Falk Symposium 147

COLITIS: DIAGNOSIS AND THERAPEUTIC STRATEGIES

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Session I

Diagnosis
Role of capsule endoscopy in Crohn's disease

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Capsule endoscopy (CE) has been shown to have the highest diagnostic yield for Crohn's disease (CD) compared to other conventional methods. The description of 3 patients with normal small bowel follow through of excellent quality and abnormal CE study suggestive of CD served as a milestone in accepting CE as the gold standard for the diagnosis of CD of the small intestine. In meta-analyses on patients suspected of having CD, the diagnosis was confirmed by CE in two thirds of the patients, by small bowel follow through in one quarter, by CT enterography in 40% and by ileoscopy in one half of the patients.

However, the use of CE in patients suspected of having CD is not routinely recommended because of the risk of a retained capsule. Fortunately it does not occur too often (< 5%) and in some it may be solved by the administration of corticosteroids. Prior administration of a patency capsule may identify those at risk.

In order for a CE to be diagnosed as a negative study, one should verify that the ileocecal valve has been reached. In one quarter of the patients the batteries finish prior to reaching the ileocecal valve.

NSAIDs may cause mucosal erosions which mimic CD. It is therefore important to obtain the list of medications taken by each of the patients with CE-diagnosed CD.

It is important to keep in mind that a small number of mucosal erosions and petechiae are seen in the small bowel of up to 15% of the normal population. Thus the diagnosis should be reserved only to those patients with unequivocal findings. It is prudent to postpone the diagnosis of CD and to wait for further evidence rather than to misdiagnose it.

At our center we performed CE on 78 patients who had symptoms compatible with CD. All patients underwent a comprehensive gastrointestinal work-up which was negative. Patients were divided into 4 groups based on their symptoms: anemia, diarrhea, abdominal pain, combination of diarrhea and abdominal pain. The prevalence of CD among these groups was 12%, 12.5%, 0% and 45% respectively. None of the patients retained the capsule.

The outcome of the majority of patients in whom the diagnosis of CD was established has been improved as a result of a better therapy.
Colonoscopic diagnosis of Crohn’s disease (CD)

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Endoscopy, combined with biopsies from both abnormal and normal looking areas, remains the diagnostic cornerstone of CD:

Aphthoid lesions are considered early and rather characteristic lesions, yet non-pathognomonic abnormalities. Indeed aphthoid lesions can occur in many other conditions such as Yersinia, TBC, Behçet etc. Aphthoid lesions occur on top of lymphoid cell collections. They are often surrounded by a conspicuous rim of erythema, corresponding to a coronal ring of dilated capillaries. Whether aphthoid lesions are the starting point of the myriad of larger ulcerous defects, so characteristic for full blown disease is still unsettled. An alternative hypothesis suggests that ulcers are the equivalent of focal ischemic infarction subsequent to vasculitis and vascular occlusion.

Small bowel CD ulcers tend to arise along the mesenteric margin, a site supplied by short end-arteries.

Wireless capsule endoscopy can detect Crohn-like lesions that otherwise were difficult to detect. Such minute to small abnormalities need to be differentiated from drug-induced alterations and even occasional findings in healthy individuals which, if true, is disturbing.

Mucosal healing became possible with current anti-inflammatory therapy and should become the final outcome of therapy.

The simple endoscopic score for CD by Daperno et al (Gastroenterology 2002;122: A216) is a more acceptable scoring system for routine practice.
How, what and when to biopsy

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The biopsy pathology of ulcerative colitis, Crohn's disease and their mimics can be confusing. It is made more straightforward by the provision of an adequate amount of clinical information including the drug history and the endoscopic appearances. It is made even more straightforward if in addition to this biopsies are taken from appropriate sites.

Biopsies taken early in the history of the disease may present difficult differential diagnosis from an infective colitis. Crypt architectural distortion may take six weeks to develop. The presence of both basal plasma cells and lymphoid aggregates are helpful in differentiating inflammatory bowel disease from infection whereas superficial oedema and neutrophil collections in the lamina propria are more likely to be found in infective colitis. It is important to biopsy early in the disease to exclude infection. It is equally important to biopsy inflammatory bowel disease at the time of a relapse to exclude superimposed infection due to recognisable organism, viral inclusions or pseudo-membranous colitis. Cytomegalovirus and pseudo-membranous colitis are two common superimposed infective conditions, which may cause difficulty, which, can be diagnosed relatively easily with appropriate biopsy, microbiology and studies for Clostridium difficile toxin in the stool.

Biopsy of normal mucosa - When normal mucosa is seen at endoscopy in a patient with a known history of IBD or a patient who is being investigated for the presence of IBD it is still very important to biopsy the normal mucosa, preferably at more than one site. The normal mucosa in someone with diarrhoea and no previous history may reveal the presence of microscopic colitis or isolated granulomas in Crohn's disease or the presence of minimal change colitis. Biopsies of normal mucosa in somebody with a known history of IBD may reveal granulomas in Crohn's disease or persistent architectural distortion in ulcerative colitis or the biopsy may return to normal and then the biopsy series should be re-evaluated.

Biopsy of ulcers - It is useful to biopsy the edge and base of ulcers but one also must be careful to biopsy the non-ulcerated mucosa to achieve accuracy of diagnosis. Biopsy of ulcers and ulcer edges may reveal malignancy or superimposed infection. In particular cytomegalovirus infection or occasionally it may reveal malakoplakia or amyloid.

Biopsy of polyps - Biopsies of polyps in IBD are often less helpful than removal of the polyp. Biopsies of polyps may reveal cytomegalovirus, adenoma, DALM or a benign inflammatory polyp.

Distribution of colitis - It is important to place biopsies from different sites in differentially labelled containers to maximise the information about the distribution of the colitis. In particular sigmoid colitis has a very large differential diagnosis. It may related to colitis and its association with diverticular disease or maybe Crohn's disease and infection or
partly resolved ulcerative colitis with relative rectal sparing. It is very important in this circumstance to be certain to biopsy not only the sigmoid but also the rectum since diverticular colitis does not affect the rectum.

Distribution is also important in the assessment of caecal patch lesions in ulcerative colitis or to assess whether or not Crohn's disease is present. It has to be remembered, however, that ulcerative colitis may be microscopically patchy after treatment.

Biopsies after surgery - Ileostomy end: Biopsies from an ileostomy end will reveal flattening of villi and focal acute and chronic inflammation and these features may be highly misleading if there is a suspicion of pre-stomal ileitis or Crohn's disease biopsies along the ileum from the ileostomy should also be taken.

Anastomotic biopsies - It is known that Crohn's disease will recur on the proximal side of the anastomosis. Biopsies from here may be helpful.

Diversion of pre-existing inflammatory bowel disease - The biopsy findings of diverted ulcerative colitis may resemble those of Crohn's disease whereas those of Crohn's disease may return to normal and may resemble those of ulcerative colitis.

Biopsies for dysplasia - There is increasing evidence that targeted biopsies for dysplasia or more useful than random biopsies. If, however, polyps and DALMS are biopsied the surrounding flat mucosa must also be biopsied to help differentiate adenomas from DALMS, as the management is quite different. Cyclosporine related histological changes might mimic dysplasia.

Biopsies in pouch dysfunction - It has to be remembered that in patients with symptoms of pouchitis the pouch may not be the only site of disorder and indeed may not be the site of disorder. The pre-pouch ileum and the columnar cuff below the pouch both have to be considered.

Summary
In conclusion, pathologists working together with their endoscopists with an adequate clinical history and drug history and endoscopic information will provide the most useful service in inflammatory bowel disease for the benefit of the patient.
Traps in the diagnosis of ulcerative colitis

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Numerous pitfalls exist in interpreting biopsies (and sometimes resections) from patients with ulcerative colitis (UC). These can exist at the gross/endoscopic level by an atypical distribution of disease or at the microscopic level when biopsies (and sometimes resections) do not have the typical histological pattern or distribution associated with UC, or sometimes masquerade as other conditions. Sometimes extra-intestinal disease, especially that occurring in the upper GI tract, may lead to immediate consideration of upper GI involvement of Crohn's disease (CD) rather than UC.

1. Atypical gross/endoscopic distribution of disease.
   UC is most frequently a disease that involves the rectum and extends proximally for a variable extend before there is reversion back to normal mucosa which can be abrupt or occur over a several cms of bowel. Traps include:

   a) **Presence of a cecal or periappendiceal patch.** This is an area of overt colitis either surrounding the appendiceal origin, and often associated with acute appendicular inflammation that is mucosal and therefore asymptomatic, or takes the form of an area of inflammation in the cecum that may also include the ileocecal valve. The trap is to regard these as discontinuous disease and therefore indicative of skip lesions and therefore Crohn's disease.

   b) **Apparent rectal sparing with gradual transition to typical colitic mucosa.** This usually occurs in patients already on therapy when healing may begin preferentially in the rectum, and does not always require therapeutic enemas. It occasionally happens spontaneously also. Histologically, the rectum is invariably involved with typical changes of UC (some degree of architectural distortion, an excess of chronic inflammation including deep plasma cells, and neutrophils that are invariably cryptophilic).

   c) **Rectal sparing with aphthoid ulcers in the transition to typical colitic mucosa.** A small proportion of patients present in this manner but they usually have severe disease. Further, if they come to colectomy such patients may have little or no indicators of prior inflammation (architectural distortion etc). The options are to consider such patients as a variant of indeterminate colitis, but given the ambiguity of this term is such that it may be better called "colitis of unknown etiology" (not unknown type as this tends to imply that severe disease is either UC or CD, whereas some fulminant colitides exhibit features of neither).

   d) **Features that suggest CD rather than UC.** This includes overt focality or patchiness including apparent sparing of segments of bowel, thereby mimicking CD. While this can be seen following any sort of therapy it can also be seen at presentation, especially in the pediatric population. Some of these gradually evolve into typical UC over a year or two.
A further feature that may raise the question of CD, and again especially in the pediatric population, is the presence of overt gastric or duodenal disease (or both) in Helicobacter negative patients (Helicobacter tends to dominate and mask disease in the stomach and proximal duodenum). Duodenitis can be severe and tends to affect the first part. Gastric disease can affect part or all of the stomach and be quite focal with aphthoid ulcers. Histologically the characteristic feature of CD is focal chronic active Hp negative gastritis. However, it is becoming increasingly apparent that patients with UC, especially in the pediatric population and those with severe large bowel disease, may develop upper GI disease that also tends to resolve following diminution of activity of large bowel disease by medical therapy or colectomy.

In patients with severe (fulminant) disease, a variety of features may be present that cause the diagnosis of Crohn's to be considered. This includes overt focality/sparing macroscopically, and sometimes microscopically, either in the form of geographic regions being spared or longitudinal ulcers with virtually normal mucosa between them that can also mimic typical cobblestoning and ulceration both macroscopically and microscopically. In severe or fulminant colitis, the diagnosis of CD rests on finding either granulomas beyond the mucosa and areas of ulceration so that foreign material or other causes are not issues, or of transmural lymphoid hyperplasia, which does not include polymorphous transmural inflammation that can be seen in any fulminant colitis. Knife like fissuring can also occur and are also typical of fulminant colitis of any cause and do not imply CD. The distinction is clearly important in patients in whom an ileo-anal pouch anastomosis is being considered.

A final mention must be made of both the endoscopic and histological aspects seen with bowel preparation, and in particular those found using oral Fleet's, which can cause aphthoid ulcers endoscopically and lamina propria neutrophils which can invade the crypts microscopically. They have been shown to resolve within a few days if the patient is re-scoped then without further bowel preparation.

2. Microscopic features that can trap the unwary.
All of the macroscopic patterns described previously have histological counterparts where the possibility of exactly the same traps exists; in some the histological issues have also been mentioned. Many of these depend on an understanding that these traps exist. For example, unless the pathologist is aware that the cecal patch exists, the finding of overt cecal colitis, then normal mucosa until the distal disease is reached would immediately look like a skip of Crohn's disease. Similarly, the fact that in resolving colitis it is possible to get focality of chronic inflammation from marked to normal with a few cms of bowel can also lead to erroneous consideration of Crohn's disease. However other purely microscopic features can also trap the unwary.

a) Biopsies of aphthoid ulcers. The finding of an erosion or ulcer with adjacent crypts that are virtually uninvolved in the inflammatory process, and in which part of the same biopsy is virtually normal, is not part of the picture of typical UC, in which erosions and ulcers take place in an
inflamed mucosa. Such biopsies cannot therefore be interpreted readily as being "consistent with UC". The exception is in severe or fulminant colitis of any cause, including UC. In the absence of evidence of this in other biopsies or from clinical history, the appearances immediately suggest CD, which is characterized by focal disease such as this. Knowledge of the setting in which biopsies have been obtained. While it is a very useful exercise to identify these lesions entirely on histological grounds, the full spectrum within which they occur needs to be appreciated. While one can back the odds that lesions such as this will come from patients with CD most of the time, it is not all of the time, hence the need to know the clinical context in which the biopsies were taken.

b) **Rectal sparing.** As discussed previously, this is usual endoscopic and biopsies often show typical architectural distortion. However, in patients in whom the diagnosis is made quickly and the patient treated, while the deep plasma cells and acute inflammation are present, the architectural distortion has not occurred, so that in subsequent biopsies the biopsies may appear completely normal histologically. Indeed, some patients who have remained quiescent for years but previously had architectural changes can return to what appears to be normal mucosa. The implications of this is that it is impossible to take biopsies to "exclude UC", as normal biopsies are indeed "compatible with" quiescent UC.

c) **Atypical presentations - especially children.** While most children present with typical UC (often extensive) some present either with very severe disease with the traps of fulminant colitis previously described, or with focal disease that more resembles CD than UC. However, young children (e.g. < 6 years old) can present with morphological features that really resemble acute infectious (self-limited) colitis rather than UC, and it is only when one appreciates that the patient has been symptomatic for months in the apparent absence of identifiable organisms, parasites, or toxins, that the diagnosis of atypical IBD has to be considered. Such patients can go on to typical UC or CD and while one wonders whether the underlying predisposition to IBD has perhaps been manifest by the uncultured infection, the evidence is lacking.

d) **Other mimics of UC.** There are a variety of mimics of UC. Perhaps the best is that seen in patients with diverticular disease (*diverticular colitis*) which cannot only mimic UC endoscopically and histologically, but can evolve to apparent typical UC. Yes the initial presentation is atypical in that there is usually rectal sparing - the other situation in which there may be rectal sparing. *Microscopic/lymphocytic/collagenous colitis* can all be seen in patients with established UC. As this can include some degree of architectural distortion (usually mild), an increase in chronic inflammation including an excess of plasma cells which can reach the muscularis mucosae, and Paneth cell metaplasia distally, and some neutrophils, on rare occasions one needs to know the endoscopic appearances (colitis or pretty normal) to come to the correct diagnosis.
**Allergic colitis** can have architectural distortion and an excess of eosinophils with eosinophilic crypt abscesses. It is fortunate that this is a disease of infants as some patients with quiescent UC have a marked excess of eosinophils in the lamina propria when in a relatively quiescent phase, to the point that a diagnosis of "eosinophilic colitis" (whatever this descriptive term means) is given.

**Chronic infection.** Some chronic large bowel infections (classically amebiasis but also others characterized by longstanding ulceration and inflammation) can in theory mimic IBD, but usually there is a focal character to this and organisms are usually readily identified.

**Selected references:**


Session II

Microscopic Colitis
Microscopic colitis: Epidemiology

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Microscopic colitis is a term used to define those entities characterized by chronic watery diarrhea, normal radiological and endoscopic appearance, and microscopic abnormalities in the colon. The entity includes collagenous colitis and lymphocytic colitis. Collagenous colitis differs from lymphocytic colitis by a specific histopathological feature consisting of the presence of a subepithelial collagen band (10 μm or more) adjacent to the basal membrane. Both diseases display inflammatory changes in the lamina propria and superficial epithelial damage. They are considered chronic inflammatory diseases of the colon with a benign but sometimes relapsing course.

The incidence of collagenous colitis and lymphocytic colitis was estimated in several population-based studies. The reported mean annual incidence of collagenous colitis ranges from 0.8 to 6.1 per 100,000 inhabitants. Peak incidence was observed in older women (up to 26.9 per 100,000 in women aged 60-69 years in Sweden studies). The incidence of lymphocytic colitis has ranged from 3.7 to 5.7 cases per 100,000 person-years. Female:Male ratio ranges from 4.8:1 to 9.0:1 for collagenous colitis, with a median age at diagnosis ranging from 58 to 68 years. In lymphocytic colitis the female:Male ratio is less marked: 2.1:1 or 5.0:1, and the median age is similar (58 to 70 years). On the other hand, microscopic colitis was diagnosed at a rate of 10 per 100 normal-looking colonoscopies performed in patients with chronic watery diarrhea, and of almost 20% of those patients older than 70 years.

There are reports of familial occurrence of microscopic colitis and also of microscopic colitis and inflammatory bowel disease, but no studies have been performed to determine if there are chance associations or whether a true familial predisposition exists. On the other hand, microscopic colitis does not appear to have a malignant potential.

In every patient, it is important to make a correct history of recent drug consumption. There are some medications with a suggested role in the pathogenesis of microscopic colitis or acting as triggers of diarrhea (NSAIDs, ranitidine, lansoprazole, venotonic drugs, ticlopidine, flutamide).

