-EPS group) or *L. delbrueckii* subsp. *bulgaricus* A13 strain (EPS of 27 mg/L - low-EPS group) which were given into stomach. Preventative group treated with high-exopolysaccharide strain starting 7 days before induction of colitis. The model-control and control groups were treated only with tap water. Rats were killed after seven days of treatment period. Whole colon was removed and proximal and distal colon sections were stained with Alcian blue/Safranin and Toluidine blue to demonstrate the histochemical heterogeneity of mast cells and their degree of degranulation. The following histological evaluation of sections was made under light microscopy.

Results: In distal colon segments, number of granulated mast cells was higher than all probiotic treated and control groups. Number of granulated mast cells was significantly lower in preventative group compared to colitis group (*p* < 0.05). In proximal colon segments, both granulated and degranulated mast cell numbers were not changed in colitis group. Pre-exposure to EPS induced mast cell proliferation and activation in proximal region of colon of rats in preventative group.

Conclusion: In the present study, we suggest that involvement of mast cells to IBD pathogenesis depends on location. Pre-exposure to EPS can be protects from colitis via modulation of mast cell population.
Hepatotoxicity induced by azathioprine in a patient with refractory ulcerative colitis

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The presentation of a case, in which hepatotoxicity was developed in a patient receiving azathioprine for two months as a treatment for refractory ulcerative colitis.

Introduction: Azathioprine (AZA), whose recorded side effects are in some occasions serious, is widely used to treat ulcerative colitis.

Methods: A 67-year-old man presented to our hospital with pain, persistent for the last 24 hrs, in the right hypochondrium. Laboratory tests showed transaminasemia and elevated ALP and $\gamma$-GT. Patient's had previously been treated for hypothyroidism and ulcerative colitis.

Results: Clinical evaluation revealed mild pain during palpation in the right hypochondrium. Increased levels were revealed for: AST: 488 U/L, ALT: 525 U/L, GGT: 447 U/L, ALP: 923 U/L, CRP: 17 mg/dl, while total and direct bilirubin were: TBIL = 1.8 mg/dl, DBIL = 0.9 mg/dl respectively with normal coagulation exams. The examination for viral and autoimmune hepatitis was also negative. Serological tests for tumor markers and ceruloplasmin were normal. Protein electrophoresis showed elevated percentages of b-globulins. AZA treatment was discontinued for 20 days and hepatic markers gradually improved. One month later, no disturbance at the hepatic biochemistry was detected.

Discussion/Conclusion: AZA induces two types of hepatotoxicity. More serious cholestatic hepatitis is rare and has been reported to 1% of the patients. AZA is associated with a) the induction of acute hepatitis of the cholestatic type, producing its primary histological damage in the central zone, and b) with the induction of veno-occlusive disease and nodular regenerative hyperplasia. Therefore a regular clinical and laboratory evaluation is recommended when AZA treatment is administered.
Efficacy of colesevelam in Crohn’s disease patients with diarrhea

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Introduction: Colesevelam is a potent bile acid sequestrant. There is sporadic evidence to suggest it may be useful for patients with functional diarrhea in specific disease groups. The aim of this study was to assess efficacy of colesevelam in patients with chronic diarrhea resistant to standard anti-diarrheal agents and intolerant of cholestyramine.

Methods: Data was collected on 18 patients with intractable diarrhea over 18 months. colesevelam (625 mg tds) was prescribed after standard antidiarrheal measures failed. The patients were divided in 3 groups. Group I (n = 9) Crohn’s disease patients with (n = 6) or without previous small bowel resection (n = 3). Group II (n = 4) diarrhea associated with other diseases in remission (see table). Group III (n = 5) patients where no organic cause for diarrhea was identified (functional). Patients were reviewed at monthly intervals. Parameters studied to assess response were change in stool frequency and consistency. Median follow-up was 13 months (range 0.5-17 months)

Results:

<table>
<thead>
<tr>
<th>Aetiology of diarrhea</th>
<th>Number of patients</th>
<th>Good response to colesevelam</th>
<th>Sex male/female</th>
<th>Range of follow-up (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>Crohn’s Disease (inactive)</td>
<td>9</td>
<td>8 (89%)</td>
<td>4/5</td>
</tr>
<tr>
<td>Group II: post-cholecystectomy(1), celiac disease(1), pancreatic insufficiency(1), Right hemicolectomy for adhesions</td>
<td>4</td>
<td>4 (100%)</td>
<td>1/3</td>
<td>3-13 months (12 months)</td>
</tr>
<tr>
<td>Group III</td>
<td>Functional</td>
<td>5</td>
<td>0 (0%)</td>
<td>2/3</td>
</tr>
</tbody>
</table>

None of the patients experienced side-effects and gender did not influence response.

Discussion/Conclusion: Colesevelam is useful in Crohn’s disease diarrhea irrespective of bowel resection or disease activity. Good response was also noted in chronic diarrhea associated with other causes. No benefit was seen in patients with functional diarrhea.
The prevalence of the microscopic colitis and celiac disease in the patients with irritable bowel syndrome

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**Gazi University Medical Faculty, Pathology Clinic, Ankara, Turkey

**Background**: Irritable bowel syndrome has a high prevalence. Consensus diagnostic criteria (ROME II) based on symptoms have been established to aid diagnosis. Microscopic colitis, encompassing collagenous and lymphocytic colitis, is diagnosed by histologic criteria. Both celiac disease (CD) and microscopic colitis (MC) can be misdiagnosed as irritable bowel syndrome (IBS).

**Aim**: This study aims to find the prevalence of celiac disease and microscopic colitis among patients diagnosed as irritable bowel syndrome in patients fulfilling ROME II criteria.

**Methods**: 91 consecutive new patients who fulfilled Rome II criteria for irritable bowel syndrome (IBS), and 52 healthy controls for CD (age and sex matched), and 41 healthy controls for MC (age and sex matched) were investigated. Healthy control cases who were selected among the subjects routinely undergoing upper endoscopic and colonoscopic examination for check-up. Celiac disease was diagnosed by analysis of serum IgA antigliadin, IgG antigliadin, and endomysial antibodies (EMA) and duodenal biopsy. Microscopic colitis was diagnosed by segmenter colonoscopic biopsy. Ethical approval was obtained from the Ethics Committee of Gazi University Medical Faculty.

**Results**: The patients with irritable bowel syndrome were subdivided according to ROME II criteria into three groups: 21 (23%) were constipation predominant, 57 (62.7%) diarrhea predominant, and 13 (14.3%) had diarrhea and constipation. Two control groups had no CD or MC. 91 patients with irritable bowel syndrome had positive antibody results and douodenal biopsy, 7 of them had celiac disease and 9 had microscopic colitis. The prevalence of CD was 8.8% (8/91) in participants with irritable bowel syndrome. Nine cases of microscopic colitis (7 lymphocytic, 2 collagenous) were diagnosed in this study. The prevalence of MC was 9.9% (9/91). Compared with matched controls, irritable bowel syndrome was significantly associated with CD and MC (p < 0.05). All the patients with CD and MC had diarrhea predominant of IBS.

**Conclusions**: Celiac disease is a common finding among patients labelled as irritable bowel syndrome. In this sub-group, a gluten free diet may lead to a significant improvement in symptoms. Routine testing for celiac disease may be suggested in all patients being evaluated for irritable bowel syndrome. These data clearly demonstrate that a considerable group of patients with diarrhea-predominant IBS have microscopic colitis and celiac disease. This study shows that a probable overlap could be seen in a subgroup of IBS patients.
Prospective assessment of Helicobacter pylori gastritis in children and adolescent with newly diagnosed inflammatory bowel disease before introduction of any pharmacological treatment

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Introduction: Helicobacter pylori (Hp) gastritis has been reported to be unusual in children with inflammatory bowel disease (IBD). A reduced prevalence of Hp infection in adults with IBD has been attributed to the pharmacological treatment. However, the role of different medications remains controversial giving the open possibility that the low Hp infection rate is not therapy related.

Methods: We studied 94 consecutive children with newly diagnosed IBD according to the Porto criteria, including 50 with Crohn’s disease (CD) and 44 with ulcerative colitis (UC). One hundred and four children referred for gastroscopy because of functional dyspepsia served as a control. Hp was detected with a rapid urease test and Hp gastritis was diagnosed on histology examination with hematoxylin-eosin and Giemsa staining of biopsies taken from the antral and corporal part of the stomach.

Results: The results revealed a highly statistically lower prevalence rate of Hp gastritis in children with IBD as compared with controls (9.6% vs. 38, 4%, p < 0.0001). Of UC, 2/44 children and of CD patients 7/50 were diagnosed with Hp gastritis (4, 5% vs. 14%, p < 0.005). There was no statistical difference in mean age of the IBD onset between Hp gastritis positive and negative patients (14, 3 ± 3.75 vs. 13, 6 ± 4.3 years).

Discussion/Conclusion: Hp-positive gastritis was not unusual in children with IBD, however they were less likely to be infected with Hp than their age and sex matched controls. The prevalence of Hp gastritis was significantly higher in CD compare to UC patients. Reduced Hp gastritis rate in IBD children could not be attributed to the medical treatment.
A clinical evolving study of ulcerative colitis over a 15 years period

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Introduction: Ulcerative colitis is a chronic disease, with a continuous course, and frequent relapses. It usually affects persons aged 20-40 years old as well as elderly people. Its manifestation can vary from mild to severe forms and from local to general symptoms. The aim of this paper was to study the clinical evolution of the ulcerative colitis during a 15 years period.

Material and methods: This study was made on 75 patients during a 15 years period. The patients were aged between 23-71 years and the gender proportion was 69% males, 31% females.
All of the patients were investigated by the means of clinical and complex paraclinical exams.

Results: We used a treatment scheme based on Salofalk®. The evolution was favorable according to the stage, 44% from the mild cases and 22% from the severe ones. The complications we encountered were local (pericollitis 10%, toxic megalom 8%, and intestinal perforation 4%) or global (anemia 65%, liver problems 62%, cancer 25%).
The portrait we developed for the classic victim is: elderly, severe form, extended intestinal bleeding, frequent episodes, and presence of anemia.

Conclusions: Recto-colitis and the complications that follow this disease are very severe and life-treating. Therefore, it is recommended that a physician should be consulted and his advice should be followed. Frequent check-ups are also a good idea.
Treatment of hemorrhagical rectocolitis with Salofalk® enemas and Salofalk® suppositoria

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State Medical and Pharmaceutical University “Nicolae Testemitanu”, Chair of Internal Medicine nr. 5, Chisinau, Moldova

Introduction: A superior efficacy of Salofalk® versus sulfasalazine in treatment of hemorrhagical rectocolitis is well known. However, the efficacy of Salofalk®, depending on the administration form in hemorrhagical rectocolitis, remains contraversal.

The aim of the present study was to evaluate the effect of Salofalk® enemas administration versus Salofalk® suppositoria administration in treatment of hemorrhagical rectocolitis exacerbations.

Methods: The study included 34 patients with hemorrhagical rectocolitis exacerbation (19 patients with the descending colon involvements and 15 patients with proctosigmoiditis). The patients were divided in 2 groups: 18 patients were administrated Salofalk® enemas 4 g before sleep following an evacuant enema and 16 patients were given 3 g of Salofalk® suppositoria in 24 hours. The treatment lasted 28 days. Our study not included the patients with hemorrhagical rectocolitis of the ascending and transverse colon.

Results: A stable remission was obtained in 14 patients (77.7%) from Salofalk® enemas group versus 9 patients (56.3%) from Salofalk® suppositoria group. Thus, the difference between the groups was statistically significant (p < 0.05).

Discussion/Conclusion: Salofalk® enemas administration in hemorrhagical rectocolitis exacerbations proved to be significantly superior versus Salofalk® suppositoria.
Evaluation of the association of NOD2/CARD15 genotype with clinical course of Turkish Crohn’s disease patients

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Background and aim: NOD2/CARD15 mutations are associated with susceptibility to Crohn’s disease. In addition, independent data suggest that NOD2/CARD15 variants are associated with early onset disease, involvement of the terminal ileum, and fibrostenosing disease. However, the contribution is subject to considerable ethnic and even regional variation. The aim of this study was to determine the frequency of NOD2/CARD15 mutations in Turkish Crohn’s disease patients, and to evaluate the genotype-phenotype interactions.

Materials and methods: 45 Crohn’s disease patients (32 male, 13 female) with a mean age of 38.7 ± 12.1 (range: 19-78) were enrolled into the study. The three major polymorphisms (R702W, G908R, 3020insC) on NOD2/CARD15 gene were studied from the peripheral blood genomic DNA. R702W and G908R mutations were studied by PCR-RFLP method, and 3020insC mutation was studied by DNA sequencing.

Results: No homozygote mutation was detected. Heterozygote R702W, G908R, and 3020insC mutations were detected in 4 patients, 3 patients, and 4 patients, respectively. The frequency of R702W, G908R, and 3020insC mutations were found to be 4.4%, 3.3%, and 4.4%, respectively. The overall mutation frequency was found to be 12.2%. There was no statistically difference between the clinical course of the patients with (n = 34) and without (n = 11) mutations (p > 0.05).

Conclusion: NOD2/CARD15 gene polymorphism was found to be high in Turkish Crohn’s disease patients. However, genetic polymorphism was not associated with the clinical course of the Crohn’s disease in this study.
Evaluation of 100 Crohn’s disease patients according to the Vienna and Montreal classifications

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Background and aim: Behavior, site, and progression of the Crohn’s disease are variable likely to be identified by genetic markers. Clinical classifications of the Crohn’s disease may help to define subgroups of patients suitable for future genetic studies. The aim of this study was to evaluate our Crohn’s disease patients according to the Vienna and Montreal classifications.

Materials and methods: The notes of 100 Crohn’s disease patients regularly followed up at our outpatient clinic were reviewed retrospectively. The behavior and location of the disease according to the Vienna and Montreal classifications were determined.

Results: Of the 100 patients, 55 were male and 45 were female with a mean age of 42.7 ± 14.9 years (range: 15-79). The mean age of the patients at the time of diagnosis was 36.2 ± 15.2 (range: 7-74). All of the patients were sporadic, and 58 patients were smokers. Extraintestinal manifestations were diagnosed in 15 patients. Abdominal pain was the most frequent initial complaint observed in 75 patients. 10 patients have been diagnosed during the appendectomy operation. Overall, 32 patients have been operated. Data of the patients according to the Vienna and Montreal classifications are summarized in table.