On the other hand, it has been described that 0 to 30% of patients with microscopic colitis have associated celiac disease. Association of collagenous colitis with HLA-DQ2, similar to the pattern seen in celiac disease, has been suggested by one group, but not corroborated by other authors who found an association of these HLA genes with lymphocytic colitis but not with collagenous colitis.
Diarrhea (three or more bowel movements per day) lasting more than 4 weeks is a common symptom in adults. The prevalence is approximately 1-5%, making it a major cause of disability. Many patients do not seek medical attention unless the diarrhea is associated with other symptoms such as weight loss. Nevertheless, the effect of chronic diarrhea on quality of life and health-care expenses is considerable. Patients with chronic diarrhea, with or without the passage of blood, are likely to be fully investigated, inclusive one or other form of endoscopy with biopsy. Several studies show that colonoscopy and biopsy is useful in the investigation of patients with chronic diarrhea who had a macroscopically normal colon at colonoscopy, yielding a histological diagnosis in 22-31% of patients. Various forms of colitis can thus be present in the absence of radiological and endoscopic lesions. These include infections (spirochetosis, post-infectious irritable bowel syndrome, C. difficile infection …), drug-related colitis, inflammatory bowel diseases (minimal change colitis), allergy-associated colitis and microscopic colitis including variants and atypical cases. In 1993, a French and an American research group suggested the use of “microscopic colitis” as an umbrella term to cover the forms of colitis in which there was histological but no endoscopical or radiological abnormality. The term had in fact been introduced already in 1980 for a condition characterized by chronic diarrhea and a mild increase in inflammatory cells in the colonic mucosa which was macroscopically normal. It was later shown that the most distinctive feature of this condition was a marked increase of the number of intraepithelial lymphocytes. The condition was therefore renamed “lymphocytic colitis”. It appeared to be different from “collagenous colitis”, a condition firstly reported in 1976 and characterized by a mucosa with a markedly thickened subepithelial collagen layer and an increase of inflammatory cells in the lamina propria. Collagenous colitis and lymphocytic colitis were the two first and still are the main types of microscopic colitis. Various other types such as microscopic colitis with giant cells have been reported. They might or might not be distinct nosological entities. Genuine microscopic colitis must not be confused with other types of colitis. In rare cases, Crohn’s disease or ulcerative colitis may present a microscopic colitis-like pattern. The etiology of microscopic colitis remains unclear. Luminal noxious agents may be important. Various drugs have been reported to be responsible for cases of lymphocytic or collagenous colitis. Both collagenous and lymphocytic colitis can therefore be subdivided in separate categories. Lymphocytic colitis can be idiopathic, drug-related, celiac disease-related or infectious in origin, while collagenous colitis can be idiopathic, infectious or drug-related.
Mechanisms of pathogenesis

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The aetiology of microscopic colitis is unknown and is likely multifactorial. At present, it is considered to represent an abnormal immunologic reaction to an agent in the gut lumen in predisposed individuals.

Genetics
The importance of genetics is largely unknown. A small number of familial cases with collagenous and lymphocytic colitis, even mixed, have been reported. Whether these associations are due to genetics, environmental factors or chance cannot be assessed.

Luminal agent
Diversion of the faecal stream by an ileostomy normalises or reduces the characteristic histopathologic changes in collagenous colitis, and recurrence of symptoms and histopathologic changes are seen after closure of ileostomy.

Infectious agent
The sudden onset of the disease in some patients and the effect of various antibiotics support a possible infectious cause. Association with microscopic colitis and infections with Campylobacter jejuni and Clostridium difficile have been reported. Yersinia enterocolitica has been detected in patients prior to the collagenous colitis diagnosis, and it was found that antibodies to Yersinia species were more common in collagenous colitis patients than in healthy controls.

Drug-induced
There are reports on drug-induced microscopic colitis especially on lymphocytic colitis. Most reports concern ticlopidine, Cyclo 3 Fort, selective serotonin reuptake inhibitors and lansoprazole. In a case-control study the use of NSAIDs was significantly more common among collagenous colitis patients than in controls. The number of reported cases of drug-induced microscopic colitis, however, is small and a chance association is possible.

Bile acids
Data on bile acid malabsorption in microscopic colitis are conflicting with findings of bile acid malabsorption of 27-44% in collagenous colitis and of 9-60% in lymphocytic colitis. Cholestyramine is effective in patients with concomitant bile acid malabsorption, but even in patients without bile acid malabsorption. This emphasises the importance of the faecal stream and the therapeutic effect may be related partly to binding of luminal toxins.

Nitric oxide
Colonic nitric oxide (NO) production is greatly increased in active microscopic colitis. The levels of NO correlates with clinical activity and histopathology. NO is an inflammatory mediator but whether its role in microscopic colitis is proinflammatory or protective remains unclear.
**Secretory or osmotic diarrhoea**
Diarrhoeal pathophysiology in collagenous colitis has been regarded as secretory caused by an impaired epithelium and the inflammatory infiltrate, and decreased reabsorption of electrolytes and water due to the collagenous band. Studies on the influence of fasting on diarrhoea in collagenous colitis indicated, however, that osmotic diarrhoea was predominant.
Microscopic colitis: Treatment

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A variety of therapeutic agents have been used in microscopic colitis. However, the number of controlled trials is small.

In detail, most regimens are only supported by case reports or small, non-controlled series. Thus, recommendations for therapy remain empirical and have included antidiarrhoeal agents, aminosalicylates, antibiotics, systemic corticosteroids, bismuth subsalicylate or subnitrate, cholestyramine, ketotifen, verapamil, pentoxifylline, spasmylytics, azathioprine, methotrexate, cyclosporine and octreotide. In a recently published pilot trial the efficacy of E. coli Nissle 1917 has been shown in 14 patients with collagenous colitis.

Regarding the benign course of the disease and the fact that a considerable proportion of patients respond to simple medical therapy such as antidiarrhoeal agents (e.g. loperamide) or cholestyramine (in case of biliary component influence), these types of drugs should still be considered as first-line therapy, if cessation of certain medication (NSAIDs) failed.

The potential role of NSAIDs remains controversial. The study by Riddell et al. (1992) indicates a higher proportion of patients with NSAIDs in collagenous colitis compared to controls. For practical use the discontinuation of NSAIDs is recommended. In collagenous colitis controlled studies have focused on bismuth subsalicylate (1 trial), prednisolone (1 trial) and budesonide (3 trials, 1 metaanalysis). In addition, there is no evidence for controlled trials in lymphocytic colitis.

Bismuth
Bismuth subsalicylate has been tested in a placebo-controlled study in 14 patients with collagenous and lymphocytic colitis which is published in abstract form (Fine et al. 1999). Non-responders were treated cross-over subsequently. The primary response rate was 7/7 in the bismuth group, and 5/6 in the non-responder group.

Prednisolone
Systemic corticosteroids are effective in reducing the stool frequency. Therapy is limited by the high number of undesired effects related to high bioavailability. 50 mg prednisolone daily were not superior to placebo in a controlled clinical trial (Munck et al. 2003). Limitations of this study are the small number of patients (n = 12) and the short duration of therapy (2 weeks).

Budesonide
Budesonide is a lipophilic steroid with a high receptor binding affinity and a high first pass effect in the liver. Thus, the bioavailability of budesonide is rather low (≈ 11 %). With respect to the location of the subepithelial collagen layer and the lymphocytic infiltrate in collagenous colitis the pharmacological profile of budesonide seems to be suitable for a rational luminal therapy of collagenous colitis.
As shown in a total of three appropriately conducted controlled clinical trials in collagenous colitis (Baert et al., 2002; Miehlke et al., 2002; Bonderup et al., 2003), a combined analysis (Chande et al., 2004) as well as in case report series and non-controlled pilot trials, budesonide proved to be very effective in inducing clinical and histological remission in collagenous colitis. Budesonide is the only intervention for which strong clinical evidence of benefit exists for clinical as well as histological improvement in collagenous colitis.

The primary outcome measure in nearly all trials was clinical remission or improvement as characterised by decreased stool frequency or stool weight or consistency. Moreover, a decrease of further accompanying complaints has also been considered. Histological response was investigated as secondary outcome measure and has been classified as decrease in inflammation activity or thickness of collagen band in the lamina propria.

Bajor et al. (2003) presented a poster at the DDW 2003 indicating that the $^{75}$SeHCAT values increased in all but one patient after 8 weeks of budesonide treatment. Thus, the clinical effect of budesonide may be mediated by an upregulation of the active bile acid uptake in the terminal ileum leading to a reduced bile acid load to the colon. Furthermore, levels of vascular endothelial growth factor (VEGF) significantly decreased after treatment with budesonide.

In conclusion, as has been shown in a recently published meta-analysis (Chande et al., 2004) of the randomised controlled clinical trials available, budesonide (9 mg o.d. for 6-8 weeks) is effective in the treatment of collagenous colitis with very high clinical (81% vs. 17%) and histological (61% to 100% vs. 4% to 33%) response rates as compared to placebo.

The long-term treatment of collagenous colitis is still under discussion. The recurrence rates after termination of the acute phase therapy are high. In this regard, the important questions to be answered in the near future are: Is there an indication for a maintenance treatment of collagenous colitis? Which drug should be used? At which dose?

Surgery is described as an ultimate, but very rarely applied alternative in severe, unresponsive collagenous colitis. It has been shown that ileostomy leads to a reduction of the collagen band and lymphocytic infiltrate in collagenous colitis. These data indicate the possible influence of a luminal agent in collagenous colitis.

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Session III

Predicting Outcomes
Predicting the natural history of IBD

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The initial clinical presentation of IBD is very heterogeneous with respect to severity, location, behavior, presence of extra-intestinal manifestations or complications. The natural course of IBD is characterized by flare-ups altered with periods of remission and most patients will have to take medication for a large part of their life. Overall, around 75-90% of IBD patients will need to undergo some form of surgery within 10 years of diagnosis. IBD is a dynamic disease which phenotypically evolves and progresses with time. There have been attempts to identify predictive factors for disease evolution in a patient although good prospective predictors are currently lacking. The majority of Crohn's patients will be diagnosed before the age of 40 years and will present with inflammatory disease (non-stenosing, non-penetrating). As the disease duration increases, more than 50% of patients will eventually evolve towards either strictureting or penetrating disease. Especially disease localized to the ileum alone will be complicated by stricture formation, whereas ileocolonic disease is more often complicated by a penetrating complication. With respect to disease severity, population-based studies suggest that most patients have a chronic intermittent disease course, while < 20% will have an unremitting disease course and 10% a prolonged remission.

For ulcerative colitis, some studies suggested that previous appendectomy is associated with a less severe disease course, although there is debate. The beneficial effect of appendectomy on the risk of colectomy seems additive to that of current smoking. Studies undertaken in the 1960s reported an unfavorable course and prognosis in patients over the age of 60 years. Recent surveys on the contrary have suggested that the course of IBD in the elderly patient is similar to the other age groups. However, more common distal colitis and less extensive colonic and diffuse small bowel disease have been reported. The disease also responds well to medical treatment in the majority of elderly patients, and surgical intervention is only required rarely for complications or unresponsive disease.

Even after resection of the diseased bowel in CD patients, new lesions can be visualized endoscopically within weeks to months after surgery in the neoterminal ileum. The evolution of these lesions mimics the natural history of ileal CD at the onset. Therefore, if we are able to prevent recurrence of early lesions, we could probably interrupt the natural course of the disease. The medical advances in CD and UC over the past years have altered our treatment goals. Improvement of symptoms is no longer satisfactory and modification of the clinical course has become a major goal. Treatments that induce healing of the intestinal mucosa may therefore provide particular clinical benefits, including sustained response or remission. In this respect, azathioprine and infliximab are able to heal the mucosa and are introduced much earlier in the course of the disease. Despite this change in management, the cumulative risk of developing strictureting or penetrating intestinal complications and intestinal resection seems unchanged. However, data are scarce and one should possibly conclude that their effect on the natural history of the disease and on the need for surgery is still largely unknown.
Predicting the outcome of severe ulcerative colitis

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Up to 30% of patients with ulcerative colitis (UC) may require colectomy. The majority of these will be for acute severe colitis not responding to medical therapy or in patients with chronic relapsing disease that is steroid refractory or steroid dependent. Patients may also need colectomy after developing dysplasia or cancer complicating UC. Predicting which patients may be at risk of colectomy would have a number of advantages at diagnosis and during admission with acute severe disease:

- At diagnosis ‘high-risk’ patients could receive appropriate counselling about
  - Optimal obstetric management
  - The potential need for surgery, stoma, pouch etc.
  - The possibility of early introduction of thiopurine therapy
- During admission with acute severe disease clinicians could offer high-risk patients
  - Early and appropriate introduction of ciclosporine etc.
  - Early discussion with surgeons and stoma nurses

The most well documented and validated predictors of the need for colectomy are clinical scoring systems. A number of these specify criteria that predict severe disease such as the original and modified versions of the Truelove and Witts criteria and the uncomplicated Walmsley Simple Clinical Colitis index. These scoring systems, however, do not specifically address the need for colectomy. The most widely quoted scoring system used in this setting is the Travis or Oxford criteria which state that on day 3 after admission (and appropriate intensive treatment for acute severe colitis), 85% of patients who passed stool more than 8 times a day or passed stool between 3 and 8 times a day and had a CRP > 45 mg/l would require colectomy. More recently the group from Edinburgh demonstrated that stool frequency, hypoalbuminaemia and colonic dilatation within 3 days were independent risk factors for colectomy. In this study a scoring system based on these criteria could predict 85% of patients who would fail medical therapy. These data give a sensitivity of 85% and a specificity of 75% for non-response.

Other data have suggested that small bowel dilatation on plain abdominal X-ray may predict colectomy although this has not been validated. Other data have suggested that mucosal appearance during (careful!) colonoscopy (i.e. frank ulceration) may predict the need for colectomy in acute UC. Colonoscopy in acute severe disease is not widespread practice as many clinicians are understandably reluctant to perform colonoscopy in such a setting.

Some studies have suggested that histological changes alone or in combination with macroscopic colonoscopy views may be useful in predicting colectomy. An increase in epithelial apoptotic cells; increased frequency of crypt abscesses and a reduction in number of eosinophils have all been proposed as histological markers of severe UC.
More recently clinicians and scientists have attempted to use our increased understanding of the genetic basis of the inflammatory bowel diseases as a starting point for identifying genetic markers that predict poor outcome in UC. The first marker that identified patients at risk of colectomy was the rare HLA-DRB*0103 allele. This association with extensive and severe colitis has been widely reproduced in cohorts from around the world. An association with an allele in the gene encoding the IL-receptor antagonist (IL-1 RA) has also been proposed as a genetic marker for severe disease. More recently both our group and the group from Edinburgh have focused attention on the gene encoding a p-70 glycoprotein pump (multi-drug resistant gene-1 [MDR-1]). Elevated expression of the glycoprotein pump is seen in patients with IBD refractory to medical treatment. A polymorphism within MDR-1 is associated with colectomy in UC. Other genetic markers within the NFκB/innate immunity pathway are also associated with disease behaviour in UC. A genetic panel of HLA-DRB*0103, MDR-1 and a polymorphism in the map kinase gene MEKK-1 is strongly associated with colectomy (p = 0.0001).

Future work will need to concentrate on combining clinical, biochemical, (serological), radiological and genetic markers in larger cohorts in order to improve the clinicians’ ability to predict outcome in severe UC.
Who gets extraintestinal manifestations?

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Up to 25% of patients with inflammatory bowel disease develop extraintestinal manifestations. The commonest of these are peripheral and axial arthropathies, but erythema nodosum and uveitis are also common, whilst conditions such as pyoderma gangrenosum and primary sclerosing cholangitis are less common. For some patients these manifestations are transient and mild, but for some patients they may be severe and more debilitating than the bowel disease itself. The exact mechanism which causes inflammation outside the gut is unclear, and a number of theories have been advanced including autoimmunity and genetic predisposition. The associations with genetic and clinical factors have also been studied, and it is these that are the best predictors of who will develop extraintestinal manifestations, although none is sufficiently accurate to be of significant use in day to day clinical practice.

Primary sclerosing cholangitis - Clinical features associated with PSC include a total colitis, which tends to run a rather quiescent clinical course, and which it has been suggested may be a different entity from conventional ulcerative colitis. PSC is also associated with the presence of pANCA and with possession of HLA-B8.

Peripheral arthritis, uveitis and erythema nodosum - This group of conditions appear as distinct but overlapping conditions which may occur in association with each other or in isolation. The presence of one of this trio is a strong predictor of the development of the others, with 15-25% of arthritis patients developing uveitis compared to 2% of IBD patients without peripheral arthritis. Other clinical predictors include the presence of colonic disease in Crohn's disease. There are also relatively strong genetic associations, which are seen most clearly in peripheral arthritis and erythema nodosum. By dividing peripheral arthritis into 2 distinct forms it is possible to determine distinct HLA associations:-

Type 1 (pauciarticular) affects less than five joints including a weightbearing joint. The swelling is acute and self-limiting and associated with relapse of the IBD in the majority of cases. It lasts for a maximum of ten weeks, although 10-20% will develop persistent problems. It is associated with the presence of HLA-DR103 and B27.

Type 2 (polyarticular) affects five or more joints, and affects a wide range of joints but particularly the metacarpophalangeal (MCP) joints. It often causes persistent problems with a median duration of 3 years. It is associated with the presence of HLA-B44.

Erythema nodosum is associated with the presence of the-1031C polymorphism in the TNFα gene promoter.

However, despite these associations none is strong enough to allow a sufficiently high positive predictive value to be clinically useful. The best defined of these groups is the patients with recurrent type 1 arthritis in whom 65% are HLA-DR103 positive compared to 3% of controls.
Ankylosing spondylitis and isolated sacroiliitis - Ankylosing spondylitis is relatively uncommon in IBD (occurring in 1-6% of patients) but isolated sacroiliitis may be much more common (occurring in up to 20% of UC patients and 40% of Crohn's disease patients). There are currently no helpful clinical predictors of which patients will develop these conditions. The presence of HLA-B27 has a very strong positive predictive value (much stronger than in idiopathic AS), but a much lower negative predictive value. This is because 50-80% of IBD patients with AS possess HLA-B27 compared to 10% of controls and 94% of idiopathic AS, so there are more HLA-B27 negative AS patients with IBD than in idiopathic IBD. However, the risk of developing AS in HLA-B27 positive is probably much greater in IBD (50-100%) than in HLA-B27 positive people without IBD (1-11%). It has been speculated that the reason for this may be the combined genetic predisposition and antigenic load being admitted through the inflamed and leaky gut.

Thus the study of EIMs in IBD has lead to some interesting findings in relation to pathogenesis, particularly in the field of genetics. If these findings can be replicated and made more specific they may yield clinically useful prognostic indicators.
Colitis: Predicting outcomes - who gets cancer?

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The risk of colorectal cancer is increased in ulcerative colitis, but the magnitude of this increase remains controversial, as does the putative benefit of colonoscopic surveillance.

It is clear that patients with ulcerative colitis have diverse colonoscopic appearances encompassing a range of disease activity as well as more or less specific macroscopic features of neoplasia. Determining colonoscopic markers for cancer risk could allow stratification of particularly high- and low-risk patients and thereby permit better-targeted surveillance.

In the St Mark’s case-control study we sought colonoscopic markers of colorectal neoplasia risk. Each patient with colitis-associated neoplasia detected over a 15 year period was matched with two non-dysplastic colitic controls. Data were collected on post-inflammatory polyps, scarring, strictures, backwash ileitis, the presence of a shortened, tubular or featureless colon, severe inflammation, and when surveillance colonoscopies appeared normal.