Conclusion: General characteristics of Turkish Crohn’s disease patients are similar to those from western countries. These clinical classifications may help us to define subgroups of patients suitable for future genetic studies.

<table>
<thead>
<tr>
<th>Vienna</th>
<th>Montreal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of diagnosis</td>
<td></td>
</tr>
<tr>
<td>A1 = 48</td>
<td>A1 = 1</td>
</tr>
<tr>
<td>A2 = 52</td>
<td>A2 = 47</td>
</tr>
<tr>
<td>A3 = 52</td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td></td>
</tr>
<tr>
<td>L1 = 38</td>
<td>L1 = 38</td>
</tr>
<tr>
<td>L2 = 16</td>
<td>L2 = 16</td>
</tr>
<tr>
<td>L3 = 43</td>
<td>L3 = 43</td>
</tr>
<tr>
<td>L4 = 3</td>
<td>L4 = 1</td>
</tr>
<tr>
<td>L1 + L4 = 1</td>
<td>L3 + L4 = 1</td>
</tr>
<tr>
<td>Behavior</td>
<td></td>
</tr>
<tr>
<td>B1 = 74</td>
<td>B1 = 71</td>
</tr>
<tr>
<td>B3 = 17</td>
<td>B3 = 12</td>
</tr>
<tr>
<td>B1 + P = 3</td>
<td></td>
</tr>
<tr>
<td>B3 + P = 5</td>
<td></td>
</tr>
</tbody>
</table>
Granulomatous cheilitis in a patient with Crohn’s disease: A pictorial follow-up description

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Departments of Gastroenterology¹, and Oral Medicine², “Saint Panteleimon” General State Hospital, Nicea, Greece, and 4th Surgical Department³, University of Athens, Athens, Greece

Introduction: Oral lesions in patients with Crohn’s disease (CD) are considered to be an important extraintestinal manifestation.

Methods: The aim of this presentation is to describe a very unusual case of a patient with CD in whom significant swollen of the lower lip not only preceded the diagnosis of CD, but it was manifested as an early clinical index of the activity of the disease as well.

Results: A man aged 31 was admitted in our department on August 1999 with chronic diarrhea and loss of weight. His symptoms started on 1998 at the age of 24. Two years previously he noticed an enlargement of the lower lip which contrasted significantly with the previously normal appearance of his mouth. CD involving the terminal ileum and large bowel was subsequently confirmed on the basis of the findings of colonoscopy, enteroclysis and histology. Conservative treatment resulted in clinical and laboratory improvement. During the following years the disease was running with exacerbations and remissions. Interestingly enough, during the follow-up period the impressive enlargement of the lower lip, went in parallel with the exacerbations of the disease being quite normal during the periods of remission.

Discussion/Conclusion: Significant swollen of the lower lip could be the first manifestation of CD. Exacerbation of the lip lesion could be an early clinical sign compatible with relapse of the underlying intestinal disease.
Beneficial effect of a polymeric feed, rich in TGF-β on adult patients with active Crohn’s disease: A pilot study

Department of Gastroenterology, “Saint Panteleimon” General State Hospital, Nicaea, Athens, Greece

Introduction: So far, nutritional support with polymeric diet rich in TGF-β has been studied only in children with Crohn’s disease (CD) with satisfactory results. There are no data concerning the effect of this kind of diet in adult patients with CD. The aim of this pilot study was to present our initial experience on the use of polymeric diet rich in TGF-β in patients with mild or moderately active CD.

Methods: Twenty nine patients with active CD received Modulen IBD as an exclusive diet for 4 weeks (50 g x 5/day). Patients continued to be on their regular conservative treatment. Activity of the disease was assessed at the beginning and after 4 weeks using CDAI. Various anthropometric parameters and serum estimations were carried out at the beginning and after 4 weeks of the application of the special diet.

Results: Clinical improvement was noticed in 69% (20/29 patients). No change of the situation or worsening was noticed in 9 patients (31%). The main alterations on anthropometric, hematological and biochemical parameters estimated before and after the application of the special diet are shown in the table.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight</td>
<td>61.7 ± 13.8</td>
<td>63.2 ± 13.6</td>
<td>0.003</td>
</tr>
<tr>
<td>Body mass index</td>
<td>21.2 ± 4.5</td>
<td>21.7 ± 4.0</td>
<td>0.002</td>
</tr>
<tr>
<td>Skin fold thickness</td>
<td>13.9 ± 7.5</td>
<td>15.1 ± 8.7</td>
<td>0.039</td>
</tr>
<tr>
<td>Mid arm circumference</td>
<td>26.7 ± 4.5</td>
<td>28.1 ± 4.8</td>
<td>0.004</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.14 ± 0.62</td>
<td>3.6 ± 0.41</td>
<td>0.049</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>494.5 ± 105.4</td>
<td>424.3 ± 92.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Folic acid</td>
<td>4.9 ± 3.1</td>
<td>6.7 ± 3.9</td>
<td>0.038</td>
</tr>
<tr>
<td>CRP</td>
<td>30.6 ± 26.2</td>
<td>11.3 ± 14.6</td>
<td>0.011</td>
</tr>
<tr>
<td>Immunoglobulin B</td>
<td>126.8 ± 68.2</td>
<td>151.4 ± 103.4</td>
<td>0.017</td>
</tr>
</tbody>
</table>

(Discussion/Conclusion: Dietetic intervention with polymeric diet rich in TGF-β represents a quite satisfactory therapeutic modality in adult patients with mild to moderately active CD. However, these results must be confirmed in larger, randomized, placebo controlled clinical trials.)
Osteoporosis in children with IBD

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**Aim:** To study bone mineral density (BMD) in children with Crohn’s disease (CD) and ulcerative colitis (UC)

**Methods:** We observed 50 children (29 boys and 11 girls) with IBD (18 children with CD and 32 with UC) 5 to 18 years old. All children were provided dual x-ray absorptiometry. We included in our investigation only the children, who hadn't history of corticosteroid treatment. The following criteria were used for evaluation of BMD: Z scores > -1 considered as normal BND, decrease Z score > -2.5 as osteopenia and decrease > -2.5 as osteoporosis.

**Results:** BMD decrease was found in 30 examined children (60%). In 19 children osteopenia was diagnosed and 11 children had osteoporosis. The significant differences between CD and UC were not revealed. The score of BMD didn't depend on children's age and gender. We established the followship with disease duration: in disease anamnesis more than 3 years the amount of children with osteopenia increased from 8% to 31%, although significant correlation between Z scores and disease duration wasn't found. The correlation was determent between Z score and PCDIA (r = 0.663, p < 0.01) and not determent between Z score and inflammation activity of UC.