Cases (n = 68) and controls (n = 136) were well matched. On univariate analysis, cases were significantly more likely to have post-inflammatory polyps (OR 2.14; 95% CI 1.24-3.70), strictures (OR 4.22; 1.08-15.54), shortened colons (OR 10.0; 1.17-85.6), tubular colons (OR 2.03; 1.00-4.08) or segments of severe inflammation (OR 3.38; 1.41-10.13); and less likely to have had a macroscopically normal-looking colonoscopy (OR 0.40; 0.21-0.74). After multivariate analysis, a macroscopically normal-looking colonoscopy (OR 0.38; 0.19-0.73), post-inflammatory polyps (2.29; 1.28-4.11), and strictures (4.62; 1.03-20.8) remained significant. The 5-year risk of colorectal cancer following a normal-looking colonoscopy was no different from that of matched general population controls.

Our own data and those from other centres suggest that long-term use of 5-aminosalicylates may reduce cancer risk (see also Session VII). Long-standing extensive Crohn’s colitis probably poses a similar risk to that from ulcerative colitis.

In conclusion those with IBD at most risk of colon cancer are those with long-standing extensive colitis. It appears that macroscopic colonoscopic features help predict this risk. Features indicative of previous/ongoing inflammation signify an increased risk, but by contrast a macroscopically normal-looking colonoscopy returns the cancer risk near to that of the general population. Future surveillance strategy planning should be guided usefully by these observations.
Session IV

Corticosteroid Therapy
Why do they not always work?

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Steroids are the mainstay of treatment for active inflammatory bowel disease either in oral or parenteral dosage. However, the full range of mechanisms by which steroids exert their anti-inflammatory functions have only recently emerged. Steroids complex with the glucocorticoid receptor and may either produce effects through trans-activation of genes or through trans-repression. Many of the effects on inflammation are mediated through trans-repression with inhibition of NF-kappa-B activity. In addition, steroids exert anti-inflammatory effects through modulation of mRNA stability and through histone de-acetylation. Steroid failure has been associated with multiple factors both genetic and acquired. Potential mechanisms include genetic defects in receptor function or in signalling function. In addition, a wide variety of pharmacogenetic factors may influence steroid pharmacokinetics. We have previously demonstrated that high levels of lymphocyte expression of the PGP-170 drug exporter pump is associated with failure of steroid therapy. Such expression could be mediated either through genetic polymorphisms in the mdr-1 gene or through acquired changes affecting expression of mdr-1. Such acquired changes in expression include potential significant alterations induced by the alternative medical product St John’s wort whose active ingredient hypericin is a potent inducer of mdr-1. Other potential mechanisms for treatment failure include intrinsically high disease activity and altered signalling and transcriptional factors mediated through other external factors. Hence, multiple mechanisms may contribute to failure of steroid therapy in inflammatory bowel disease. Detailed analysis of treatment resistance and treatment failure may permit the development of new approaches to maximise therapeutic impact.
Budesonide for ulcerative colitis

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The frequent adverse effects associated with the use of glucocorticosteroids (GCS) prompted the development of a new group of drugs with equivalent efficacy and a more benign adverse event profile. The pharmacological development of novel GCS has been more difficult in ulcerative colitis because of variations in colonic pH, transit time, and bacterial metabolism. Prednisolone metasulfobenzoate, fluticasone propionate, tixocortol pivalate, beclomethasone dipropionate and budesonide have been evaluated [1]. The GCS budesonide with high topical activity and a high rate of metabolism has been administered in an oral controlled-release formulation. Because of the use of new drug delivery systems that target the bowel wall as the pharmacokinetic compartment of interest, budesonide has been called - "a model of targeted therapy" [2]. It seem to give an overall treatment result in active ulcerative colitis approaching that of prednisolone but without suppression of plasma cortisol levels [3]. However, so far trials of enteric-coated budesonide have not been effective in the setting of distal colitis

A new pH-modified release capsule (Budenofalk®) was used to study the pharmacokinetics, pharmacodynamics, and safety of two dosage regimens of budesonide capsules and to obtain efficacy information. Budenofalk® 9 mg daily was administered as a single dose 9 mg in 8 patients with active distal ulcerative colitis for 8 weeks [4]. A pharmacokinetic profile and pharmacodynamic profile (cortisol, lymphocytes and neutrophils) was performed at day 5. In the 9 mg o.d. group, higher peak concentrations and systemic availability was found compared to the 3 mg t.i.d. group. Cortisol suppression was more pronounced after 9 mg o.d. than after 3 mg t.i.d. Lag-time, AUC and pharmacodynamic effects were comparable (14% mean decrease lymphocyte count and 26% mean increase neutrophil count). Mucosal biopsy specimens in the distal colon revealed significant budesonide levels with both regimens.

After 8 weeks, 71% in the 9 mg o.d. group and 38% in the 3 t.i.d. group responded. The endoscopic index improved from 10 ± 2 to 2 ± 3 (p <0.001) with 9 mg o.d. and from 9 ± 2 to 4 ± 4.7 (p = 0.02) with 3 mg t.i.d.

Studies to date have had small numbers, and relatively low statistical power, however, the pharmacokinetic and pharmacodynamic profiles found indicate that Budenofalk® reaches the distal part of colon and rectum. This limited study suggests thatBudenofalk® is effective in distal colitis and side effects are rare. Based on these observations a large clinical trial using 9 mg o.d. is indicated to confirm efficacy and assess further possible side effects. Clinicians can consider this drug as a reasonable option for patients with this disorder.

For the treatment of proctosigmoiditis the use of enemas has been well established although due to the fact that budesonide is not stable in aqueous forms, the recent development of budesonide foam using small volumes has given similar results in comparison with hydrocortisone acetate foam. Foam offers patients better tolerability than an enema and an improved quality of life. A multicenter randomized, controlled trial
in Israel, Italy and Germany it was shown in a sub-group of patients who had not responded to rectal administration of mesalazine, that 23 of 44 (52%) patients who received budesonide responded favorably to the foam, as compared with 14 of 38 (37%) patients who received hydrocortisone foam (P = ns). This study demonstrated that rectal administration of budesonide for a period of eight weeks is safe and has no substantial effect on the serum cortisol level. The lack of an effect the serological marker enzymes of bone metabolism (bone-specific alkaline phosphatase and serum osteocalcin), further supports the safety profile of budesonide when administered for a period of eight weeks [5].

References


How do I use corticosteroids in Crohn's disease?

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Application of systemic steroids results in the majority of patients with IBD in a decrease of inflammation and clinical symptoms. However, in particular in Crohn's disease effects are somewhat limited and side effects occur rather frequently. In analogy to respiratory disorders “topical” or “non-systemic” steroids have been developed using initially rectal application and later-on pH- or time-dependent slow release oral preparations. While enemas have been preferentially used in ulcerative colitis, the oral preparations have focussed on Crohn's disease. Although different substances have been tested thus far only budesonide has made it into routine treatment.

In Crohn's disease steroids are still the mainstay of treatment for active flares although the success rate when assessed in a longer range is relatively limited. However, not all patients in general practice need steroids as recently demonstrated in population-based studies.

It has been found that oral budesonide is slightly less effective than conventional steroids while side effects are considerably less frequent. This is also reflected by a lesser suppression of the HPA axis and adrenal function. Considering efficacy and side effect profile most patients with mild to moderate active disease can be treated first line with oral budesonide. With the pH-dependent release preparation higher doses than 9 mg per day may be effective in more active disease. This needs to be tested, however, in an accordingly designed trial. Although the maintenance trials have not been really successful the drug is used for remission maintenance in clinical practice due to personal experiences of many physicians. In my eyes, however, budesonide in oral release forms is helpful for induction of remission but should be substituted by other drugs for maintenance treatment if needed. Thus far combinations of budesonide and other drugs have not been tested systematically although this may be a good idea.

If budesonide does not induce remission systemic steroids (prednisolone) will be needed after exclusion of other causes of symptoms such as fibrotic strictures or chologenic diarrhea. When remission has been achieved the drug should be tapered and withdrawn. If early relapse occurs a repeated course of prednisolone and addition of azathioprine or methotrexate is used.
The identification of NOD2/CARD15 as a Crohn's disease-associated gene has given us a substantial clue towards understanding its pathogenesis. Although the functional implications of the Crohn's-related NOD2/CARD15 mutations are not fully understood it is known that the NOD2 protein is expressed in the cytoplasm of macrophages and Paneth cells, that the Crohn's related mutation is within the leucine-rich region of NOD2 that interacts with bacterial cell wall peptidoglycan, and that epithelial cells transfected with mutant NOD2 are unable to kill phagocytosed Salmonella whereas the same cells transfected with wild-type NOD2 are able to do so. These findings are in keeping with Crohn's disease occurring as a result of an inability of macrophages to kill intracellular bacteria. Further support for this comes from the rare inherited diseases Chronic Granulomatous Disease and Glycogen Storage Disease Type 1b, both of which are associated with a phagocyte defect in killing of intracellular bacteria and both of which are associated with intestinal disease that closely mimics Crohn's disease. Recent studies have shown an increase in mucosa-associated bacteria in Crohn's disease, particularly E. coli, and have shown that these E. coli are able to live and proliferate within macrophages in vitro. Immunohistochemical studies of Crohn's disease tissue have shown macrophages containing intracellular bacteria, particularly E. coli, Listeria and Group F Streptococci. The best characterised environmental agent for Crohn's disease - smoking - has been shown to be associated with an inability of pulmonary macrophages to kill Listeria - an obligate intracytoplasmic organism that replicates within macrophages.

If Crohn's disease is a consequence of ineffective clearance by macrophages of intracellular (and probably intracytoplasmic) bacteria then corticosteroids would seem a highly inappropriate treatment. There is good evidence to show that this is the case. Although corticosteroids are a cheap and effective way of achieving short term symptomatic relief this only beats placebo for the first three months and by the end of one year's treatment there is no benefit over placebo. Moreover, there is no impact on mucosal healing. The general side effects of steroids are well known but recent studies have shown that their use is particularly associated with severe sepsis in Crohn's disease. They greatly increase not only the risk of serious post-operative sepsis but also increase 9-fold the risk of serious intra-abdominal or pelvic abscess in patients with Crohn's disease. Interestingly azathioprine and mercaptopurine are not associated with these risks for bacterial sepsis and their use has been shown to heal mucosal ulcers moreover they have been shown to be effective in the absence of corticosteroids. Azathioprine and mercaptopurine should therefore no longer be thought of as steroid-sparing but as effective therapies in their own right.

Should corticosteroids ever be used in Crohn's disease? I think it depends what you mean by Crohn's disease. I now argue that isolated colonic Crohn's disease is a separate condition from "typical" ileal or ileo-caecal Crohn's disease. Isolated colonic Crohn's disease has been shown not to be associated with mutations of NOD2/CARD15, moreover it tends to occur in members of the same family as ulcerative
colitis but with smokers being at risk for colonic Crohn's disease and non-smokers at risk for ulcerative colitis. Isolated colonic Crohn's disease and ulcerative colitis share similar HLA class 2 antigen associations, and are both associated with pANCA positivity and ASCA negativity. It is therefore looking increasingly likely that isolated colonic Crohn's disease and "typical" ulcerative colitis are phenotypic variants of the same condition as part of a spectrum with indeterminate colitis in the mid-point. Although isolated colonic Crohn's disease tends to respond to antibiotics such as metronidazole whereas ulcerative colitis does not there are occasions when we resort to corticosteroids to settle it particularly if antibiotics and azathioprine have failed. In "typical" ileal or ileo-caecal Crohn's, however, we find that we can always manage the disease satisfactorily without corticosteroids. Often there are two or more reasonable alternative therapies which might include antibiotics such as ciprofloxacin or clarithromycin, enteral feeding, azathioprine or methotrexate with infliximab if relapse occurs despite these and surgery - typically laparoscope-assisted right hemicolecotmy - for the patient with a short ileal stricture and no previous surgery.

Crohn's disease is the only condition for which physicians commonly prescribe high dose corticosteroids with no expectation of having any useful effect on the long-term course of the disease. Although they "buy a quick fix" for the first three months, from then on their use is nearly always detrimental yet, once started, they are often hard to stop. Better not to start then!

References


Session V

Azathioprine
Azathioprine: Mechanism of action

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Azathioprine and its metabolite 6-mercaptopurine (6-MP) are immunosuppressive drugs that have been discovered by G. Ellion more than 45 years ago. They are used in organ transplantation and autoimmune and chronic inflammatory diseases such as inflammatory bowel diseases (IBD: Crohn’s disease, ulcerative colitis). In IBD azathioprine and 6-MP have been successfully used since 1962 and these drugs are currently considered as gold standard for maintenance of remission in IBD patients. However, their molecular mechanism of action has been a matter of debate. We have recently identified a unique role for azathioprine and its metabolites in the control of T cell apoptosis by modulation of Rac1 activation upon CD28 costimulation. We found that azathioprine and its metabolites induced apoptosis of T cells from patients with Crohn’s disease and control patients. Apoptosis induction required costimulation with CD28 and was mediated by specific blockade of Rac1 activation via binding of azathioprine generated 6-ThioGTP to Rac1 instead of GTP. The activation of Rac1 target genes such as MEK, NF-kappaB and bcl-xL was suppressed by azathioprine leading to a mitochondrial pathway of apoptosis. Azathioprine thus converts a costimulatory signal into an apoptotic signal by modulating Rac1 activity. These findings explain the immunosuppressive effects of azathioprine and suggest that 6-Thio-GTP derivates may be useful as potent immunosuppressive agents in autoimmune diseases and organ transplantation.

Source:
I Tiede, G Fritz, S Strand, D Poppe, R Dvorsky, D Strand, HA Lehr, S Wirtz, C Becker, R Atreya, J Mudter, K Hildner, B Bartsch, M Holtmann, RS Blumberg, H Walczak, H Iven, PR Galle, MR Ahmadian, MF Neurath
CD28-dependent Rac1 activation is the molecular target of azathioprine in primary human CD4+ T lymphocytes.
Pharmacogenetics of azathioprine - useful in clinical practice?

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Genetic regulation of the metabolism of azathioprine (AZA) and 6-mercaptopurine (6-MP) provides the best example of a clinical application of pharmacogenetics in inflammatory bowel disease. Understanding the complex metabolism of these drugs may offer some clues in optimizing their use in clinical practice. The thiopurine methyl transferase enzyme (TPMT) plays an important role in the determination of thiopurine toxicity and efficacy. TPMT screening before drug initiation might have significant impact on patient outcome from a safety perspective but controversy still remains as to whether TPMT-based dosing strategy is safer than weight-based strategy with close follow-up of laboratory tests. Another genetic variation in the metabolism of AZA has been ascribed to a polymorphism in the gene encoding inosine triphosphate pyrophosphatase (ITPase) but application of ITPase genotyping tests does not seem to improve the identification of patients at risk of toxicity with AZA/6-MP therapy. Further work is needed on the role of other candidate genes that may be involved in thiopurine toxicity. Metabolite monitoring may provide approach to thiopurine dose optimization in patients who are failing standard dose therapy. As with TPMT testing, it is not considered as standard of care in the absence of prospective controlled study demonstrating its superiority to empiric dose adaptation. Recent advances in the under standing of the mechanism of action of thiopurines and the prominent role of the 6-thioguanine triphosphate nucleotide may offer some new therapeutic benefit of metabolite monitoring in the management of IBD.
When to start and for how long?

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Abstract not received by the copy deadline.
Azathioprine: Long-term side effects

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The purine analogs, azathioprine (AZA) and 6-mercaptopurine (6MP), are cornerstones of therapy of steroid-dependent, steroid-refractory, and fistulizing inflammatory bowel disease (IBD). In clinical trials, between 0% and 15% of patients discontinue azathioprine due to adverse events. Retrospective case series, which may reflect more of a "real-world" experience with azathioprine, suggest that up to 25% of IBD patients discontinue purine analogs due to adverse events. Polymorphisms in the thiopurine methyltransferase (TPMT) gene explain some of these events, especially early leucopenia. Other adverse reactions such as pancreatitis, influenza-like symptoms and rash may be explained by recently characterized polymorphisms in the inosine triphosphate pyrophosphatase (ITPA) gene. Less is known about adverse events occurring over the long-term. These side effects can be classified as infectious, hematological, neoplastic and hepatic. Infectious complications of azathioprine therapy cannot be solely explained by leucopenia. Delayed leucopenia cannot be explained by TPMT polymorphisms. Potential drug interactions between AZA/6MP and other IBD medications, such as 5-aminosalicylate agents and infliximab, will be discussed. The relative risk of lymphoma appears to be mildly elevated in IBD patients on purine analog therapy. Finally, there are cases of significant hepatic injury, including veno-occlusive disease and nodular regenerative hyperplasia, following long-term use of AZA/6MP therapy. While most of these cases have been described following thioguanine treatment, such injury has occurred following therapy with AZA or 6MP. The role of purine analogs in contributing to adverse birth outcomes remains controversial.
State-of-the-Art-Lecture

Surgery for ulcerative colitis

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Abstract not received by the copy deadline.
Session VI

Immunomodulatory Therapy
How to use infliximab?

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Infliximab (IFX) is a chimeric mouse/human monoclonal antibody to tumor necrosis factor (TNF) which is effective in induction and maintenance of remission for refractory luminal and fistulizing Crohn's disease. Remission rates with IFX amount to 30-40% within 4 weeks after the first infusion, while another 30-40% experiences a considerable improvement in their symptoms. Response rates are generally higher in younger patients, in patients with colonic disease and those using concomitant immunosuppressives.

In the large ACCENT I trial, the administration of IFX 5-10 mg/kg at regular 8 week intervals was shown to be effective in maintaining remission with complete steroid withdrawal in more than 30% of initial responders. A comparison between 'scheduled' (automatic) and episodic ('on demand') treatment strategies with IFX based on the ACCENT I data clearly demonstrated that the former approach was superior based on response and remission rates, mucosal healing, antibody formation and need for surgeries and hospitalizations. Clinical response improved from week 2 to week 10 in the scheduled retreatment group (from 58% to 69%) compared to practically no improvement in the episodic group. Among patients having an initial response but losing response and need to cross over to a higher dose, 90% regained a response when crossed over from 5 to 10 mg/kg and 80% when crossed over from 10 to 15 mg/kg.

Given the widespread use of IFX worldwide, more attention is being given to long-term toxicity and efficacy aspects. The TREAT registry included 5,807 patients with Crohn's disease (2,850 treated with IFX and 2,957 controls) at academic and community practices in the US and was established (retrospectively) to study long-term safety issues. For a mean follow up of 0.9 years no differences in mortality and cancer were observed. Tuberculosis and congestive heart failure after IFX were not reported. Infusion reactions occurred in 5.4%, severe reactions in 0.16%. The incidence of serious infections was 1.27 per 100 patient-years within 3 months of an IFX infusion compared to 0.85 per 100 patient years in controls. Multiple regression analysis showed that the severe infections were rather associated with prednisone than with IFX (RR = 2.32). In 66 reported pregnancies no differences in miscarriage rates and neonatal complications were reported. The study's preliminary conclusion stated that the safety of IFX is similar to that of other Crohn's disease treatments.

The immunogenicity of IFX is a major issue with impact on efficacy and allergic reactions. In a Belgian cohort, approximately 45% of patients developed HACA after the first IFX infusion and this number increased to around 60% after the 3rd infusion. Concomitant immunosuppressive therapy suppressed the formation of HACA in 24/56 (43%) patients as compared to 52/69 (75%) patients without immunosuppressives and this resulted in higher serum IFX concentrations 4 week after the infusion (p < 0.001). The presence of HACA concentrations of > 8.0 μg/ml prior to an infusion was predictive of a shorter duration of response (35 days vs. 71 days, p < 0.001) and carried a higher risk of infusion reactions (RR 2.40, p < 0.001). An alternative strategy to reduce
immunogenicity of IFX is pretreatment with 200 mg hydrocortisone prior to the infusion. This approach diminished the formation of HACA from 42% to 26% of patients, accompanied by a decrease in infusion reactions from 24% to 15%. In this study, HACA positivity was associated with lower remission rates (0 vs. 70%), lower clinical response rates (48 vs. 86%), higher rate of infusion reactions (40% vs. 4.7%) and occurrence of severe infusion reactions (28% vs. 0%). All together, it seems to be of paramount importance to prevent antibody formation with all possible means in order not to jeopardize future treatment in patients who are often refractory to other treatments.

Fistula formation is a problematic complication of Crohn's disease affecting up to 45% of patients. The majority of patients not responding to antibiotics and immunomodulators can be treated successfully with IFX. In the ACCENT II trial, patients with a response of their fistulizing disease to 3 induction infusions of IFX at week 0, 2 and 6 received further IFX or placebo maintenance infusions on an 8-weekly schedule for the total duration of one year. The fistula response (> 50% of fistulas discontinued draining) and complete closures rates (remission) were significantly higher in patients treated with IFX than in those treated with placebo (response 46% vs. 23%; p = 0.001) (remission 36% vs. 19%; p = 0.009). IFX alone and IFX as an adjunct to exam under anesthesia and seton placement were compared in a group of 32 consecutive patients with fistulizing Crohn's disease. The group with combined approach achieved a better initial response (100% vs. 82.6%, p = 0.014), had lower recurrence rates (44% vs. 79%, p = 0.001) and longer time to recurrence (13.5 months vs. 3.6 months, p = 0.0001) compared with patients receiving IFX alone.

In conclusion, the advent of the first biological agent for the treatment of Crohn's disease has led to major changes in our therapeutic approach and overall management of Crohn's disease.
Biologic agents for ulcerative colitis

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There have been few trials of biologic agents in ulcerative colitis (UC). This is likely to reflect the perceived success of other treatments: UC can be cured by surgery and, in the mid-late 1990s, ciclosporine therapy was at its most popular. Consequently, there have been numerous attempts to find novel agents to treat Crohn's disease (CD) for which surgery is not curative, while the need to develop new approaches for UC has been less pressing.

Initial studies in UC have tended to follow the design of studies in CD; this is particularly true of infliximab and natalizumab. However, studies of basiliximab have broken this mould having only been performed in UC.

Anti-TNF Antibodies

TNFα concentrations are raised in the blood and mucosa of patients with active IBD of both types compared to healthy controls. It was logical to use anti-TNF antibodies in UC after they had been found useful in CD. The first trial, with CDP571, improved disease activity in an open label study of 15 patients with UC, however, the improvement was not sustained. Further studies have not been reported with this agent. The early reports of infliximab in the treatment of UC were also open label series; the results were often positive, though not always. However, data from open studies should always be treated with caution. A present, five small randomised controlled trails of infliximab in UC have been reported; three have been published in full, the remainder are in abstract form. Sands et al. reported 8 patients randomised to receive single infliximab infusions, (3 had 5 mg/kg, three 10 mg/kg and two 20 mg/kg), and three patients received placebo: 50% of the infliximab treated patients responded by week 2. The authors were encouraged by the response rate. We have reported a study in moderately severe steroid resistant UC; 23 had infliximab and 20 placebo. A single infusion 5 mg/kg was administered, non-responders were offered open label treatment (10 mg/kg). After 2 weeks, the remission rate was 3/23 and 1/19 for active and placebo treatments respectively, by week 6, the rates were 9/23 (39%) and 6/20 (30%), respectively. We concluded the regimen did not support the widespread use of infliximab in the management of glucocorticoid-resistant UC. Ochsenkühn et al reported that 5 of 6 patients who were randomised to receive 5 mg/kg infliximab after three weeks; the response continued until follow-up at 13 weeks. Armuzzi et al. performed a randomised open label study of infliximab compared to methylprednisolone, in moderate to severe glucocorticoid dependent UC. Three infliximab infusions were administered (0, 2 and 6 weeks). The reported remission rate was 9/10 with infliximab. However, 8/10 patients who received methylprednisolone also went into remission. This study appears encouraging, however, the response to methylprednisolone in a group of patients dependent on glucocorticoid therapy is odd. Finally, Järnerot et al. reported the outcome of a randomised trial of infliximab treatment in moderate and severe patients with UC. Significantly more patients who received placebo underwent colectomy (14/21) when compared to those who had infliximab (7/24). These authors concluded infliximab was a safe and effective rescue therapy.
Recently, two large randomised controlled trials of infliximab in UC have been completed. Act 1 and Act 2 used similar schedules to Accent 1 and Accent 2. The data will presented at the forthcoming DDW: Rumours abound that the response rate was significant.

**Anti-CD3 Antibodies**
The results of a phase 1 study of humanised anti-CD3 monoclonal antibody, visilizumab, treatment of severe steroid-refractory UC have been reported. Data from 26 recruited patients were published in abstract, 8 received 15 µg/kg iv days 1 & 2, 18 had 10 µg/kg iv days 1 & 2. 17 of 20 patients followed up had a sustained response. Significant side effects were not evident. Further trails are warranted.

**Anti-α4 Antibodies**
Natalizumab has been found useful in Crohn's disease and multiple sclerosis. One open label study has been reported in UC; 10 patients received a single infusion (3 mg/kg), 5 showed a good response by week 2, and 6 by week 4. The drug was well-tolerated, however, recent concerns over its safety in MS patients has led to the withdrawal of natalizumab pending further review.

**IL-2 Receptor Antibodies**
Basiliximab is licensed for the prophylaxis of allogenic renal transplantation. Laboratory investigation now suggests its action is to potentiate glucocorticoids, or inhibit steroid resistance. In an open study in UC, 30 patients received a single dose of basiliximab; 10 had severe UC and 20 moderate UC. By 8 weeks, of the severe patients 50% had achieved full remission, of the moderate group had 80% improved, 70% achieving full remission. This exciting result was not found in a study of another IL-2 receptor antibody, daclizumab. This difference is likely to lie in study design: Daclizumab was not used as a steroid enhancer.

**Conclusion**
Biologic agents have revolutionised our management of difficult Crohn's disease. Present data in UC give us a tantalising glimpse into the future: Not all biologic agents will work for all patients. As is so often the case, the devil will be in the detail of study design and patient selection.
Immunomodulatory therapy: Safety of immunomodulation

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Azathioprine, 6-mercaptopurine
Since the initial report of 6-mercaptopurine (6-MP) for the treatment of UC in 1962, immunomodulatory therapy has gained an important role in the management of IBD. Azathioprine (AZA) and 6-MP are thiopurine analogues that modulate immune response via inhibition of purine biosynthesis, interference of cytotoxicity of natural killer cells and T cells, and reduction of suppressor T cell function and thus cell-mediated immunity. Upon administration, AZA is quickly metabolized nonenzymatically to 6-MP within the red blood cells. 6-MP is then enzymatically converted to active end products called 6-thioguanine nucleotides (6-TG). A competitive enzyme, thiopurine methyl-transferase (TPMT), also converts 6-MP to the inactive metabolites, 6-methylmercaptopurine (6-MMP).

Since approximately 11% of the general population has mutant TPMT genotypes and consequent low or absent TPMT enzyme activity, AZA or 6-MP therapy in these individuals is associated with an increased bone marrow toxicity due to shunting of 6-MP metabolism toward the excessive production of 6-TG nucleotides. It is recommended in the FDA guideline that the determination of TPMT genotype or enzyme activity prior to initiation of medications may allow appropriate dosing and minimize potential toxicities, although no controlled studies have evaluated such a practice. Identifying patients who are homozygous for low activity TPMT alleles can detect the approximately 1 in 300 patients who will experience severe leucopenia during treatment (Reuther LO et al. APT 2003). However Colombel and colleagues (Gastroenterology 2000) have demonstrated that most instances of leukopenia occur later in the course of therapy and are not predictable by baseline TPMT status.

Methotrexate
Methotrexate (MTX) is a folic acid antagonist that has both antimetabolite and anti-inflammatory activities. It inhibits dihydrofolate reductase, thymidine synthetase, and other enzymes involving deoxyribonucleic acid (DNA) synthesis. It also interferes with the production of the proinflammatory cytokines IL-1 and IL-2. The bioavailability of oral MTX is nearly 100% at low dose of MTX (< 25 mg/week). Intramuscular MTX is given to increase compliance and bioavailability and decreases GI side effects, but it has not been proven to be superior to the oral form.

Potential toxicities of MTX include leukopenia, nausea, vomiting, and rarely, hypersensitivity pneumonitis. Hepatic fibrosis is one of the most serious sequela of long-term therapy with MTX. A pre-treatment liver biopsy is indicated in patients who have abnormal liver associated laboratory chemistries and those at potential high risk for hepatic toxicity (ie obese and individuals who consume ethanol). During the induction period (16 weeks) patients should receive liver associated laboratory chemistries frequently and complete blood count every 2 to 4 weeks. During maintenance patients should receive complete blood count periodically every 4 weeks-12 weeks while on MTX as well as liver associated laboratory chemistries. Given the lack of consensus at this point liver biopsy cannot be recommended for patients who have received a cumulative dose in excess of 1.5 g.
With regard to the problem of nausea, this tends to develop for a period of approximately 24 to 48 hours after weekly injection. This adverse effect can be managed by co-administration of oral folate (1-5 mg daily), use of antinauseant (metoclopramide, ondansetron) or dose reduction.

Cyclosporine A
Cyclosporine A (CyA) is alipophilic undecapeptide extracted from the soil fungus Tolypocladium infantum gams. It acts by binding to an endogenous peptide (cyclophilin), which blocks the entry of activated T lymphocytes into the S phase of the cell cycle, thus inhibiting the production of IL-2. It also alters B cell function by inhibiting T helper cells. Furthermore, it decreases recruitment of cytotoxic T cells and blocks other cytokines including IL-3, IL-4, gamma interferon, and TNF-alpha(a).

Side effects of CyA reported during the treatment of IBD include hypertension, seizures, paresthesias, tremor, gingival hyperplasia, hypertrichosis, electrolyte abnormalities, opportunistic infections, and nephrotoxicity.

Serum electrolytes, creatinine, cholesterol, and liver chemistry values should be monitored prior to initiation of CyA. Patients with impaired creatinine clearance and a serum cholesterol < 120 mg/dL at baseline should not receive CyA to minimize the risk of nephrotoxicity and seizures, respectively.

Patients receiving intravenous CyA should have high performance liquid chromatography (HPLC) CyA concentration and serum electrolytes determined daily, while patients receiving oral CyA should have these studies weekly. The CyA dose should be adjusted to achieve HPLC trough CyA concentrations between 200 and 300 ng/mL. When performing trough levels the levels need to be obtained 1 hour prior to the next dose and CyA needs to be administered every 12 hours in order to obtain valid trough levels. The dose should also be decreased when s-creatinine increases by 30% from baseline. Additionally, Pneumocystis carinii pneumonia prophylaxis with trimethoprim-sulfamethoxazole is recommended. The usual dose is one double strength pill every Monday, Wednesday, and Friday.

Tacrolimus
Is a macrolide antibiotic with actions similar to CyA but with a 100-fold greater potency with rapid onset.

Side effects that can be seen with the use of tacrolimus include nephrotoxicity, hyperkalemia, diarrhea, nausea, flushing, tremor, paresthesia, insomnia, alopecia, hirsutism, and gingival hyperplasia.

Cancer and mortality
Cancer and mortality is not an issue in immunosuppressive therapy given the drugs are handled with care in the treatment of the patients.

Pregnancy
In accordance to FDA recommendations drug toxicity to the fetus can be categorized as: "A" = controlled studies show no risk, "B" = no evidence of risk in humans, "C" = risk cannot be ruled out, "D" = positive evidence of risk, "X" = known danger, contraindicated in pregnancy.
Azathioprine, 6-MP, CY-A during concievement and pregnancy should not lead the clinician to suggest the mother therapeutic termination. Whereas methotrexate has known danger to the fetus.

PREGNANCY fetal drug toxicity

- Vitamin pill
- 5-asa, Infliximab, metoclopramide, Ciprofloxazine, antacids, cholestyramine, Loperamide
- Steroids, budesonide, CY-A, Tracolimus, PPI, NSAIDs, Codeine
- Metronidazole (after 1.trimester safe B), tetracycline, Sulphonamides, Azathioprine, 6MP, aspirin
- Methotrexate, Thalidomide

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"A"=controlled studies show no risk  "B"=no evidence of risk in humans
"C"=risk cannot be ruled out  "D"=positive evidence of risk
"X"=known danger, contraindicated in pregnancy

Breastfeeding:
No data are available on azathioprine and 6-mercaptopurine, and their use should be discussed on an individual basis. There are no data to support the use of cyclosporine and tacrolimus in breastfeeding.
Session VII

Cancer and IBD
Chromoendoscopy

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Diagnosis of colitis associated dysplasia or colon cancer in patients with ulcerative colitis is difficult due to the often flat and multifocal growth of such neoplastic lesions. Thus, random biopsies are recommended during colonoscopy to survey patients with long standing ulcerative colitis. Recently, chromoendoscopy in combination with newly developed high resolution or magnifying endoscopes have shown a significant increase in the yield for diagnosis of neoplasia in patients with ulcerative colitis. Pan-chromoendoscopy with methylene blue or indigo carmine allows detection of suspicious lesions. With the help of magnifying endoscopy surface analysis becomes possible and the so-called pit pattern classification differentiates between neoplastic and non-neoplastic lesions with high accuracy. Chromoendoscopy is a safe technique and adds no more than 10 minutes to the standard colonoscopy, but allows a 4- to 5-fold increase in the detection of neoplastic lesions. However, a distinction between colitis associated neoplasia and sporadic adenoma is not possible with this new technique and remains a common problem in the survey of patients with ulcerative colitis. Sporadic adenoma can be cured by polypectomy, whereas colitis associated neoplasia requires surgery (proctocolectomy). Recently, three randomized controlled studies have shown the improved detection of neoplastic tissue by means of chromoendoscopy. If strict guidelines for chromoendoscopy (SURFACE) are followed, chromoendoscopy should evolve into the new standard in surveying patients with long standing ulcerative colitis.
Can we prevent cancer by current drugs?

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The risk of colorectal cancer (CRC) is increased in ulcerative colitis (UC), although with considerable geographic variations. Both duration and extent of UC are important risk factors for CRC, as is the presence of primary sclerosing cholangitis and family history of CRC. Efforts to reduce this risk have focused on colonoscopic surveillance as the best alternative. However, there has been a growing interest in a possible role for pharmacologic chemoprevention of CRC in patients with UC. A series of epidemiological, experimental and preliminary clinical trials strongly suggest that 5-aminosalicylic acid (5-ASA) is a protective agent against the development of dysplasia and CRC. The mechanisms behind the chemopreventive properties of 5-ASA are not fully elucidated but the drug may share similar molecular targets as non-steroidal anti-inflammatory drugs. This in turn can be explained by the close molecular similarity. Ursodeoxycholic acid has been shown to reduce the risk of neoplasia in UC patients with primary sclerosing cholangitis and animal data supports a chemopreventive role. However, data is still fairly limited. Evidence suggests, but does not prove, that folic acid is chemopreventive in patients with UC.

The strongest data favouring a chemopreventive role in patients with UC is by far for 5-ASA. From available studies a dose of at least 1.2 g 5-ASA/day is associated with a significant reduction of colorectal cancer risk. Furthermore, it seems as an early treatment start, before low-grade dysplasia has developed, is essential. Despite the epidemiological and pharmacological evidence, further studies are needed to clarify the exact role in the chemoprevention of colorectal cancer in inflammatory bowel disease. In the meantime prophylactic treatment with 5-ASA can be used liberally due to a favourable safety profile.
Cancer and IBD: Will molecular understanding help?

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Introduction
Colorectal cancer (CRC) is one of the most serious complications of Crohn’s disease (CD) and ulcerative colitis (UC). 5-aminosalicylic acid (5-ASA) is among the oldest anti-inflammatory agents in use today for the treatment of IBD. After oral or rectal administration, 5-ASA acts locally into the colon and is absorbed by colonic epithelial cells. Therapeutic effects of 5-ASA associate anti-inflammatory and potential anti-neoplastic mechanisms. Mesalazine is the only treatment associated with statistically significant reduction in the risk of developing CRC. However, despite numerous experimental studies, the basic mechanism of action of 5-ASA reducing incidence of CRC remains unknown.

Recently, we identified 5-ASA as a new peroxisome proliferator-activated receptor gamma (PPARγ) ligand and demonstrated that 5-ASA anti-inflammatory effects are PPARγ-dependent. PPARγ is a nuclear receptor responsible for the regulation of cellular events ranging from glucose and lipid homeostasis to cell differentiation and apoptosis. PPARγ is expressed in various organs including particularly adipose tissue and colon, with an upregulation in various types of cancer cells. PPARγ plays an important role in the maintenance of mucosal integrity in the intestine. Their high affinity synthetic ligands such as thiazolidine diones are involved in the regulation of colon carcinogenesis acting as an early tumor-suppressor gene prior to damage to the APC/β-catenin pathway. PPARγ is expressed in most colon cancer cell lines and its activation inhibits cell growth and differentiation.

To better understand the anti-neoplastic effects of 5-ASA in the colon, we investigated if PPARγ may be the molecular target of 5-ASA involved in the prevention of CRC.