**Conclusion:** BMD decrease was diagnosed in 60% children with IBD. There were no considerable differences between CD and UC. The score of BMD in children with CD depended on disease activity.
Plasma thrombin-activatable fibrinolysis inhibitor and plasminogen activator inhibitor-1 levels in inflammatory bowel disease

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Introduction: Patients with inflammatory bowel disease (IBD) have an increased risk of thromboembolic events. Hypofibrinolysis has been suggested as one of the possible pathogenetic mechanisms. Plasminogen activator inhibitor type 1 (PAI-1) and thrombin-activatable fibrinolysis inhibitor (TAFI) are considered as inhibitors of fibrinolysis. The aim of the present study was to measure TAFI as well as PAI-1 plasma levels in IBD patients compared to healthy controls.

Methods: 128 IBD patients (66 ulcerative colitis [UC] 62 Crohn’s disease [CD]) and 37 healthy controls were enrolled. PAI-1 and TAFI plasma levels were assessed by means evaluation of two commercially available ELISA Kits (Berichrom*PAI and ASSERACHROM TAFI respectively). Their relationship with clinical parameters of UC and CD was also assessed.

Results: Mean plasma PAI-1 levels were significantly higher in both UC patients (3.9 ± 1.3 IU/ml) and CD patients (4.0 ± 1.5 IU/ml) compared with healthy controls (3.2 ± 1.1 IU/ml) (P = 0.02). On the other hand mean plasma TAFI levels were significantly lower in both UC patients (14.8 ± 3.1 µg/ml) and CD patients (13.3 ± 3.4 µg/ml) compared with healthy controls (17.4 ± 3.0 µg/ml) (P < 0.0001). Patients with active disease had higher but not significant different PAI-1 compared with patients with inactive disease (P = 0.07). No significant association between plasma TAFI levels and disease activity was also found. Concerning disease localization no significant associations with these markers was found in both diseases.

Discussion/Conclusion: PAI-1 plasma levels are increased whereas TAFI levels are decreased in IBD patients. These results suggest that the procoagulant state in IBD is maybe mediated by these alterations of PAI-1 and TAFI.
Ulcerative colitis and viral hepatitis

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The Republican Clinical Hospital, Chisinau, Moldova

Introduction: Liver pathology is the most common extraintestinal disorder associated with ulcerative colitis (UC). Primary sclerosing cholangitis, autoimmune chronic hepatitis, fatty hepatosis, cryptogenic cirrhosis are not uncommon in UC.

The aim of the study was to investigate the frequency and clinical features of viral hepatitis B and C associated with UC in Moldova - the region with low indices of UC incidence and prevalence, but with very unfavorable indices of morbidity and mortality from liver diseases.

Methods: A group of UC patients (187) was observed during more than 15 years. The mean duration of associated viral HBV and HCV infections was 8.7 ± 1.3 years. The following methods were used: clinical, endoscopic, ultrasonography, liver enzymes (ALT, AST, GGT, alkaline phosphatase etc.), immunological and viral markers etc.

Results: Chronic viral infections HBV and HCV were observed in 9.0% (17) of UC patients: HBV hepatitis – 9 patients (4.8%); HCV hepatitis – 7 (3.7%) and mixed HBV + HCV infection – 1 person (0.5%).

Significant interrelation between activity, clinical evolution and outcome of the liver pathology; activity of viral infections and clinical forms and evolution of UC was not revealed. Clinical evolution of chronic viral hepatitis B and C had no any characteristics dependent on clinical features and evolution of UC. As a result of progression of viral infection at 2 patients was formed liver cirrhosis.

Discussion/Conclusion: An essential number of UC patients have associated viral hepatitis B or C (9.0%). However, the certain correlation between clinical and evolution features of US and viral hepatitis was not revealed.
Cytokines in children with inflammatory bowel diseases

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Introduction: Imbalance between pro- and anti-inflammatory cytokines is one of determinative factors in inflammatory bowel disease (IBD) pathogenesis. Cytokine status of children hasn’t been thoroughly studied yet.

Methods: 56 children with IBD from 6 to 17 years old, 41 of them with ulcerative colitis (UC), 15 with Crohn’s disease (CD). Serum cytokine value IL-1β, TNFα and IL-4 was defined by IFA.

Results: It was proved, that children with IBD has serum value of all studied cytokines higher than that of relatively healthy group (p < 0.05). IL-4 level of most children with CD was constantly higher than that of children with UC (286.7 ± 58.8 pg/ml and 127.2 ± 33.9 pg/ml). IL-1β of children in an active phase of disease was higher, than that of those with lower activity, in remission (p = 0.03) with UC and with CD (p = 0.04) and reflected the acuteness of the process. In the group with continuous course of UC IL-1β and IL-4 were higher than that of children with recurrent course (p = 0.04). Patients with abenteric manifestations such as hepatitis, arthritis the IL-1β and IL-4 levels were lower than that of children without them (p = 0.01). The serum cytokine value of children with IBD, who received steroid therapy, was lower (IL-1β, p = 0.04), than that of those who received 5-ASA. Children with CD, who received steroid therapy, had IL-4 definitely higher than that of those who received 5-ASA.

Discussion/Conclusion: The serum cytokine value of children is connected with the character of the course of disease, its phase, activity, abenteric manifestations and the character of the therapy.
Correlation between endoscopic severity and the histologic activity index in inflammatory bowel disease

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¹Ankara University Medical School Gastroenterology Department, Ankara, Turkey
²Ankara University Medical School Pathology Department, Ankara, Turkey

Introduction: Colonoscopy findings allow evaluating the disease activity in inflammatory bowel disease (IBD). But since direct visual appreciation doesn't definite the disease severity, pathologic evaluation requires. We aimed to examine the relationship between the endoscopic severity and histopathologic activity index in this study.

Methods: 96 patients (23 Crohn’s disease [CD], 73 ulcerative colitis [UC]) with IBD evaluated with colonoscopy. CD patients were as follow: 4 patients with ileitis, 12 with ileocolitis, and 7 with colitis. UC patients were as follow: 24 patients with distal colitis, 25 with left-sided colitis, and 24 with total colitis. The severity was divided into three categories: grade 1 = mildly active, grade 2 = moderately active, and grade 3 = severely active.

Results: Patients with normal colonoscopy found grade 1 histologic activity index (HAI). 2 of 4 mildly active colonoscopic lesions (50%) showed grade 3 HAI. 14 of 22 (63%) moderately active lesions showed grade 3 HAI. 51 of 67 (76%) severe active lesions showed grade 3 HAI.

Discussion/Conclusion: The HAI reflects the colonoscopic activity especially in severely active disease. We thought if the colonoscopy shows severe disease, biopsy maynot necessary but in mild forms pathologic confirmation requires.
An alternative treatment option when conventional therapy fails in Behçet's disease: Infliximab

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Behçet’s disease (BD) is a chronic, relapsing, multisystem inflammatory disorder characterized by recurrent oral and genital ulcers, cutaneous lesions and uveitis. Rare manifestations include gastrointestinal involvement, arthritis, central nervous system involvement and vascular lesions. Gastrointestinal involvement of BD is termed "entero-Behçet's," and this mainly affects the ileocecal region and the colon. The involvement of perianal region by aphthous lesions is a rather rare clinical presentation of BD and usually confined to the childhood period. The most common symptoms of entero-Behçet’s disease are abdominal pain, nausea, vomiting, diarrhea with or without blood in the stool, and constipation. The gastrointestinal manifestations of BD usually appear 4-6 years after the onset of the oral ulcers. The intestinal lesions are usually resistant to medical treatment and recur frequently after surgical therapy. The frequency of gastrointestinal involvement varies from 0% to 60%.

The principle aim in the treatment of Behçet's disease is the modification of inflammatory response. Several drugs are used in the treatment of BD such as corticosteroids, colchicine, thalidomide and pentoxifylline. TNF-α is an important cytokine which plays an important role in immunopathogenesis of autoimmune diseases. Infliximab (IFX) is a chimeric monoclonal antibody against TNF-α and is being used for treatment inflammatory bowel disease since the beginning of this century. There are several reports in the literature showing successful use of IFX in Behçet associated uveitis and some papers concerning the use of IFX in gastrointestinal involvement of Behçet's disease in adults. We report a 16 year-old girl with Behçet’s disease who responded poorly to corticosteroids and other immunosuppressive agents. IFX therapy was started and after the second dose her oral and genital ulcers disappeared and diarrhea improved.
Analysis of ulcerative colitis patients in Ondokuz Mayis University: Report of 90 cases

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Introduction: The aim of this study was to evaluate the demographic and clinical features of patients with ulcerative colitis (UC) who were followed up in our clinic.

Methods: We retrospectively analyzed UC patients who were newly diagnosed and also previously diagnosed as UC between January 2003-July 2006. The diagnosis of UC was made by clinical features, endoscopic appearances, and histopathologic findings. The sex and age distributions, disease duration, extent of disease, disease activity, used therapies and extraintestinal manifestations have been investigated.

Results: Ninety UC patients with a median age of 43.5 ± 12.3 years (range 18-75 years) were identified. 53.3% (n: 48) were female and 46.7% (n: 42) were male. The median disease duration was 27.9 ± 24.5 months (range 2-125 months). The extent of the disease were as follows: proctitis in 9, proctosigmoiditis in 29, left-sided colitis in 27, extensive colitis in 19 and pancolitis in 6 patient. Extraintestinal manifestations were seen in 14.4% (n: 13) which were as follows: oral aphthous ulcers in 4, conjunctivitis in 3, erythema nodosum in 2, arthritis in 2, cholelithiasis in 1, sclerosing cholangitis in 1, anal fistulas in 1, pyoderma gangrenosum in 1 and uveitis in 1 patient. There were more than one extraintestinal manifestations in one patient. The disease activity (Truelove-Witts classification) in UC patients were as follows: mild in 32 (35.6%), moderate in 29 (32.2%), severe in 29 (32.2%). Thirty percent of patients were smokers. In mild-moderate activity, mesalamine tablet and/or mesalamine enema or salazopyrine were used; corticosteroids were administered to unresponsive patients (n: 9). In severe activity, steroids were used. In steroid refractory disease cyclosporine A (n: 7) and azathioprine (n: 3) were used. Surgical treatment was applied to 2 patients who failed to respond to immunosuppressive therapy.

Discussion/Conclusion: Ulcerative colitis is a disease that causes important mortality and morbidity. In our study, there was no gender difference in patients. The disease activity was: mild-moderate in 67.8%, severe in 32.2%. Extraintestinal manifestations were seen 28.9% of patients.
Evaluation of our Crohn’s disease patients with upper gastrointestinal tract involvement

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Aim: The aim of this study was to evaluate the upper gastrointestinal tract involvement in Crohn’s disease (CD) patients followed in our inflammatory bowel disease clinic.

Method: The registration report of CD patients with upper gastrointestinal tract involvement (esophagus, stomach, duodenum and jejunum) were evaluated according to their epidemiological findings, follow-up periods during 1993 to 2006.

Findings: A total of 237 (59% male, 41% female) CD patients were registered. The mean age was 35.6 years. Eleven of 237 patients (4.6%) had upper gastrointestinal system involvement at the time of diagnosis or during follow-up periods. The mean age, male to female ratio and mean follow of duration of 11 patients were as follows 37.2 years (19-60), 45.5%/54.5%, and 86 months. Five patients (45.5%) had fibrostenotic, 2 (18.2%) had fistulizing, and 4 (36.4%) had inflammatory type disease behavior. Two patients had history of smoking. Upper gastrointestinal tract involvement was diagnosed at same time of CD diagnosis in 6 patients, during the first follow-up year in 2 patients, at the 3rd and 15th years of follow-ups in two patients respectively. Upper gastrointestinal tracts involvement were generally diagnosed by barium examination of small intestine and esophagogastroduodenoscopy in 8 patients. Two patients diagnosed during operation, the other diagnosed by the help of abdominal tomography. Seven patients had operation history due to CD. None of the patients had esophageal involvement. Nine of 11 patients had ileal and/or colonic location.

Conclusion: Upper gastrointestinal tract involvement ratio was similar the literature, although esophageal and gastric locations were reported lower than the literature. The gastrointestinal tract involvement was diagnosed during the first year of CD or at the time of CD diagnosis. The age of these patients were higher than the literature and seen especially mid or late 30s. Diagnosis was done by barium examination of small intestine and esophagogastroduodenoscopy. It should be better to investigate upper gastrointestinal tract periodically in CD with ileal and/or colonic location.
Location of our ulcerative colitis patients according to Montreal classification: Is there any change by the years?

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Aim: The aim of this study was to assess the location and the location changes by the years according to Montreal classification in our ulcerative colitis (UC) patients.

Method: The registration reports of the 729 UC patients from our inflammatory bowel disease clinic database between 1993 to 2006 were evaluated and 163 of them who had no history of operation and followed-up at least 5 year were included into the study. The location of the UC was evaluated according to Montreal classification.

Findings: The mean age of the patients was 41.1 years and the mean follow-up period was 142 months. The male to female ratio was 51.5% and 48.5 respectively. Ulcerative proctitis, distal colitis and extensive UC were diagnosed at the beginning in 39.9%, 37.4% and 22.7% of the patients respectively. The 2th year and the 5th year disease location ratios of the patients were as follows: 33.7% and 32.5% for ulcerative proctitis, 37.7% and 35.6% for distal colitis, 25.3% and 31.9% for extensive UC.

The second year follow-up locations of 64 patients who had ulcerative proctitis at the beginning were as follows: 75% of them had ulcerative proctitis, 20.3% had distal colitis, 3.1% had extensive UC and one patient was completely normal. 62 patients with initial distal colitis continued the follow-ups as 8.1% ulcerative proctitis, 75.8 distal colitis, 11.3% extensive UC, 4.8% normal at the 2nd year. The same evaluation was done for 37 extensive UC patients at the 2nd year and 86.5% of them continued as extensive UC, 8.1% of them had ulcerative proctitis, 2.7% had distal colitis, and 2.7% had normal findings.

65 patients who had ulcerative proctitis at the beginning continued as ulcerative proctitis in 69.2% of the cases at the 5th year, 21.5% of them had progressed into distal colitis and 9.2% progressed into extensive UC. 62 patients with distal colitis were continued as distal colitis in 66.1% of the patients, 11.3% improved to ulcerative proctitis, and 22.6% progressed into extensive UC. 86.5% of the 37 extensive UC patients had extensive UC at 5th year and 10.8% improved into distal colitis, 2.7% improved ulcerative proctitis.