Results
5-ASA regulates epithelial cell proliferation, apoptosis and growth through PPARγ
We evaluated in two colon carcinoma cell lines, HT-29 STD and CACO-2, the involvement of PPARγ in the regulation of cell growth induced by 5-ASA. Compared to untreated cells, incubation of HT-29 cells for 24, 48 and 72h with a clinically relevant concentration of 5-ASA (30 mM) resulted in a significant inhibition of cell growth evaluated by cell count. Similar results were obtained with the two positive controls rosiglitazone (10⁻⁵ M) and etoposide (50 mM) used at optimal concentrations. Growth inhibitory activities of 5-ASA and rosiglitazone were abolished by administration of the specific PPARγ antagonist GW9662 (10⁻⁶ M), demonstrating that reduction of cell growth by 5-ASA is dependent on PPARγ. Similar results were found with CACO-2 cells. According to previous in vitro and in vivo observations, inhibition of epithelial cell growth by 5-ASA seems to be likely mediated through anti-proliferative and pro-apoptotic activities. To address this possibility, we first evaluated the involvement of PPARγ in the anti-mitogenic effect of 5-ASA by nuclear protein Ki-67 staining expressed in proliferating cells and necessary to maintain cell proliferation. In comparison to untreated HT-29 cells, 5-ASA for 48h inhibited by 63% cell proliferation (35 ± 4% stained cells vs 94 ± 1% stained cells, p < 0.001). Administration of the specific PPARγ antagonist GW9662 blocked the anti-proliferative effect of 5-ASA. Similar results were
found with CACO-2 cells. Similarly to rosiglitazone, the pro-apoptotic capacity of 5-ASA identified by labeling DNA strand breaks using a terminal transferase dUTP nick end labeling (TUNEL) assay was also abolished by the PPARγ antagonist GW9662 in HT-29 SDT. Similar results were found with CACO-2 cells.

5-ASA has an anti-tumoral effect in vivo
To gain further evidences in vivo of the anti-neoplastic effects of 5-ASA, we evaluated the therapeutic effect of 5-ASA using SCID mice engrafted with human tumoral epithelial cells of the colon (HT-29 STD). After 10 to 21 days of treatment, a 60 to 66% reduction of tumor weight and volume was observed in SCID mice receiving 5-ASA (5 or 50 mM) compared to control mice or mice receiving GW9662 alone. Results were similar when mice were treated with 5-ASA at 5 or 50 mM. This anti-tumorigenic effect of 5-ASA was completely abolished by simultaneous intraperitoneal administration of GW9662, demonstrating that in vivo, the anti-neoplastic effect of 5-ASA on human colon cancer cells is dependent on PPARγ expression.

Conclusion
We demonstrate that PPARγ is the key receptor for 5-ASA which mediates its anti-neoplastic effects in the colon. This is based on in vitro studies on cell growth, proliferation and apoptosis, and validated in vivo in a humanized model of colonic cancer in SCID mice engrafted with human tumoral epithelial cells.
Management of low-grade dysplasia in inflammatory bowel disease

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In an effort to control the increased risk of colorectal cancer (CRC) in inflammatory bowel disease (IBD), most patients choose to follow a program of periodic colonoscopic surveillance rather than consider prophylactic total proctocolectomy. While there is no definitive proof that surveillance colonoscopy reduces CRC mortality in patients with IBD, there is reasonable evidence that it works and to date, surveillance colonoscopy, despite its failings, is the best approach available. Surveillance colonoscopy is initiated after approximately 7-8 years of ulcerative colitis (UC) and the same strategy should be applied to patients with Crohn's colitis affecting a substantial extent of colonic mucosa.

The goal of surveillance is to detect precancerous dysplastic lesions or cancers that are early stage and potentially curable. Because of the high rate of simultaneous, as well as subsequent CRC when high-grade dysplasia (HGD) is detected, few would argue with the general policy of performing colectomy for HGD. This assumes, of course, that the interpretation of HGD is made by at least one, and preferably two, expert GI pathologists skilled in interpreting dysplasia using the International IBD Dysplasia Morphology Study Group criteria, and that the patient is an appropriate surgical candidate. The issue of how to manage low-grade dysplasia (LGD) is more controversial, in large part because of questions surrounding the natural history of this lesion. One important contribution to our understanding of the biology of LGD is the notion that polypoid LGD can often be managed endoscopically without resorting to surgery. The caveat here is that the polypoid dysplastic lesion must be completely resected endoscopically, biopsies around the base of the polyp must be free of dysplasia, and there should be no dysplasia elsewhere in the colon.

Excluding patients with endoscopically manageable polypoid LGD, a strong argument can be made to consider colectomy in patients who demonstrate flat LGD. This strategy is supported by several lines of evidence. First, at the initial finding of flat LGD, there is an approximate 19-20% risk of an unsuspected cancer already being present in the colon. Second, progression to CRC can occur even during surveillance. This may be due to prolonged intervals (more than 2 years) between surveillance exams, related to patient or physician factors. Also, cancers can arise in a patient with LGD without progressing through HGD, and the inability to confirm a diagnosis of LGD (or HGD) on subsequent colonoscopies does not mean that the risk of cancer decreases over time. Third, several studies indicate that the actuarial rate of progression of LGD to either HGD or cancer is 35-55% at 5 years. This rate is considerably lower in other studies for reasons that are not clear but might be due to the inclusion of patients with indefinite dysplasia, more liberal colectomy rates, true geographic/regional differences, or other factors. Finally, there are no accurate markers of progression for patients with LGD to help us stratify risk. Even patients with unifocal flat LGD appear to have the same risk of progression as those with multifocal LGD. One exception might be the small subset...
of patients with primary sclerosing cholangitis who have a particularly high risk of CRC compared to UC patients without PSC.

Unlike the growing literature that demonstrates regression of sporadic adenomas with chemopreventive agents such as aspirin and calcium, no study has yet demonstrated comparable dysplasia-reversing activity for chemopreventive agents in patients with IBD. With respect to detection, however, the application of chromoendoscopy during surveillance appears to be an important advance that helps to reveal these often invisible or subtle lesions in a colitic colon. While considerably more LGD lesions are detected, it is not yet known how, or if, this will change the natural history of LGD. We may find that despite "earlier" detection of LGD, rates of progression to HGD and CRC are similar to those in the pre-chromoendoscopy era. This is fertile ground for careful followup studies. In addition, if molecular markers of cancer risk in the stool, tissue, or blood can be identified, these may hold promise for helping us stratify those patients who are likely to progress to CRC.

**Suggested reading:**


Low grade dysplasia - what to do?

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Observational studies have shown patients with long standing, extensive ulcerative colitis to have a greater risk of developing colorectal cancer than the normal population. As a result most authorities advocate a policy of colonoscopic surveillance with multiple biopsies for patients who fall into this category. Those with cancer are advised to undergo total colectomy to treat the condition and to eliminate the risk of other areas of the colon becoming similarly affected. Many without cancer however have histological changes of intra-epithelial neoplasia that are categorized as "indefinite", "low grade" (LGD) and "high grade" dysplasia (HGD). In HGD cytological and architectural abnormalities are identical with cancer except that there is no invasion through the muscularis mucosa, these patients have a 50% likelihood of harbouring invasive cancer. Macroscopic lesions containing low grade dysplasia (DALM) also carry a high risk of cancer and colectomy is usually recommended for them though it may be difficult to distinguish a DALM arising from the colitic colon from an incidental tubular adenoma which (by definition) is dysplastic but carries a relatively small risk of malignancy and does not imply a field change of pre-malignancy as does a DALM.

The major controversy is how to manage LGD discovered in flat colitic mucosa. Some argue that 50% of these lesions progress to HGD or cancer within five years (1,2). Others contend that a diagnosis of LGD must be viewed with caution because when independent experienced gastrointestinal pathologists are provided with the same material they come to widely different opinions as to whether or not dysplastic changes are present (3-5). Secondly, because studies in patients with established LGD who have been followed over a long period have shown that only 10% or less develop cancer within ten years, a figure not significantly different from controls (5,6). Thirdly, the concept that LGD will usually progress to HGD has not been adequately documented and dysplastic changes present one year may disappear the next. For this reason they argue that total colectomy with its inherent risks and decline in quality of life cannot be justified on the basis of the evidence available. An alternative approach is to recommend more intensive surveillance for these patients.

References:


Session VIII

New Therapeutic Approaches
Leukocytapheresis

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Recently published studies have suggested that leukocytapheresis is a useful adjunct to therapy of inflammatory bowel diseases after failure of conventional treatment. Leukocytapheresis involves extracorporeal removal of leukocytes either by adsorptive systems or by centrifugation. There are two commonly used adsorptive systems, one contains cellulose acetate beads (Adacolumn, Otsuka, Japan) and the other, a polyester fibre filter (Cellsorba, Asahi-Kasei, Japan). Neutrophils and monocytes bind to cellulose acetate beads of the Adacolumn system, whereas the polyester fibre system removes neutrophils, monocytes and lymphocytes.

In several open and three controlled trials using both systems for adsorptive apheresis in ulcerative colitis (UC) remission rates with a wide variation were observed. Mostly 40 to 80% of patients came into remission after the therapy. In a pilot study we evaluated the potential of leukocytapheresis with Cellsorba filter (LCAP) in UC. 20 patients suffering from chronic active steroid-dependent UC (CAI according Rachmilewitz: 6-10) were recruited. Azathioprine was not effective in these patients or induced side effects. LCAP was performed weekly for 5 weeks (intensive therapy). After this treatment patients in remission were randomized in two groups followed by tapering the steroids. In one group LCAP was continued monthly for 5 months (maintenance therapy) whereas patients in the second group were not treated with LCAP. Remission of disease was achieved in 14 of 20 patients after intensive therapy with LCAP. After the maintenance therapy 5 of 8 patients had no disease activity without steroids. Only 1 of 5 patients treated with intensive therapy but without following maintenance therapy was still in remission without steroids after 5 months.

There are only few studies using leukocytapheresis in Crohn’s disease (CD). We performed an open trial to treat CD with granulocyte and monocyte adsorption apheresis (GMCAP, Adacolumn system). 18 steroid-dependent patients with chronic active CD (CDAI 200-400) were involved in this trial. All patients did not respond to azathioprine. GMCAP was performed twice a week for three weeks and weekly for additional three weeks. Remission of CD was achieved in 8 of 18 patients.

Different mechanisms are discussed to explain the reduction of clinical activity induced by leukocytapheresis. Removal of activated circulating leukocytes, decreased production of cytokines and down-regulated adhesion molecules after apheresis, removal of platelets with their mediators and activation of the complement system were reported.

Apheresis treatment is a safe therapeutical option. In our studies no severe side effects were observed. Only few patients had nausea or reduction of blood pressure.

Further well-designed randomized controlled trials are needed to confirm the results of the preliminary studies. In patients refractory to aminosalicylates and immunosuppressive drugs leukocytapheresis might be a suitable therapy.
Helminths

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Loss of immune tolerance to the normal enteric bacteria is a leading hypothesis regarding the etiology of IBD. Genetic traits influence the frequency and clinical course of IBD, but are not the central cause of these diseases. Environmental factors greatly affect the chance for disease as suggested by the geographic variations in IBD frequency and may prove more influential than genetic predisposition. Good hygiene is a risk factor for IBD. Helminths are worm-like organisms that can live within the host. People acquire helminths through exposure to contaminated food, water and soil. Epidemiological data suggest that helminth infection protects from immunological diseases. Favorable clinical trials using helminths to treat human IBD support this concept. Live enteric helminthic parasites, helminths with a systemic distribution and even non-viable schistosome ova can shield animals from IBD. The protection coincides with induction in the lamina propria of Th2 and regulatory cytokines like IL10, TGFβ and PGε2, and local development of regulatory-type T cells. These regulatory factors (e.g. IL10, TGFβ) and regulatory cells suppress pro-inflammatory cytokine production (e.g. IFNγ and IL12 P40) in the LPMC and inhibit expansion of T cells that drive inflammation. Future studies will determine if helminths or derivatives from these animals will prove highly effective for prevention or treatment of IBD and other immunologic diseases.
Probiotics and inflammatory bowel disease

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Non-pathogenic micro-organisms may contain or produce molecules of potential therapeutic interest. This led to the concept of using ingested living micro-organisms to produce and transport these molecules to targets in the proximal or distal intestine. Several characteristics of this pharmacological approach are very original: potential for in vivo production of active molecules, for targeting immune cells, for presenting immunogenic molecules in a microbial context, for duodenal delivery using bile sensitivity.

This communication will summarise facts and ideas about the use of probiotics in IBD. It will consider the following points:

• Results of randomised controlled trials (in specific situations of pouchitis, ulcerative colitis, and Crohn's disease), including our new double-blind trial which recently showed that Lactobacillus johnsonii LA1 does not prevent postoperative recurrence of Crohn's disease.
• Elements of pharmacokinetics
• Mechanisms of action
• Safety of this approach (exceptional cases of infections have been observed in non-IBD patients, especially patients with central venous catheters hospitalised for severe conditions)
• Potential for using new agents or genetically modified micro-organisms (ongoing trials in humans with Crohn's disease).
• Probiotics, prebiotics, synbiotics

This communication aims to convince the audience that
1 - this approach has proven therapeutic effects in specific situations (especially pouchitis and prevention of relapse of ulcerative colitis) and potential.
2 - extrapolation of effects between products is not possible and one should avoid excessive enthusiasm or systematic scepticism.
A profound transformation is currently under way that will have a major impact for the future management of Crohn's disease. During recent years, we have witnessed a sharp increase in both molecular information, produced by genomics, proteomics and other high-throughput methods, and clinical information, including data from medical records and clinical trial records. On the other hand, the developments in information technology have exploded and is currently at a point where the datasets from both the molecular and clinical types of information can be effectively integrated and analyzed. The number of biobanks is steadily increasing, and it is well recognized that through these strategies, and this acceleration of research, the outcome of complex diseases such as Crohn's disease will improve dramatically.

During this presentation, an overview is given of the most recent therapeutic developments in Crohn's disease that is likely to set the research agenda of these coming years. New molecular therapeutic targets are discussed, as well as different potential therapeutic approaches. Lessons from the past are reviewed in order to optimize future therapy.

In addition, the concept of "personalized medicine" will be examined and its translation to Crohn's disease will be discussed. The development of disease-specific biobanks will be analyzed and as an example, the operational plan for the Dutch IBD Biobank will be presented.

The future of a complex and often destructive disease such as Crohn's disease will be largely determined by unprecedented levels of collaboration within the IBD community as well as the willingness of partnerships with the information technology sector and local and national governments in order to achieve these goals.
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POSTER ABSTRACTS

Poster Numbers 1 - 81
Colonoscopic evaluation of polyps: Our experience

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Polyps are one of the most common conditions affecting the colon and rectum. Although most polyps are benign, certain polyps may eventually turn cancerous. Therefore, total colonoscopy is the most accurate method of detecting polyps and it allows immediate biopsy or polypectomy.

This study included 600 patients and their average age was 53, between 19 and 96. 360 patients were males, 240 were females. Single polyp in 545, 2 polyps in 40 and 3 or more polyps in 15 patients were found. The sizes of polyps were less than 1 cm in 90%, 1 to 2 cm in 7% and more than 2 cm in 3% of the patients. Localizations of the polyps were 25% in the rectum, 20% in the sigmoid colon, 13% in the descending colon, 10% in the transverse colon, 7% in the transverse colon, 11% in the ascending colon and 14% in the cecum.

Polyps were located in the distal colon about 60% of our cases. Most of the polyps were less 1 cm diameter and single high grade dysplasia is seen rarely in polyps which are less than 2 cm diameter. Polypectomy procedure is more effective for the colonic cancer prophylaxis in the polyps smaller than 2 cm. Average age was 56 in polyp seen patients in our study. Colonoscopy should be done as a screening test in the fifth decade. Therefore polyps may be found with smaller size.

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The prevalence of microscopic colitis in patients with rheumatoid arthritis

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Background and aim: Microscopic colitis with its collagenous and lymphocytic forms, is relatively common and its association with some autoimmune diseases such as rheumatoid arthritis (RA), Hashimoto’s thyroiditis, celiac disease, may imply that autoimmunity play a role in its pathogenesis. Review of the literature revealed merely case reports and small series exhibiting the association of microscopic colitis and RA. In this study, we aimed to investigate the prevalence of microscopic colitis in patients with RA comparing with a control group.

Materials and methods: A total of 19 patients with RA were enrolled to the study between August 2002 and June 2004 (male: 8, female: 11, mean age: 53.7 ± 11.4 yr, range: 31-71). Fifty-six patients without RA who were performed colonoscopy for usual indications served as control group. Ileo-colonoscopic examination was carried out in both the study and control groups. Biopsies obtained separately from terminal ileum and from all colonic segments. Biopsy specimens were evaluated for the presence of lymphocytic and collagenous colitis by assessment of the number of intraepithelial lymphocytes (> 20 per 100 intercryptal epithelial cells for lymphocytic form) and the thickness of the subepithelial collagenous band (> 10 μm for collagenous form). Besides, possible amyloid deposits were investigated by crystal-violet staining.

Results: Microscopic colitis was detected in 3 of 19 patients with RA, yielding a prevalence of 15.7%. Of these three patients, 1 was collagenous colitis (53 yr, female) and other 2 were lymphocytic colitis (53 yr, female, 64 yr, male). In control group, lymphocytic colitis was found in one patient (1.78%, 1/56). When this figure was compared with those of control group, there was significant difference between two groups (p = 0.047). The patient with collagenous colitis in the study group had a chronic watery diarrhea for about 10 years but other two patients with lymphocytic colitis had no gastrointestinal symptoms. Amyloid deposition in colonic mucosa was observed in a patient from control group, but not in any patients with RA.

Conclusion: It was demonstrated that the prevalence of microscopic colitis in patients with RA was higher than those of patients without RA. The result obtained from this preliminary study seems to support autoimmune pathogenesis of microscopic colitis.
Nonspecific erosions: Is this a sign of inflammatory bowel disease?

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Aim: To evaluate the reasons of nonspecific erosions detected by colonoscopic examination.

Materials and Methods: Patients admitted International Hospital Endoscopy Unit for colonoscopic examination between 1998-2004 years were evaluated retrospectively. Cases had nonspecific erosions were enrolled in this study.