If the change of disease location by the time evaluated there was a significant disease extension when the initial findings compared with the 2nd year (p = 0.01) or the 5th years (p = 0.001). But there was no significant progression between the 2nd and the 5th years (p = 0.56).

There was no relation by the change of disease location with sex, age and the treatment.

Conclusion: The location of the disease progress by the time similar with the literature and the significant change occur especially in the first years.
Evaluation of our operated ulcerative colitis patients

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Aim: The aim of this study is to evaluate the relation between the preoperative location and activation and postoperative pouchitis ratio in our ulcerative colitis (UC) patients.

Methods: Sixty out of 730 UC patients followed in our inflammatory bowel disease clinic who were operated due to UC were included into the study.

Findings: The operation ratio in UC patients was 8.3%. The mean age of 60 patients (32 male, 28 female [53.3%/46.7%]) was 36.1 (15-75) years. The mean time period between the diagnosis and the operation was 29.3 (0-240) months. Operation was performed in the first follow-up year in 61.9% of the patients. The initial disease activity of the patients was as follows 63.3% (n = 32) had severe disease, 21.7% (n = 13) had moderate disease and 15% (n = 9) had mild disease. Extensive UC (n = 41), distal colitis (n = 18) and ulcerative proctitis (n = 1) was seen in 68.3%, 30.0%, 1.7% of the patients respectively at the time of diagnosis. 46 of the patients continued the follow-ups after operation. Pouchitis was diagnosed in 58.7% of them. 74.1% of the patients with pouchitis had extensive UC and 25.9% had distal colitis. 66.7% of extensive UC and 46.7% distal colitis were developed pouchitis during postoperative follow-ups.

Conclusion: The colectomy need for UC is seen mostly in the first year and the need decreases by the following years. Colectomy was performed in 30% of the patients at the and pouchitis rate is higher than the literature.
Clinical activity and disease progress according to Montreal classification in ulcerative colitis

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Aim: The aim of this study was to assess the clinical activity and disease progress according to Montreal classification in our ulcerative colitis (UC) patients

Method: the registration reports of the 730 UC patients from our inflammatory bowel disease clinical database between 1993 to 2006 were evaluated according to Montreal classification for activity and the course of the disease retrospectively.

Findings: the mean age of the patients was 40.4 years. The male to female ratio was 57.1% and 42.9% respectively. When the disease activity was concerned 1.9% of the patients was asymptomatic, 46.6% had mild disease, 28.4% had moderate disease and 23.1% had severe disease at the beginning. The same parameters were 37.1%, 41.9%, 14.9%, 6.1% respectively at the end of second year. 216 patients were continued follow-ups at the end of 5th year. 162 had no history of operation at 5th year and 50.6% of them were asymptomatic, 31.5% had mild disease, 4.6% had severe disease.

Disease activity was significantly reduced when the initial activity was compared with the 2nd and 5th year results. There was not a significant improvement between the 2nd and the 5th year comparison of disease activity scores.

461 patients had regular follow-ups for one and/or more than one years. If the disease course was concerned 42.6% of patients had no or only one attack in a year, 10.8% had, 2 attacks in a year, 3.8% had 3 or more attacks in a year, 0.4 of the patients had fulminant course. There was no significant relation with the age and sex and the disease course.

Conclusion: the disease activity was improved and relapses were decreased during the treatment. The maintenance treatment can be the main factor for some patients had not more than one attack. Initial disease activity was seemed to continue at the same manner during the following years.
The predictor parameters of relapse in ulcerative colitis

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Introduction: Ulcerative colitis (UC) is a chronic, relapsing inflammatory bowel disorder. The aim of this study is to assess whether clinical, biological and histological parameters in quiescent UC predict time to clinical relapse.

Patients and methods: 41 patients (28 females, 23 males, age 19-60) with ulcerative colitis were treated and followed-up. Colonoscopies with biopsies and serum analyses (serum erythrocyte sedimentation rate, C-reactive protein, leukocytes) were performed every 6, 12 months and at the time of relapse.

Results: During the one year follow-up 15 patients relapsed. When comparing: disease duration, leukocyte count, hemoglobin, platelet count, albumin, sedimentation rate, C-reactive protein, there was no statistical difference in relapses versus non-relapses. A greater proportion of females (64%) then males (36%) relapsed. The women who relapsed were under 40 years. In females but not in males a greater number of relapses were associated with subsequent relapse (p < 0.01). Presence of active colitis on histology specimens, lamina propria leukocytes, and cryptitis was associated with higher relapse rate in females (p = 0.6). Features of chronic colitis (crypt atrophy, basal plasma cells) were also associated with a higher relapse rate in females (p = 0.6).

Conclusions: Gender differences were seen in patients with respect to relapse. A greater number of prior relapses, the presence of lamina propria leukocytes, cryptitis, crypt atrophy, and basal plasma cells were associated with a higher risk of UC relapse in females but not in males.
Amebiasis in IBD: Silent passenger or disease modifier?

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Introduction: Amebiasis in inflammatory bowel disease (IBD) often presents as concomitant infection or superinfection causing exacerbation of underlying colitis or making it to become manifest.

Aim is to determine the prevalence of amebiasis in IBD patients and to investigate if any correlation exists between the presence of amebiasis and localization of colitis or presence of any extraintestinal manifestation and choice of therapy.

Methods: 61 patients who were diagnosed as IBD by endoscopic, histopathologic, radiologic and laboratory examinations at two units of Acibadem Hospital over the last 2 years were included in this study. Of all the cases, 42 were diagnosed as ulcerative colitis (UC) and 19 as Crohn's disease (CD) (Table I). In every patient with bloody diarrhea, direct microscopic examination of fresh stool samples were combined with Entamoeba histolytica (EH) stool antigen test.

Results: Amebiasis was found in 10 (23.8%) of UC patients, but none of the CD patients. The presence of amebiasis didn't make any difference in terms of disease localization, frequency of extraintestinal manifestations and usage of immunosuppressive treatment. All patients with EH infection responded to treatment with metronidazole and diloxanidefuroate when necessary.

Discussion/Conclusion: In our patient population especially UC patients are more prone to amebic infestation. No correlation could be found between site of involvement, type of extraintestinal manifestation and the choice of treatment with the coexistence of amebiasis and UC.
Table I. Characteristics of patients with and without amebiasis and IBD

<table>
<thead>
<tr>
<th></th>
<th>Existence of amebiasis among UC patients (n: 10)</th>
<th>UC patients without amebiasis (n: 32)</th>
<th>CD patients (none have amebiasis) (n: 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>41 (19-65)</td>
<td>37 (25-82)</td>
<td>35 (18-63)</td>
</tr>
<tr>
<td>Male/Female</td>
<td>5/5</td>
<td>17/15</td>
<td>8/11</td>
</tr>
<tr>
<td>Localization of illness</td>
<td>pancolitis: 4 left-sided colitis: 6</td>
<td>pancolitis: 10 left-sided colitis: 12</td>
<td>ileitis: 1 sacroileitis: 1 oral aphts: 1 arthralgia: 2</td>
</tr>
<tr>
<td>Extraintestinal manifestations</td>
<td>arthralgia: 1</td>
<td>Ankylosing-spondylitis: 2 arthralgia: 1</td>
<td>renal stone: 1 oral aphts: 2 arthralgia: 2</td>
</tr>
<tr>
<td>Treatment</td>
<td>immuno-suppressives: 2 mesalazine: 8 metronidazole: 10</td>
<td>immuno-suppressives: 10 mesalazine: 22</td>
<td>immuno-suppressives: 12 mesalazine: 7</td>
</tr>
</tbody>
</table>
The predictive value of capsule endoscopy in the differential diagnosis of indeterminate colitis

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Background: In a proportion of patients with Inflammatory Bowel Disease (IBD) clinical features including endoscopic and biopsy findings are inadequate to make a definite diagnosis of ulcerative colitis or Crohn’s disease. In these cases, in which an overlap of diagnostic criteria exists, the term indeterminate colitis is used.

Aim: To assess the predictive value of wireless capsule endoscopy (WCE) in establishing a certain diagnosis in patients with indeterminate colitis.

Methods: From October 2003 to October 2006 all patients with indeterminate colitis subjected to WCE entered the study. Prior to capsule endoscopy they had been subjected to small bowel follow through or enteroclysis, as well as upper and lower gastrointestinal endoscopy where biopsy specimens were obtained. Although these patients were diagnosed as having IBD, a specific diagnosis of ulcerative colitis or Crohn’s disease was not made. WCE was considered diagnostic of Crohn’s disease if multiple aphthoid ulcers, more than 3 greater ulcers, strictures or extensive mucosal edema, erythema and erosions were identified.

Results: During the study period 13 patients (7 men/6 women, mean age 35.25 ± 12.65 years) with indeterminate colitis were subjected to WCE and in 5 of them (38%) a diagnosis of Crohn’s disease was made according to the capsule findings. The entire small bowel was examined in all cases and the mean small bowel transit time was 268 minutes.

Conclusion: Capsule endoscopy is a valuable tool in the investigation of patients with indeterminate colitis since a significant proportion of them can be categorized as having Crohn’s disease.
Balloon dilatation in patients with Crohn’s disease

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Study aim: To evaluate long-term outcome, safety and efficacy of the balloon dilatation procedure (BD) in patients with strictures caused by Crohn’s disease (CD).

Background: Patients with CD often develop gastrointestinal strictures with a loss of quality of life. The average CD patient is likely to undergo surgery once or twice in a lifetime due to gastrointestinal complications.

Methods: Data from 28 patients with CD were analyzed retrospectively from April 1997 until October 2006. Patients were clinically examined by abdominal ultrasound and completed a standard questionnaire about change in pain and quality of life from November 2005 to July 2006. Median follow-up was 36.9 months (range 4.5-94) with a median number of balloon dilatations of 2.46 (range 1-7) per patient.

Results: In 28 patients 69 BD were performed. No severe complications occurred. Prior to the procedure 22 patients (78.6%) had undergone surgery and 6 (21.4%) had de novo stenoses. Thirty nine dilatations (56.5%) were performed at the site of the ileoascendostomy. 45 BDs (65.2%) were technically successful. There is an inverse correlation between technical success and length of stenosis (p = 0.008). Furthermore the success correlated with the time interval between BDs in individual patients (p = 0.025). Five patients (17.9%) were BD failures and required surgery. The patients experienced on average a 2.12 point decrease of pain on a visual analogue scale (range: 0-6, 0 = no pain) after BD. Furthermore, an improvement of other stricture-related symptoms was observed after BD.

Conclusion: BD is a safe and in most patients successful therapy for CD-related strictures, is an alternative to surgery or postpone it and improves quality of life.
Changes in salivary components in patients with Crohn’s disease

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2Department of Conservative Dentistry and Pedodontics

Background: One of the uncommon manifestation of Crohn’s disease (CD) is oral cavity and that fact could have an influence on changes in salivary components.

Aim of the study: The aim of study was to estimate changes in salivary components in patients with CD in comparison to healthy volunteers.

Material and methods: We examined 19 patients with CD, 7 male and 12 female in age 23 to 67 (mean age 41.3). Each patient was taken a salivary sample in order to assess salivary flow rate, pH, buffer capacity, carbohydrates, phosphatic, calcium, protein, glucose, total sialic acid (TSA – Total Sialic Acid) and its fraction (GSA – Glikozylic Sialic Axcid; FSA – Free Sialic Acid) concentration. Control group was composed of healthy volunteers.

Results: Salivary flow rate was lower in patients with CD, than in control group (0.24 vs. 0.4 ml/min, respectively), saliva pH was alkalic (10 vs. 6.8), with lower buffer capacity (3.5 vs. 4.7 mmmol/l) and carbohydrates concentration (21.6 vs. 24.09 mmol/l), with increased phosphatic level (17.05 vs. 12.6 mmol/l). Calcium concentration in saliva was comparable in both group (4.52 vs. 4.07 mEq/l), as well as a protein (1.73 vs. 1.25 mg/ml), whereas glucose concentration was significantly higher in patients with CD than in healthy persons (13.86 vs. 2.09 mg%). TSA was decreased in patients with CD than in healthy volunteers (6.63 vs. 9.54 mg%), also at GSA (4.45 vs. 5.49 mg%) and FSA fraction (2.18 vs. 9.99 mg%).

Conclusions: According to obtained data we concluded that in patients with CD salivary flow rate is lower than in control group and its pH was alkalic. Higher glucose concentration in saliva samples taken from CD patients may be the cause of higher tendency for dental plaques forming which a reveals greater susceptibility for tooth decay and parodontium diseases.
Gastroesophageal reflux disease and it’s influence on intensification of ailments in patients with Crohn’s disease

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**Background:** One of the most important and predominating ailment in patients with Crohn’s disease (CD) is a severe abdominal pain. However, sometimes in that patients during upper gastrointestinal tract endoscopy, changes in oesophageal mucosa are found and it is probably result of gastroesophageal reflux disease (GERD).

**Aim of the study:** Aim of our study was to confirm GERD in patients with Crohn’s disease and it’s estimation on intensification of ailments in patients with CD.

**Material and method:** We examined 19 patients with CD, 7 male and 12 female in age 23-67 (mean age 41.3). Each patient underwent gastroesophagoscopy, oesophageal manometry, pH-metry and anamnesis regarding reflux disease symptoms was collected.

**Results:** Only 3 patients (15.8%) had typical GERD symptoms, 16 patients (84.2%) had no complaints from upper gastrointestinal tract. Changes in endoscopy were not frequent: 2 patients (10.5%) had an oesophagitis A LA, 1 person (5.3%) – oesophageal ulcer and all of them had gastritis. According to pH-metry GERD was diagnosed in 18 patients (94.7%) with CD. During oesophageal manometry lower esophageal sphincter pressure (LESP) mean value was normal (26.18 mmHg ± 2.33). Five (26.3%) patients had a normal esophageal corpus peristalsis but 14 (73.6%) had non specific esophageal motility disturbances. Each patient with diagnosed GERD had continue basic Crohn’s disease treatment and additionally had involved proton pomp inhibitor (PPI - pantoprazole 40 mg per day). All the patients had a significant improvement in general feeling and decrease abdominal pain and discomfort.