Results: 102 patients (57 male) were enrolled. Mean age and mean follow up period of patients were 44.1 ± 12.7 years and 31.3 ± 13.7 months, respectively. Symptoms during the admission were abdominal pain (56.5%), diarrhea (30%) and rectal bleeding (13%). Colonoscopic findings accompanied with nonspecific erosions were as follows: hemorrhoid 56.2%, rectosigmoid adenomatous polyp 25%, diverticula 15%. Nonspecific erosions were scattered on ileal (25.5%), ileocolonic (20.6%), rectosigmoid (28.4%), left colon (22.5%) and transverse/cecum (3%). 34.7% of patients were used NSAID and/or aspirin. Although, no specific agent detected, infectious disease suspected with high CRP and diarrhea in 8.8% of patients and nonspecific antibiotics were given. However, 5-ASA was given 8.8% of patients (5-ASA po to 5 patients with ileal and ileocolonic erosions; 5-ASA supp to 4 patients with rectosigmoid erosions), even no diagnostic findings for inflammatory bowel disease. Symptoms and signs were regressed during the follow-up period. The other patients did not take specific therapy for nonspecific erosions. Although majority of patients (34.7%) were used regular NSAID drugs/aspirin, there was no reason nearly half of the patients.

Conclusions: NSAID drugs and aspirin are responsible for nonspecific erosions in most of the patients. Some of them may be the first sign of IBD. But, we need further prospective studies to evaluate this subject.
The effects of UDCA use in alkaline reflux gastritis

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Background/aims: The reflux of duodenal content to the stomach results in gastric mucosal destruction and gastritis. Gastric operations, cholecystectomy, cholelithiasis and gallbladder disfunction have role in development of alkaline reflux gastritis. In this study we aimed to evaluate the effects of UDCA on the endoscopic view of gastric mucosa in the patients with alkaline reflux gastritis and the symptomatic cure of the patients.

Material and Method: Patients applied to our clinic with dyspepsia whom had been diagnosed alkaline reflux gastritis by endoscopic procedure were involved to the study. The number of patients included in this study was 64 (38 female, 26 male). Double biopsy sample was taken from gastric antrum and H. pylori infection and gastritis were diagnosed by histopathological examination. All H. pylori positive patients were taken omeprazole (20 mg bid/day), amoxicillin (1000 mg bid/day), clarithromycin (500 mg bid/day) for 14 days. H. pylori negative patients were taken antiacids and proton pump inhibitors. After 6 week treatment period patients without symptomatic and endoscopic improvement either H. pylori positive or negative were given to acid suppression agents and UDCA (250 mg bid/day) for 1 month. After 1 month treatment, control endoscopy was performed and symptomatic improvement evaluated.

Results and Conclusion: H. pylori frequency in alkaline reflux gastritis was found 64.06% (41/64). While H. pylori eradicated in the rate of 73.17% (30/41) by omeprazole-amoxicillin-clarithromycin therapy in H. pylori positive patients, symptomatic improvement was 41.46% (17/41). In the most of cases gastric mucosal bile secretion and pang gastritis viewed endoscopically. 24 patients who have no symptomatic improvement were taken UDCA (250 mg bid/day) for 1 month. After 1 month in the endoscopic control pang gastritis were regressed to antral gastritis in the most of cases and 22 patients have shown (91.6) symptomatic improvement. In the conclusion for symptomatic and endoscopic improvement in alkaline reflux gastritis the use of UDCA will show successful results.
Macroagglage microaggregations in patients with inflammatory bowel disease: Does it really have any role in the diagnosis of Crohn’s colitis?

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Introduction: Recent studies have advocated that the presence of macrophage microaggregations (MM) may be a criterion in the diagnosis of Crohn's colitis (CC). Thus the aim of this study is to investigate the role of MM to differentiate ulcerative colitis (UC) and Crohn's colitis (CC).

Materials and methods: We analyzed the role of MM in 29 patients with UC (group 1), 26 patients with CC (group 2) and 22 patients without diagnosis of inflammatory bowel disease (group 3). After obtaining an inform consent, esophagogastroduodenoscopy was performed to all patients and biopsies were taken from non-lesion regions of stomach and duodenum. Biopsy materials underwent immunohistochemical staining for the microscopic investigation of the presence of MM (CD69). Also, determination of pANCA and ASCA (Ig G, A) was done with ELISA in serum samples.

Results: The mean age of disease of patients in groups 1, 2 and 3 were 41.3 (20-62), 39.2 (20-59) and 36.5 (26-51) years respectively. The CD69 positivity with immunohistochemical staining was 46.2% in group 1, 41.3% in group 2 and 9.1% in group 3 (p < 0.05, Chi square test). No statistically significant difference was obtained between the groups in terms of ASCA and p-ANCA.

Conclusions: We were not able to confirm the results obtained from former studies that MM in gastroduodenal mucosa may be an indicator of CC. Further studies should be done to clear the role of MM.
Ulcerative colitis and Crohn’s disease: Prevalence, diagnosis and treatment

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During 8 years (1997-2003) the morbidity of inflammatory bowel diseases such as Crohn’s disease (CD) and ulcerative colitis (UC) don’t increase in our region. Every year gastroenterological department of Regional Clinical Hospital admits from all patients 1.85-2.73% with UC and 0.3-0.53% with CD. We observed 127 patients with UC (male 54.5%, female 45.5%) and 18 patients with CD (male 55.6%, female 44.4%) in age of 35 ± 3.2 and 45.8 ± 1.2 accordingly.

Diagnostic criteria of these diseases were clinical symptoms - intestinal and extra-intestinal, roentgenografic, endoscopic and histological signs of every illness. There were anemia, intoxication, acceleration ESR as extraintestinal symptoms, but arthral manifestation was rarely.

UC was characterized by chronic organical diarrhea, including blood, pus and mucus in stool; fever, loss of flesh; arthritis and hepatitis were diagnosed rarely. The typical clinical form of UC was proctosigmoiditis and rarely total colitis was registered. In 46% cases were formed polyps of rectosigmoid segment.

The next symptoms were observed in CD: abdominal pain, diarrhea, loss of flesh, fever; arthritis and hepatitis, pararectal pus fistulae were registered rarely. Ileocecal segment was affected mainly. 18% patients had formed bimucosa allied fistulae. 27.8% patients had an abdominal operation.

Severe and moderate forms of disorders prevailed. The mortality in CD was 22.2%.

Histological finding of UC mainly detected the infiltration of tunica mucosa with polymorphonuclear leukocytes, eosinophils; crypts abscesses and polyps were rarely. CD was characterized by submucous epithelioid cell granulomae without giant Pirogov-Largengans’s cells and caseous necrosis.

Pathogenetic therapy consisted of 5-ASA, including Salofalk®, 25% patients took glucocorticoids.
Use of power Doppler sonography to assess activity of inflammatory bowel disease

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Introduction: Sonographic investigation of the intestinal wall has been introduced in the diagnosis of inflammatory bowel disease (IBD). Mainly bowel wall thickness (BWT) have been analyzed. The clinical usefulness of measurement of BWT is questionable, since it does not allow differentiation between inflammation and fibrosis. Angiographic studies have demonstrated an increased vascularization of bowel wall in active IBD. Power Doppler sonography (PDS) allows imaging of tissue vascularization in a new dimension. Value of PDS in determining activity of IBD is not sufficiently understood. We aimed to investigate the vascularization in the diseased bowel wall by PDS in patients with IBD.

Methods: Twenty patients with IBD (14 patients with ulcerative colitis, six patients with Crohn’s disease) were enrolled into the study. Eight patients with ulcerative colitis and four patients with Crohn’s disease had clinically and endoscopically active disease. Colonoscopies were done before PDS examination in all cases. After scrutinizing all abdomen by a gray-scale ultrasonography, thickened bowel were chosen and vascularization changes shown by PDS.

Results: Two out of eight patients with active ulcerative colitis detected no BWT and increased vascularity in PDS. In these patients had distal ulcerative colitis. In other active disease, an apparently increased vascularity was depicted both in patients with ulcerative colitis and Crohn’s disease. However, PDS findings were completely normal in patients with remission.

Discussion/Conclusion: Increased wall thickness and enhanced vascularity are highly characteristic findings for active IBD. PDS can detect active IBD successfully and it has a considerable advantage of being a non-invasive technique.

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Infliximab improves bone mineral density in patients with Crohn's disease

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Background: Crohn's disease patients frequently develop metabolic bone disease. TNF-α increases maturation of osteoclasts, reduces osteoblast maturation and induces Vit. D resistance. Infliximab may improve BMD by reducing these effects.

Aim: To examine the effect of treatment with infliximab on BMD in patients with Crohn's disease.

Methods: BMD was measured by DEXA in 18 patients with CD treated with infliximab, and 16 group-matched CD patients not receiving the drug (controls). T-scores, measured at baseline and after treatment, were analyzed using the Mann-Whitney and Chi-Square tests, Spearman and partial correlation coefficients.

Results: There were no significant differences in age, sex and duration of disease between the treated and control groups. All infliximab treated patients and 43.8% of controls had received corticosteroids. The treated group received 2-13 infusions of infliximab. Mean baseline femur neck T-scores were -1.24 ± 1.25 in treated and -0.91 ± 1.36 in control patients (NS). Mean ΔT- in the femur neck improved in treated patients (+0.04 ± 0.5) and deteriorated in controls (-0.18 ± 0.36) (p = 0.034). T-scores improved in 72.2% of treated and 18.8% of controls (p = 0.005). Baseline femur neck T-scores were inversely correlated with ΔT-scores controlling for number of infusions and interval between BMD measurements (partial r = -0.58, p = 0.018). There was no relationship between ΔBMD and number of infusions. BMD did not improve in the lumbar spine.

Conclusions: Infliximab treated patients demonstrated improvement in femoral neck BMD while group-matched CD controls deteriorated. Patients with lower baseline measurements benefited most from infliximab treatment and this may be a consideration in treatment decisions.
Prevalence and incidence of ulcerative colitis (UC) among patients with enteritis infectiosa

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Introduction: The period from the appearance of the first symptoms to diagnosis UC is often very long. The early symptoms are not specific so other reasons for rectal involvement are usually considered in the beginning. The main indicating sign from a clinical point of view "diarrhea" is often intense and this is the usual cause for the patients to be treated for enteritis infectiosa in our clinic.

Aim: To follow clinically and laboratory patients with UC for the last 3 years in the clinic of infectious diseases in Plovdiv.

Method: For one year nearly 1500 patients with diagnosis enteritis infectiosa are treated in the clinic. In the last three years from all cases with the above diagnosis 12 were with UC. The diagnosis was confirmed by anamnesis, clinical course, biochemistry, endoscopy and histology.

Results: The average age of patients was 30-35 year. Both sexes were almost equally distributed 7 male and 5 female. Seven of 12 patients were with primary attack of the disease. The initial symptoms were intestinal bleeding, diarrhea, abdominal pain, fatigue and dehydration 3-7 days before the hospitalization. The endoscopic picture was characterized by patchy redness, edema and mucosal hemorrhages.

Conclusions: The number of cases with UC increases for the last 3 years: 12 cases compared with 11 cases for the preceding 8 years (1994-2001). The early diagnosis and treatment with Salofalk® contribute for better prognosis.
Eosinophils in inflammatory bowel disease correlated with disease activity

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Background: Increased numbers of normal and functionally activated eosinophils have been shown in colonic mucosa of inflammatory bowel disease (IBD) patients. A pathogenic role for the eosinophils has not been fully clarified in IBD.

Aim: To investigate the degree of eosinophilic infiltration on colonic mucosa of patients with ulcerative colitis (UC), Crohn’s disease (CD), amebiasis superimposing on UC and irritable bowel syndrome (IBS), as controls and to correlate the degree of eosinophilic infiltration with disease activity index.

Patients and method: 79 IBD (44 UC, 23 CD and 12 amebiasis+UC) and 44 IBS patients were included. Disease activity assessment was made as mild, moderate or severe with "Truelove & Witt's" in criteria UC and "Crohn's Disease Activity Index" in CD. Biopsy specimens were taken during colonoscopy from involved and uninvolved colonic mucosa of IBD patients. IBS group was also biopsied as control. Eosinophilic infiltration per x40-field at light microscope was scored as 0: occasional (average: 1-3), 1: mildly (average: 4-8), 2: moderately (average: 9-15), 3: markedly increased (average: > 15).

Results: Most IBD patients exhibited severe eosinophilic infiltration on the colonic mucosa (UC: 79.5%, CD: 78.3%, amebiasis+UC: 58.5%). While the eosinophil infiltration was 25% in IBS group, only 4.5% were severe. In both UC and CD patients, the degree of eosinophilic infiltration correlated positively with the disease activity indexes (r = +0.639 (CD), +0.571 (UC); p < 0.01) but not with IBD type or localization.

Conclusion: Infiltrating eosinophils may destroy the mucosal tissues of the colon in the active phase of IBD by working together with neutrophils and monocytes. High eosinophilic infiltration observed in our patients with IBD correlated well with disease activity. Further studies are warranted to show eosinophilic activation in disease outcome.
Analyses of cases with inflammatory bowel diseases in a private health center

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Aim: To evaluate of inflammatory bowel diseases (IBD) and to detect the frequency of indeterminate colitis.

Materials and Methods: From 1996 to 2004 October, 91 patients (44 male, 48.4%) diagnosed with IBD by colonoscopy and histology was evaluated retrospectively. Socioeconomic levels were normal and high in all patients.

Results: Mean age and mean follow-up period were 42.8 ± 12.4 years and 41.2 ± 18.7 months, respectively. 54 (59.3%) of these patients were diagnosed with ulcerative colitis (UC), 17 (18.7%) of them Crohn’s disease (CD) and 20 (22%) of them indeterminate colitis (IC). First admission time to the hospital as seasons were as follows: 34.2% spring, 31.4% summer, 22.8% autumn, 11.4% winter. While In UC (42.6% female), extent of involvement was 37.5% pancolitis, 33.8% left-sided and 28.7% distal colitis (25% with mild activity, 25% with moderate activity and 50% with severe activity); 29.4% ileal, 70.6% ileocolonic in CD and 55% ileocolonic, 30% pancolitis, 10% right-sided, 5% left-sided involvement were seen in IC. A denomatus polyp was detected in 5.7% of patients with UC. Colocolonic fistula (5.9%) and anal fissure (5.9%) were seen in few patients with CD. Also, few patients with IC had an appendectomy (5%) and anal fissure operation (5%).

Conclusions: Diagnostic distinction between UC and CD is not easy in some cases. One fourth of IBD patients are IC and ileocolonic involvement is the most common type in IC. Admission rate of IBD patients to the hospital is low in winter. Also, fistulas and operation rate is low in this group (educated and high socioeconomic levels). This may be related with early diagnosis and regular follow-up health care.
Appendix – The cornerstone of IBD

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Throughout the 1994-2001 period some 416 patients have been analyzed, who underwent appendectomy for acute appendicitis.

Of those, in 409 patients trivial inflammatory process was established. Histomorphological revision was done in one of the patients 8 months after the appendectomy, due to persistent pain in the ileocecal area. Epithelioid cells granulomae were found and further tests proved existence of Crohn’s disease.

After an uneventful period of more than 10 years, three of the patients with appendectomy developed ulcerative colitis (UC) - with mild activity in 2 patients, and moderate activity in 1 patient.

In 7 of the 416 patients with appendectomy the surgery revealed hyperemic thickening of the terminal ileum. The histomorphological investigation of the appendix established catarrhal inflammation in 6 patients and epithelioid cells granulomae in 1 patient. Later on, in the course of 4 months to 2 years Crohn’s disease was established in all 7 patients.

In quite another group of 2 patients with colectomy due to severe ulcerative pancolitis and 1 patient with pancolitis and carcinoma of the colon transversum we observed particularly interesting changes in the appendix. In 1 patient the inflammatory process in the appendix was as severe as in the colon. In 2 patients (1 with severe pancolitis and 1 with UC and carcinoma of the colon transversum) there were no macroscopic and histomorphological changes in the appendix.

Conclusions:

1. The appendix may be indifferent or involved in the inflammatory process in the colon in cases of ulcerative pancolitis.

2. Ulcerative colitis develops more often in patients without appendectomy, and where appendectomy precedes ulcerative colitis the inflammation of the colon occurs probably with less severe activity.

3. The occurrence of appendectomy may provide guidance and may help for the diagnosis of Crohn’s disease.
Thrombosis in ulcerative colitis - A life-threatening condition

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Throughout the 1971-2003 period at the Clinic of Gastroenterology of MHAT "Tzaritza Joanna" and 5-th MHAT, some 404 patients with ulcerative colitis (UC) have been monitored. Vascular complications were found in 18 patients (4.04%), where 10 were in active phase and 8 - in remission. Eight patients had UC of chronic persistent type and 10 - UC of chronic recurrent type.

Vascular complications were manifested as:

Phlebothrombosis of the veins of the lower limbs - 14 patients. Of them 4 patients developed pulmonary thromboembolism, with exitus letalis.

Phlebothrombosis of the parauterine plexus with pulmonary thrombo-embolism within 24 hours after colectomy, with exitus letalis - 1 female patient.

Mesenterial thrombosis with infarction of jejunum, laparotomy and resection of the affected segment - 1 patient.

Cerebral insult with exitus letalis - 2 patients.

The occurrence of thrombosis in patients with UC is a leading reason for vascular damage, with fatal ending in 7 of the affected patients (38.8%).
The comparison expression of Bak and Bax proteins in ulcerative colitis, Crohn's disease and colon cancer

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Aim and methods: The objective was to compared expression of pro-apoptotic proteins Bak and Bax in inflammatory bowel diseases with colon cancer. Study was performed on two groups of patients: group A - 32 patients with ulcerative colitis (UC) and Crohn's disease (CD) and group B composed of 30 patients with colon cancer. Both group were analized for Bak and Bax expression using polyclonal antibodies Bak [(N-20): sc-1035, Santa Cruz Biotechnology; dilution 1:150] and Bax [(P-19): sc-526, Santa Cruz Biotechnology; dilution 1:100].

Results: The immunostaining pattern was cytoplasmic in all investigated cases. In inflamed colonic epithelium of ulcerative colitis (UC) and Crohn's disease (CD) no expression of Bax was observed in 31/32 cases compare to expression of Bak protein, which was found in 29/32 cases. However, expression of Bak and Bax proteins were observed in dysplastic and cancer cells.

Conclusion: This study may suggest, that both proteins Bak, Bax can take part in cancer arise on the grounds of ulcerative colitis and Crohn's disease.

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Pyoderma gangrenosum and Crohn's disease

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Pyoderma gangrenosum is a dermatosis which can be associated with inflammatory bowel disease.

It is mainly described with ulcerative colitis. About 2% of patients with Crohn's disease may present this dermatosis.

We report the observation of five cases of pyoderma gangrenosum associated with Crohn's disease. They were 3 women and 2 men with a mean age of 28 years. Four patients had severe intestinal disease and one patient had an intestinal remission. Cutaneous lesions was localized at the extremities for all patients. The evolution was favourable under oral steroids in all cases. However, one patient had a precocious recurrence of the pyoderma during steroids degression. Azathioprine was so associated with steroids.