**Conclusions:** Abdominal pain, which is a predominant ailment in patients with Crohn’s disease, could be also a result of gastroesophageal reflux disease and efficacy GERD treatment may lead to significant improvement in general feeling and better effect of Crohn’s disease treatment.
Fertility, pregnancy, nursing and sexual health in inflammatory bowel disease

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Background & aims: Women with inflammatory bowel disease (IBD) represent different clinical features especially in their reproductive period. Our aim was to investigate the effects of IBD on gender specific issues such as fertility, pregnancy, nursing and sexual health in women.

Methods: Fertility, pregnancy, nursing and sexual health was inquired in 37 female patients, aged 19-81 (median 46 years), in the follow-up clinic for IBD. Twenty of them (53\%) had ulcerative colitis (UC), 17 (47\%) had Crohn’s disease (CD). Fifteen (40\%) were questioned during outpatients’ visit and 22 (60\%) had a structured telephone interview. Forty healthy women and 36 patients with irritable bowel syndrome (IBS) were enrolled as controls. Fischer’s exact test was used in statistical analysis.

Results: Twenty-three (62\%) were diagnosed in the reproductive period after the deliveries and 2 (5\%) presented disease during the pregnancy. Four patients (11\%) did not give birth after the establishment of diagnosis as they had fear of pregnancy. Three out of 37 patients (8\%) had symptoms of active disease during the pregnancy, which resulted in stillbirth, and IBD was diagnosed within the first six months after the delivery. Infertility was detected in 2 of IBD patients, 1 of IBS patients, but none of the healthy controls. Eight patients with IBD (21\%; 16\% of UC, 5\% of CD), 3 patients with IBS (6.5\%) and none of the healthy controls had dyspareunia (p = 0.002). Six patients nursed after the diagnosis of IBD. Three nursed shorter than 6 months because of active disease and three who were in remission nursed longer than 12 months. Seventeen of IBD patients (46\%), 5 of IBS patients (13\%) and 10 of healthy subjects (25\%) reported decrease in libido (p = 0.008). Nine out of 16 patients with depression reported sexual problems (p = 0.003), which were common among smokers (p = 0.007).

Conclusion: IBD has important effects on fertility, pregnancy, nursing and sexual health in female patients. Although fear of pregnancy is a common problem, fertility rates are not affected. IBD has no effect on pregnancy and vice versa. Dyspareunia, decreased libido and depression have important effects on sexual health. Nursing period is shortened because of disease activity and drugs. Female patients with IBD need to be adequately counseled before, during and after pregnancy, and if necessary psychiatric counseling must be provided.
The effect of iNOS inhibitors treatment in experimental colitis models

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Our aim was to investigate the effectiveness of aminoguanidine (AMG), an iNOS inhibitor treatment on experimental colitis model, resembling ulcerative colitis.

We induced colitis by applying 4% aseptic acetic acid (AA) in transrectal route to 18 Sprague-Dawley rats, weighing 200-300 g. Rats were divided into 2 groups. In control group (n = 9), we applied 2 ml. serum physiologic in intraperitoneal route daily for seven days. In AMG group (n = 9), 2 hours after induction, 100 mg/kg AMG was applied intraperitoneally in two hours twice a day, for seven days. At the end of 7 days, all the rats were sacrificed and the distal 10 cm part of colon were examined macroscopically and scored. In microscopic examination, edema, inflammation, ulceration, crypt hyperplasia, crypt distortion and loss of goblet cells were scored. NO levels in urine were measured by Gries method.

The histologic findings, showing the severity of colitis were reduced by AMG, application. The improvement in histologic findings were significant in AMG group comparing the control group (p = 0.001). Weight loss was significantly lower in AMG (p < 0.001). In colitis induced by AA, we showed that nitric oxide activities were depressed by AMG (p < 0.001).

In rats, colitis induced by AA, treatment reduced weight loss and colonic inflammation and depressed NO levels.
Elevated markers of thrombin generation and fibrinolysis in patients with active and quiescent ulcerative colitis

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Introduction: Prothrombotic abnormalities within the coagulation system, the presence of microvascular thrombi in intestinal mucosa and the increased risk of thromboembolic complications in patients with Inflammatory Bowel Disease, suggest that a hypercoagulable state may be an important contributing factor in disease pathogenesis. We investigated the activation of coagulation system in a cohort of ulcerative colitis patients.

Methods: Markers of coagulation activation in blood (thrombin-antithrombin complex, TAT; prothrombin fragment 1 and 2, F1+2; and D-Dimers) and markers of inflammation (erythrocyte sedimentation rate, ESR; C-reactive protein, CRP; and fibrinogen) were measured in 38 patients with active and 13 patients with long standing quiescent ulcerative colitis. Disease activity was assessed by clinical, endoscopic and histological criteria. Markers of coagulation activation were also measured in 28 healthy volunteers.

Results: There were no differences in levels of TAT, F1+2 and D-Dimers, between active and inactive ulcerative colitis. D-Dimers and F1+2 plasma levels were significantly higher in active ulcerative colitis patients compared to healthy controls. Plasma levels of TAT, F1+2 and D-Dimers did not differ between inactive ulcerative colitis patients and healthy controls. However, patients with both active and inactive ulcerative colitis had significantly higher proportions of elevated, over normal, values of coagulation markers compared to healthy controls. Correlation analyses revealed a strong correlation between ESR, fibrinogen and D-Dimers, which were also correlated with the severity and extent of ulcerative colitis.

Discussion/Conclusion: A chronic low grade activation of coagulation exists in ulcerative colitis, irrespectively of disease activity, and might be implicated in disease pathogenesis.
Anti-Saccharomyces cerevisiae antibodies (ASCAs) in celiac disease

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Introduction: Inflammatory Bowel Diseases are a group of diseases with chronic inflammation of the gastrointestinal tract, but without proven etiology. Immunologic, environmental, infective and genetic factors equally can play role in their development. Anti-Saccharomyces cerevisiae antibodies (ASCAs) are known to be positive mostly in Crohn's disease patients, but some authors also observed in other diseases, i.e. celiac disease and in a minority of healthy controls. The origin and the clinicopathological role are not clarified but ASCA positivity may predict the development of inflammatory bowel disease years before the disease is clinically diagnosed.

Methods: A cohort of patients with gluten sensitive enteropathy (30 children and 28 adult patients) from Eastern Hungary was enrolled in the study. The diagnosis was made using the formally accepted criteria. The aim was to evaluate, retrospectively, the frequency of ASCA positivity in these patients. Anti-Saccharomyces cerevisiae antibodies (ASCAs), anti-endomysium antibodies (EMA), antigliadin antibodies (AGA) and anti human tissue transglutaminase antibodies (tTGA) were investigated.

Results: Results were analyzed statistically and concluded that the results showed that ASCA positivity occurred characteristically in celiac disease and in these cases both the IgG and IgA type antibodies were proved.

Discussion/Conclusion: The cause of ASCA positivity is still unknown. Some authors have considered antibody formation as a consequence of increased mucosal permeability but it is also conceivable that ASCA positivity correlates with the (auto-) immune inflammation of small intestines and maybe it is a specific marker of (auto-) immune enteritis.
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