These observations illustrate a rare cutaneous manifestation with Crohn's disease.
Efficacy of anti-tumor necrosis factor-α therapy on frequency of sister chromatid exchanges in peripheral lymphocytes of patients with Crohn's disease

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Introduction: The analysis of sister chromatid exchanges (SCE), defined as symmetrical exchanges between sister chromatids in peripheral blood lymphocytes, has been used as indicator of chromosomal instability.

Aim: To assess the efficacy of anti-tumor necrosis factor α therapy on frequency of sister chromatid exchanges in peripheral lymphocytes of patients with Crohn's disease.

Materials and methods: A cytogenetic study was performed using Crohn's disease patients to determine whether the presence of chromosome instability is related to Crohn's disease and infliximab therapy effects results. SCE frequencies in peripheral blood lymphocyte cultures from 21 Crohn's disease patients and an equal number of healthy controls matched for sex, age and smoking habits were analysed. Of the patients, 13 were female and mean age was 32.71 ± 8.2. For each subject, 50 metaphases were scored to determine the mean SCE frequency.

Results: The mean of SCE frequency in Crohn's disease patients was 6.1 (1.7-11.2) per cell, which was significantly higher than the value of 4.8 (3.9-6.8) per cell in the matched controls (p = 0.017). Crohn's disease activity index (CDAI) and SCE frequency were significantly lower in patients treated with infliximab (p = 0.036 and p = 0.033 respectively).

Conclusion: In patients with Crohn's disease, SCE frequency is higher than healthy people. Infliximab therapy lowers CDAI and SCE frequency.
The coexistence of gene NOD2/CARD15 and ASCA in patients with Crohn’s disease (CD) and its influence on the course of disease

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Introduction: The epidemiology of IBD is still not clear. The influence of genetic and environmental factors are considered. The most important genetic background in CD are mutations and polymorphisms of gene NOD2/CARD15 in chromosome 16. There is also the higher incidence of the antibodies against Saccharomyces cerevisiae (ASCA) in patients with CD.

The aim of the study was to establish how high is the coincidence of the most often observed gene NOD2/CARD15 mutations and the presence of ASCA in patients with CD in Polish population. And in addition if this coexistence influences on the course of disease (extraintestinal symptoms, necessity of surgery presence of fistulas).

Material methods and results: We examined 136 patients with CD. The most often observed mutation of NOD2/CARD15 gene were: P268S (49.5%) and 3020insC (17.2%). In control group 32.8% and 0.7% respectively. ASCA positive CD patients were in 30.1% (IgG) and 16.2% (IgA).

Coexistence of gene NOD2/CARD15 both observed mutations and ASCA was in 22%, but for homozygote of P268S it was 35.0%.

Conclusions: The patients with the presence of NOD2/CARD15 gene mutations and ASCA positive had more often the extra intestinal symptoms (iritis, erythema nodosum, arthritis) and they had the higher necessity of partial resection of terminal ileum.
Azathioprine in Crohn’s disease - How long to treat?

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**Background:** It is now well known that azathioprine is the best option for maintenance treatment in Crohn’s disease (CD) to keep remission without side effects. We know when to start, we know the correct dose, we know how to maintain, but we are not sure when to stop or even if we must stop.

So the aim of this study is to show our 10 years experience in treating CD with azathioprine and try to answer should we stop and when.

**Material and method:** For 10 years from 1994 up till now we evaluate 24 patients with CD /14 women and 10 men from 18 to 57 years old all of them with active disease CDAI > 150 at the beginning of the treatment, localization - colon or ileo-colon, in all the cases treatment was started with azathioprine, steroids and antibiotics. For the first two years the azathioprine was 1.5 mg/kg and treatment was discontinued six months after patient was in remission. We saw more than 80% of the patients in 3 to 5 months after discontinuing treatment again with active CD. So from 1996 till now we treat all the patients with 2.0 mg/kg azathioprine in continuous regiment.

**Results:** In the past 8 years three of the patients discontinue azathioprine treatment (two men for HBV and HCV infection, one woman because of basocellular carcinoma of the nose - not related to azathioprine treatment according dermatologist), and one of them - the man with HCV infection become active and underwent surgery for stenosis of the colon. All the other 21 patients continuing treatment are for years in remission - CDAI < 100 with no side effects or any toxicity.

**Conclusion:** Continues (for years) treatment with azathioprine 2.0 mg/kg is very effective and safe treatment for Bulgarian population of CD patients and our opinion is to continue same treatment in coming years.
Exogenous and endogenous leptin and ghrelin in healing of experimental ulcerative colitis

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Introduction: Leptin and ghrelin involved in the control of food intake, have recently been detected in the gastric mucosa and implicated in gastroprotection against various noxious agents but their anti-inflammatory effects in the lower gut have been little studied.

Aims and Methods: In this study we compared the effects of vehicle, leptin and ghrelin applied subcutaneously (s.c.) in a dose of 0.5-50 µg/kg/per day on colonic damage induced in male Wistar rats by the administration of 2,4,6-trinitrobenzenesulfonic acid (TNBS, 10 mg/kg intrarectally) with or without A) suppression of NO-synthase with L-NNA (20 mg/kg i.p.), and B) inactivation of sensory nerves by capsaicin (125 mg/kg s.c.) applied with or without the treatment with leptin or ghrelin. At 2 weeks upon the TNBS treatment, the distal 8 cm of the colon was removed for the area of colonic lesions measured by planimetry, the tissue weight index and the tissue myeloperoxidase (MPO) activity. The colonic blood flow (CBF) was assessed by H2-gas clearance technique and blood was withdrawn for the measurement of plasma leptin and ghrelin levels by radioimmunoassay (RIA).

Results: Administration of TNBS resulted in macroscopic lesions accompanied by increase in tissue weight and 4-5-fold increase in the MPO activity. Leptin or ghrelin (0.5-50 µg/kg s.c.) dose-dependently attenuated the area of colonic lesions; the dose reducing these lesions by 50% (ED50) was 20 and 40 µg/kg, respectively, and produced the significant fall in tissue weight index and decreased MPO activity by about 2 folds. The ulcer healing effect in the colon evoked by both hormones was accompanied by the significant rise in the CBF (by 25%) and plasma leptin and ghrelin increments. Inhibition of NO-synthase activity with L-NNA and capsaicin-deactivation of sensory nerves attenuated significantly the leptin and ghrelin-induced increase in the healing of these lesions and accompanying hyperemia in the colon.

Conclusion: Both, leptin and ghrelin applied exogenously and those released endogenously, exert anti-inflammatory properties and accelerate the healing of ulcerative colitis and this action depends upon hyperemia probably mediated by NO and sensory nerves releasing vasoactive neuropeptides.
Peripheral rheumatologic manifestations during Crohn’s disease

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Objectives: The study was aimed to evaluate the frequency of peripheral rheumatologic manifestations in a group of Crohn’s disease patients, and to determine the risk factors.

Subjects and methods: We included 68 Crohn’s disease patients. All patients had a complete rheumatological examination. Radiographs of the sacroiliac joints and lumbar spine were performed.

Results: 40 men and 28 women with a mean age of 31 years were included. Rheumatologic manifestations were observed in 41 patients. Twenty two patients suffered of peripheral articular manifestations: arthralgias in 18 patients and arthritis in 9 cases. Peripheral articular manifestation were significantly associated to ileal location of intestinal disease. Their frequency was of 41.3% in ileal location group versus 13.6% in colic location group (p = 0.02).
Axial rheumatologic manifestations during Crohn’s disease

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Objectives: The study was aimed to evaluate the frequency of axial rheumatologic manifestations in a group of Crohn’s disease patients, and to determine the risk factors.

Subjects and methods: We included 68 Crohn’s disease patients. All patients had a complete rheumatological examination. Radiographs of the sacroiliac joints and lumbar spine were performed.

Results: 40 men and 28 women with a mean age of 31 years were included. Rheumatologic manifestations were observed in 41 patients. Axial manifestations were observed in 32 patients: ankylosing spondylitis was diagnosed in 11 cases, undifferentiated spondylarthropathy in 7 patients, sacroiliitis in 10 cases, inflammatory black pain in 3 patients and enthesopathy in 1 case. The male sex and long duration of intestinal disease were two independents factors associated to axial manifestations.
Polymorphisms in the promoter/leader sequence of vascular endothelial growth factors (VEGF) are associated with susceptibility to ulcerative colitis

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Background and Aim: VEGF has besides potent angiogenic also important pro-inflammatory functions. Increased serum levels (sVEGF) have been demonstrated in patients with IBD and variations in the VEGF gene influence VEGF expression. We hypothesised that VEGF is a good candidate gene for IBD both from a functional as well as a positional (6p21, IBD3 locus) perspective. We studied functional polymorphisms and sVEGF in a cohort of IBD patients.

Methods: 375 IBD trios (303CD/66UC/6IC) and 96 ethnically matched controls were genotyped for -C2578A, -G1154A and -G634C in the VEGF promoter/leader using DHPLC.

Results: Mean sVEGF was higher in UC patients compared to controls (536.2 vs 313.3 pg/ml, p < 0.001). The CGC haplotype (Genehunter 2.1) was significantly undertransmitted in UC (T:UT 9:25, p = 0.006). Interestingly, patients with this haplotype had lower sVEGF (399.8 ± 249.2 pg/ml) compared to the other haplotypes (615.1 ± 505.4 pg/ml, p = 0.058). In contrast, the AGG haplotype was more frequent in UC compared to controls (23.4% vs 11.2%, p = 0.004, PHASE 2.1), and a trend for overtransmission was also seen (T:UT 18:10, p = 0.13). Moreover, this haplotype was associated with higher sVEGF (665.5 ± 538.8 pg/ml) compared to the other haplotypes (419.9 ± 289.6pg/ml, p = 0.034). There was no association between haplotypes and extension of disease or need for colectomy, or with CD in general.

Conclusions: The results of this study show that VEGF might be implicated in susceptibility to UC: the CGC promoter haplotype was undertransmitted to patients with UC and associated with lower sVEGF. On the contrast, the AGG haplotype was more frequent in UC and associated with higher sVEGF. We are currently expanding our UC cohort.
Collagenous colitis: A rare presentation of an acute abdomen

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Collagenous colitis is a chronic diarrhoeal disease, mostly affecting women in their middle age. It presents as chronic watery diarrhoea that can be intermittent or continuous in nature. The prognosis is generally good, with the majority of patients getting symptomatic relief spontaneously or with a short course of a corticosteroid.

As the colon often appears normal on colonoscopy, diagnosis is made on histological demonstration of an abnormally thickened subepithelial collagen band with microscopic inflammation of the lamina propria. Its distribution may at times be patchy but usually involves the entire colon, although it tends to be most prominent in the proximal colon. Although many pathophysiological processes have been suggested, none have been proven.

We present the case of a 71-year-old woman to the Emergency Department with rapid onset abdominal distension, tenderness and guarding. The only medical history of significance was a diagnosis of collagenous colitis 3 years previously for which she was being treated with Buscopan. Her condition deteriorated while in the ED and an emergency laparotomy was performed.

Histology showed extensive colonic and ileal ulceration with focally prominent subepithelial collagen band formation. No granulomas, vasculitis or Neoplastic changes were identified.

There have been 13 reports to date in the literature of collagenous colitis presenting as an acute abdomen (11 had a colonic perforation after colonoscopy or barium enema and 2 had a spontaneous colonic perforation). This case highlights the potential life threatening complication of a disease, which is usually thought of as benign, and the rapidity in which a relatively healthy patient can deteriorate.

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Eosinophilic cationic protein in evaluation of IBD activity in children

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Inflammatory bowel disease (IBD) consisting of ulcerative colitis (UC), Crohn’s disease (CD), and indeterminated colitis (IC), seems to be a growing problem in pediatric gastroenterology.

**Aim:** was to assess the value of eosinophilic cationic protein (ECP) in evaluation of clinical activity of IBD children.

**Patients:** Eighty seven children aged from 2.8 to 20.9 yr (mean 11.8) with IBD, (38 UC, 33 CD, 16 IC) entered the study. Forty-one healthy children served as a control group.

**Methods:** Children were clinically evaluated by Truelove-Witts scale and PCDAI for UC and CD respectively. Using Roth scale each child was evaluated colonoscopically. ECP was measured in blood fluoroimmunoenzymatically. In IBD children measurement were performed at admission, and after 2 and 6 weeks of treatment.

**Results:** In the primary evaluation ECP was elevated in the whole IBD group except IC (25.12 vs. 18.8 μg/l). Values gradually decreased in the course of improvement in UC and CD but unexpectedly increased in IC subgroup in 6 week up to 24.09 μg/l. ECP showed good correlation with clinical activity of the disease in IBD group (R = 0.61, p < 0.05), with the duration of the clinical symptoms (R = 0.61, p < 0.05) and weight gain (R = 0.48; p < 0.05).

**Conclusions:** The determination of ECP seems to be a good indicator of clinical activity of CD and UC children, helping to evaluate the clinical severity.
Measures of rehabilitation for patients with applied stoma having inflammatory bowel diseases

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Purpose: To improve the technique of applying colostomas and work out a complex of measures aimed at rehabilitation of patients with inflammatory bowel diseases (IBD).

Methodology: The peculiarities of forming single trunk end colostoma were studied in experiment carried out on 38 dogs. While forming colostomas, cuffs were made of the smooth-muscle layer of the colon wall with 19 animals. The other animals had colostomas formed without smooth-muscle cuffs.

In clinic, the application of colostomas with 45 patients, who had been operated on account of IBD, was performed with regard for colon sphincter location. The colostoma locking function was estimated by the data of sphincterometric and X-ray investigations. After the elimination of inflammation alterations in the colon reconstruction-rehabilitation operations were performed.

Results: In case of forming smooth-muscle stomas animals' tonicity increased by 30%. The application of a single-trunk colostoma at the spot of one of the colon sphincters along with making up an ampule-like widening before the stoma helped to put in order the excretion of gut contents. The application of devices and obturators for colostoma control that had been worked out by the present authors improved the quality of patients' life. General and local use of Salofalk® helped to reduce inflammation alterations in the colostoma area, in the cut-of portion of the colon and became an effective preoperation preparation for reconstruction-rehabilitation operations. Intra- and postoperation infusion of antimicrobial preparations (claforan, cefobid, amoksiklav, metrogil) lessened the frequency of purulent complications.

Conclusions:

1. The improvement of colostoma locking function was obtained by forming colostoma at the spot of colon sphincters.
2. The use of Salofalk® and antibiotics in the complex treatment of patients with colostomas helped to quickly reduce inflammatory processes in the colon and in the colostoma area.
3. Devices and obturators for colostoma control were included into the complex of rehabilitation measures and improved quality of life in relation to symptoms in patients with stomas.
Peculiarities of course and treatment of severe forms of ulcerative colitis

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**Purpose:** To study the role of barrier function of the colon in development of severe forms of ulcerative colitis (UC) and to improve the results of treatment of patients with such pathology.

**Methodology:** Aerococca through digestive tract lumen were introduced into 168 laboratory animals with injuries of alimentary canal mucous layer and without injuries. Ways of aerococca penetration into vessel channel were investigated. In clinic 82 patients with severe forms of UC were under observation. Peculiarities of clinical course of UC severe forms were studied. Endoscopic, morphological, X-ray, immunological, biochemical, microbiological, ultrasonic data were used. For differential diagnostics of benignant and malignant tumors of colon the quantum analyzer of tissues was developed.

**Results:** Multiple infusion of microorganisms resulted in contamination of the whole body. In case of rectal infusion the number of aerococca was twice as big in the central blood circulation as in the peripheral blood. The patients with severe forms of UC had signs of endotoxemia. The changes of bowel microflora in all patients were observed. The conservative treatment included Salofalk® (per os and per rectum), glucocorticoids (intravenously, intramuscularly, per os and per rectum), hepatoprotectors, enzymes, antioxidants, probiotics, combinations of antimicrobial preparations (metrogil+claforan, dalacin+fortum, abaktal+amiakin), infusion therapy. After treatment toxemia reduced, endoscopic and morphological picture of colon mucosa were improved. In patients with complications (perforation, toxic megacolon, bleeding, colorectal cancer) operative treatment (hemicolectomy, colectomy, proctocolectomy) was performed. Aminosalicylates, antibiotics before and after operation were used. Colorectal cancer developed more often in patients with severe forms, with total and subtotal lesion of colon, with pseudopolyps. The risk group included patients with dysplasia 1-2 degree. After operative treatment relapses of cancer were not found for 2 years.

**Conclusions:**

1. The changes of barrier function of colon are of great importance in development severe course of UC.
2. Patients with dysplasia should undergo colonoscopy with morphological control each 3 months.
3. Combinative use of various ways of salazopreparations, glucocorticoids introducing improves the results of curing of severe forms of UC and quality of patients' life.
Differential efficacy of probiotic species in amelioration of dextran sulphate sodium-induced colitis in rats

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Background: Probiotics have emerged as a potential treatment modality for inflammatory bowel disease, however, few have undergone appropriate pre-clinical screening in vivo. We compared the effects of four probiotics on the severity of experimental colitis in rats.

Methods: Sprague Dawley rats were gavaged with 1ml probiotic [L. rhamnosus GG (Lac GG), S. thermophilus TH-4 (TH-4), B. lactis Bb12 (Bb12) and L. fermentum BR11 (BR11) at 1 x 10^10 CFU/ml] or skim milk vehicle twice daily for 14 days (n = 12). Colitis was induced between days 7 and 14 by administration of 2% dextran sulphate sodium (DSS) in drinking water.

Results: Colon length in DSS-treated rats was decreased by 17% compared to normal rats. BR11 partially prevented this reduction, with colon length 10% greater in BR11 + DSS-treated rats compared to DSS-treated rats. A crypt hyperplasia was manifest in DSS-treated rats (290 ± 40 μm) compared to normal controls (175 ± 7 μm). BR11 normalised crypt depth (CD) (199 ± 22 μm) whilst Bb12 partially restored CD (228 ± 24 μm). Lac GG and TH-4 did not prevent crypt hyperplasia. Compared to normal controls, disease activity at day 14 was elevated in DSS-treated rats receiving vehicle (3.1 ± 0.7) but was less evident in DSS-treated rats receiving probiotics, with BR11 (1.2 ± 0.6) achieving the lowest value. There was no significant effect of any probiotic on body weight, myeloperoxidase activity or epithelial cell proliferation compared to DSS-treated controls.

Conclusion: BR11 and Bb12 partially prevented features of DSS-colitis in rats, whereas Lac GG and TH-4 displayed only minimal effects.
Inhibition of dipeptidyl peptidase IV-like activity partially prevents development of experimentally-induced colitis in mice

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Background and Aims: Glucagon-like peptide-2 (GLP-2) is a potent intestinotrophic growth factor, however, its activity is limited by dipeptidyl peptidase IV (DPIV)-mediated degradation. We hypothesised that the novel inhibitors of DPIV-like activity SB-59 and CB-32 would increase GLP-2 bioavailability and hence, decrease the severity of experimental colitis in mice.

Methods: Mice were treated twice daily by oral gavage with 0.9\% saline (n = 6), or a 10 mg/kg dose of SB-59 (n = 6) or CB-32 (n = 6). Mice consumed 2\% dextran sulphate sodium (DSS) for 6 days to induce colitis followed by a recovery period of 3 and 8 days respectively for the 9 (n = 18) and 14-day (n = 18) time points. Inhibitor treatment was continued throughout the experimental period. Plasma DPIV-like activity was determined using a fluorogenic assay. Disease severity was assessed daily using a disease activity index (DAI). Epithelial cell proliferation was determined by proliferating cell nuclear antigen immunostaining.

Results: DPIV-like activity was significantly lower (p < 0.05) following SB-59 (4.70 ± 1.06 df/min) and CB-32 (4.40 ± 0.06 df/min) treatment compared to saline treatment (6.60 ± 0.90 df/min) at day 9; this was also true at day 14. Mice treated with SB-59 or CB-32 had a significantly lower DAI (p < 0.05) at days 5, 6, 7, 8 and 9 compared to saline treated mice for the 9-day trial (n = 12). Crypt cell proliferation at day 14 was significantly increased in both inhibitor groups compared to saline.

Conclusions: Inhibition of DPIV-like activity partially ameliorated experimentally-induced colitis in mice, suggesting potential as a new strategy for the treatment and control of IBD.
Therapeutic alternatives in long-term treatment of Crohn’s disease

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The study enrolled for 2 years 6 patients with Crohn’s disease (initially in activity phase). Six alternatives of long term therapy were used: A - oral corticotherapy, B - oral mesalazine, C - dexamethasone pulse therapy (DPT), D - topical melasazine associated with DPT, E - infliximab and F - oral mesalazine in association with DPT. Colonoscopy was performed every 6 months together with the CDEIS score. Every three months the patients were hospitalized, evaluating the CDAI and IBDQ scores. The following posologies were used: prednisolone 42.5 ± 3.25 mg/day for 87 weeks (A), oral mesalazine 1335 ± 318 mg/day for 76 weeks (B), dexamethasone 0.5 mg/kg intravenously monthly, in three applications followed by same dose every 3 months, for 18 months (alternatives C, D and F). Topic mesalazine was administrated intrarectally 4885 ± 845 mg/day for 68 weeks (D) and infliximab (E) in three perfusions of 5 mg/kg each, at 0, 2 and 6 weeks without any other treatment. The diminution of the CDAI mean score comparatively to initial evaluation was A: -22.5 ± 3.2%; B: -25.5 ± 4.8%; C -30.7 ± 1.9%; D -36.6 ± 1.5%; E -48.6 ± 2.6%, F -39.4 ± 3.6%. The diminution of the mean CDEIS score was -24.6 ± 10.12% (A); -31.06 ± 9.21% (B); -41.88 ± 10.05% (C); -45.12 ± 8.13% (D); -55.42 ± 9.08% (E); -49.02 ± 8.12% (F). No relapses were noted. There is significant difference between monotherapy groups (A, B, C) and mesalazine-DPT combinations. Infliximab has a greater efficiency versus D and F combinations with the advantage of single dose administration.

Conclusion: DPT in association with mesalazine and infliximab are valuable therapies long-term treatment of Crohn’s disease, with superior results versus monotherapies.
The echocardiographic evaluation of pulmonary arterial pressure and right ventricle functions in ulcerative colitis patients

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Objective: Pulmonary system is one of the extraintestinal manifestations in ulcerative colitis. The pulmonary involvement may either be restrictive or obstructive. These types of pulmonary involvement can cause some alterations in cardiac functioning as pulmonary arterial pressure. The aim of this study is to investigate the pulmonary arterial pressure and right ventricle functions, particularly.

Method: A total of 23 ulcerative colitis patients (14 women and 9 men; average age: 35 ± 1 years) and 12 healthy volunteers were enrolled in this study. Pulmonary arterial pressure, right ventricle diameter, the doppler of mitral and tricuspid tissues, deceleration time, isovolemic relaxation time of mitral and tricuspid valves were measured by echocardiography in all subjects. The clinic, pathologic, colonoscopic disease activities of ulcerative colitis and the extent of ulcerative colitis were designated in all patients. Truelove-Witts score was used for the clinic activity of ulcerative colitis.

Results: As the patients compared to the healthy volunteers; the pulmonary arterial pressures were 23.29 ± 5.36 and 18.97 ± 8.82 mmHg, right ventricle diameter was 2.92 ± 0.29 and 2.82 ± 0.37 cm, deceleration time was 130.90 ± 39.82 and 141.33 ± 50.49 ms, isovolemic mitral relaxation time was 87.00 ± 12.03 and 78.33 ± 15.26 ms, isovolemic tricuspid relaxation time was 86.38 ± 10.49 and 81.62 ± 23.13 ms, respectively. The significant difference in the two groups was only shown between pulmonary arterial pressure and mitral valve isovolemic relaxation time which was an indicator of pulmonary arterial pressure and diastolic dysfunction (p < 0.05). There was no relation between the disease activity and echocardiographic measures.

Conclusion: In ulcerative colitis patients, unrelated to the disease activity increased pulmonary arterial pressure was found by echocardiography.

Key words: ulcerative colitis, echocardiography, pulmonary
Mean platelet volume is a useful determinant which reflects the disease activity of ulcerative colitis

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Objective: To determine the relation between the disease activity of ulcerative colitis and mean platelet volume and to evaluate the clinical usage of a more simple and easier determinant.

Method: Complete blood count, C-reactive protein (CRP), erythrocyte sedimentation ratio (ESR), serum albumin and prothrombin time were measured in a total of 41 ulcerative colitis patients. The clinic, pathologic, colonoscopic disease activities of ulcerative colitis and the localisation of colonic involvement were designated. Truloeve-Witts score was used for the clinic activity of ulcerative colitis.

Results: Eleven patients were in remission (26.8%) and 30 had active disease (73.2%). The mean values were; age: 44.58 ± 15.08 (20 women, 21 men), CRP: 36.80 ± 32.90, ESR: 52.29 ± 31.23, albumin: 3.43 ± 0.65, platelets: 400780 ± 161196, MPV: 7.41 ± 1.04, prothrombin time: 13.32 ± 1.05, respectively. By the correlation analysis there was a negative significant relation between CRP and MPV (p < 0.05). The mean MPV values of the 11 patient in remission were 8.62 ± 1.15. The mean MPV values of the 30 patients who had active disease were 6.97 ± 0.53. The patients having active ulcerative colitis had lower MPV values when compared with the patients who had inactive disease (in remission) (p < 0.001). There were negative significant relations between MPV and clinical, pathological and colonoscopic activity indices (p < 0.001). However there was no relation between the extent of the disease involvement and MPV.

Conclusions: Because the active ulcerative colitis patients have lower MPV values and because there are relations between MPV and clinical, pathologic and colonoscopic indices, MPV can reflect the disease activity of ulcerative colitis.

Key words: ulcerative colitis, MPV, CRP
The acute inflammatory response is reduced at sites of skin and rectal trauma in quiescent Crohn's disease (CD)

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Background: The acute inflammatory response is reduced at sites of skin and rectal trauma in quiescent Crohn's disease (CD).

Hypothesis: Acute inflammation is attenuated in the ileum in CD.

Method: Paired biopsies were taken from the neo-terminal ileum and rectum from patients with CD or non-inflammatory controls with familial adenomatous polyposis (FAP), all of whom had ileorectal anastomoses. Each biopsy margin was re-biopsied 6 h later. The mean Harvey-Bradshaw index was 2 and mean CRP < 4 mg/l. No immuno-suppressives were prescribed. The number of cells stained with anti-myeloperoxidase (MPO) and anti-IL-8 were determined in a blind fashion in five randomly selected high power fields (hpf).

Results: Inflammation was minimal in all baseline samples. In FAP, trauma induced substantial neutrophil infiltration and IL-8 production in the ileum and rectum respectively (MPO: 201.5 and 130.0 cells/hpf; IL-8: 219.8 and 141 cells/hpf). The response was significantly weaker in CD (MPO: 86.2 and 60.0 cells/hpf; IL-8: 36.5 and 49.5 cells/hpf). The magnitude of the inflammatory response was highly correlated between each paired post-traumatic ileal and rectal sample (MPO: R² = 0.9267, IL-8: R² = 0.9194, p < 0.05).

Conclusions: This further indicates that CD may be an immuno deficiency disease.
The effects of Gingko biloba extract (EGb 761) on the acetic acid-induced colitis in rats


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Aim: Gingko biloba extract (EGb761) has an antioxidant action and an antagonistic action on platelet-activating factor. We aimed to investigate to antioxidant and histopathologic effects of Gingko biloba extract in the acetic acid-induced colitis.

Methods: Totally 22 rats were divided into three groups. Group 1 was control group. Group 2: acetic acid were given by intracolic instillation. Group 3: Gingko biloba were given 100 mg/kg intraperitoneally 6 days after 72 h from induction of colitis. We assessed to tissue and serum Malondialdehyde (MDA) levels for evaluate the oxidative stress. Colonic damage was assessed by histological examination.

Results: Tissue and serum MDA levels in acetic acid group was found statistically significantly higher than control group, respectively (p: 0.002, p: 0.034). Tissue and serum MDA levels in gingko group was found statistically meaningless higher than acetic acid group, respectively (p:0.86, p:0.68). In acetic acid group, depth of necrosis, extent of necrosis, inflammation, extent of inflammation, fibrosis and total histologic scores was statistically significant higher than control group, respectively (p:0.025, 0.25, 0.1, 0.004, 0.009 and 0.002). In Gingko biloba group, same parameters was statistically meaningless higher than acetic acid group, respectively (p:0.62, 0.93, 0.648, 0.74, 0.146 and 0.64).

Discussion: Gingko biloba did not cause to significant difference statistically on the histopathological and biochemical parameters of tissue damage in experimental colitis. It had been reported in many studies that Gingko biloba was improved to tissue damage in various organs. More studies may be useful for detect of effects of Gingko biloba in experimental colitis.

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The CCR5-Δ32 mutation confers protection against primary sclerosing cholangitis (PSC)

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Background & Aims: PSC is a progressive cholestatic disease commonly associated with inflammatory bowel disease (IBD) and characterized by fibrosing inflammatory destruction of intra- and/or extrahepatic biliary ducts. The precise pathogenesis of PSC is unknown, but immunologic, bacterial, viral and toxic factors may play a role in a genetically susceptible host. We hypothesised that chemokine receptor 5 (CCR5) would be an interesting candidate gene, both from its chromosomal location within the IBD susceptibility locus on 3p21, as well as from functional perspective. We therefore investigated the role of a frequent functional 32 bp deletion in this gene (CCR5-Δ32) and susceptibility to PSC.

Methods: A total of 86 patients with PSC (55 male/31 female) of whom 46 with concomitant IBD (21 CD, 22 UC, 3 IC) were genotyped for CCR5-Δ32. Genotypes and allele frequencies were compared to a cohort of 336 IBD patients (213 CD, 123 UC) without PSC and 313 healthy controls.

Results: The CCR5-Δ32 allele frequency in PSC was significantly lower (5.81%) as compared with healthy controls (12.14%, p = 0.017) and IBD patients without PSC (12.65%, p = 0.011). Within the PSC group, no difference was seen with respect to concomitant IBD (5.43% vs 5.95% for PSC with and without IBD respectively).

Conclusion: The frequency of the CCR5-Δ32 mutation in PSC was significantly lower compared to IBD and healthy controls, suggesting a protective effect of this variant on PSC. As intact CCR5 is necessary for internalisation of specific pathogens, reduced expression of this receptor due to the CCR5-Δ32 variant might explain protection against PSC.
Predicting outcome of ulcerative colitis with clinical parameters and simple laboratory tests

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Introduction: Despite advances in therapy of ulcerative colitis relapses involved 20-50% of patients and about one-third requires colectomy. The aim of this study was to evaluate clinical and laboratory parameters as tests for outcome prediction in ulcerative colitis.

Patients and methods: We included in this study 32 patients with ulcerative colitis evaluated between January 2000 and December 2004. Within 48 hours of admission we recorded clinical data (abdominal pain, frequency and consistency of stools, number of relapses, extra-intestinal manifestations, fever, tachycardia etc.), laboratory results (leukocyte and platelet count, prothrombin time, hemoglobin, erythrocyte sedimentation rate, serum fibrinogen, serum C-reactive protein, fibrin degradation products, serum albumin etc.), imagistic data (bowel dilatation on straight radiograph of abdomen and colonoscopic data) and we evaluated the severity by clinical disease activity index. All cases were treated with fluid administration, hydrocortisone and antibiotics and we compared data of patients who failed to respond or developed complications with data from good-responders to the treatment.

Results: 6 of 32 patients required surgical treatment and 2 patients died. Failure of medical treatment was associated with low levels of serum albumin, hemoglobin, serum fibrinogen, high levels of C-reactive protein, prothrombin time, fibrin degradation products, colonic dilatation and high clinical activity index on monovariate analysis.

Conclusions:

1. Relapses in ulcerative colitis are strongly associated with severity of the disease.
2. Clinical parameters and simple laboratory tests may be useful to predict the failure of medical treatment in ulcerative colitis.

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Relationships between therapy and cytokine serum levels in patients with cutaneous manifestations of inflammatory bowel diseases

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Introduction: Extraintestinal manifestations are common in inflammatory bowel disease (IBD) and this disorders may persist despite resolution or improvement in bowel symptoms. Erythema nodosum, pyoderma gangrenosum, aphthous ulcerations and metastatic cutaneous Crohn's disease (MCCD) usually occur in the setting of active IBD. The aim of our study is to evaluate the relationship between TNFα, IL-8 and the evolutions of skin lesions under treatment.

Patients and method: We enrolled 106 IBD patients. 29 of them have had skin lesions: 17 erythema nodosum, 2 pyoderma gangrenosum, 4 MCCD and 6 with aphthous ulcerations. Patients with erythema nodosum were treated with corticosteroid 1 mg/kg/day, patients with pyoderma gangrenosum received 2.5 mg/kg/day corticosteroid, patients with MCCD received 0.5 mg/kg/day corticosteroid and metronidazole and patients with aphthous ulcerations benefit only by adequate local treatment. We assessed the levels of proinflammatory cytokines: TNFα and IL-8 before and after therapy.

Results: We evaluated the improvement of cutaneous lesions, the bowel symptoms and the level of cytokines. We obtained good clinical results in 13 patients with erythema nodosum, in one patient with pyoderma gangrenosum, one patient with MCCD and all patients with aphthous ulcerations. In all patients we evaluated the levels of cytokines: TNFα and IL-8 in serum were significantly higher before therapy (26.12 pg/ml respectively 63.87 pg/ml) comparing levels after therapy (16.14 pg/ml respectively 19.53 pg/ml).

Conclusion: We established that TNFα and IL-8 levels decreased in all patients after therapy without relationship with clinical improvement.

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Nutritional deficiencies in ileal pouch patients

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Chronic inflammation is seen in 87% of the pouches of those who have undergone restorative procto-colectomy. These changes largely reflect normal adaptive "colonisation". Despite this, the ileal pouch is believed to retain its absorption capacity for water, electrolytes and vitamins. However, bone densitometry scans demonstrate osteopenia in 37% of those with evidence of chronic subtotal or total villous atrophy in their pouches. We aimed to assess the prevalence of anaemia, vitamin D and haematinic deficiency in pouch patients.

70 pouch patients (68 UC, 1 CD, and 1 FAP) were identified over a 1 year period where the results of biopsy assessment, using the St. Marks' Pouch Histological Score, and routine blood tests were taken on the same day.

33/70 (47%) had an acute inflammatory score of $\geq 2$, 47/70 (67%) had a chronic inflammatory score of $\geq 3$ and 47/70 (67%) had a combined St. Marks' Pouch Histology Score of $\geq 4$ suggesting histological pouchitis. Where available blood results revealed anaemia in 22/69 (32%), iron deficiency in 17/65 (26%), folate deficiency in 5/64 (8%), $B_{12}$ deficiency in 10/66 (15%) and vitamin D deficiency in 8/56 (14%).

Reversible vitamin deficiencies are common amongst pouch patients, with anaemia occurring in one third. Deficiencies in folate, Vitamin D and $B_{12}$ were more frequently seen in association with adaptive/chronic inflammation, whilst iron deficiency and anaemia were more common in those with acute inflammation changes.
Does pouchitis occur in familial adenomatous patients?

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Many believe pouchitis occurs only in ulcerative colitis and not in familial adenomatous patients (FAP) post-restorative proctocolectomy. Several early studies suggest a prevalence of 3-14%, but their validity is uncertain as the pouchitis was diagnosed subjectively. We aimed to demonstrate the true prevalence of pouchitis in FAP patients.

190 FAP pouch patients underwent pouchoscopy over a 2 year period. Inflammation was identified endoscopically in 55 (29%) of these patients, and a Pouch Disease Activity Index (PDAI) score was calculated for each using additional histological and retrospectively collected clinical data.

27 of those 55 (54%) had ulcers and 24/55 (48%) had erosions. 12/55 (24%) had an increase in their stool frequency, 11/55 (22%) had PR bleeding and 17/55 (34%) suffered cramp like pains or urgency. Histology was available in 42 with 11/42(26%) demonstrating an acute inflammatory score of ≥2, 11/42 (26%) a chronic inflammatory score of ≥3 and 13/42 (31%) had a combined St. Marks’ Pouch Histology Score of ≥4 suggesting histological pouchitis. 6/42 (14%) were diagnosed with pouchitis using the PDAI.

Endoscopic inflammation was seen in 29% of all FAP pouches, a third of which had confirmatory histopathological changes, but only 4% had a PDAI score that reached diagnostic criteria for pouchitis. It remains unclear whether this form of pouchitis represents the same disease process as that seen in ulcerative colitis pouch patients.
The role of cytokines in the pathogenesis of ulcerative colitis

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Background/aim: One of the most important directions of the study of ulcerative colitis (UC) pathogenesis is the research of cytokines' production. Tumor necrosis factor α (TNF-α) and interleukin-1 α (IL-1α) are known as the most active proinflammatory cytokines. In this study we evaluated changes in TNF-α and IL-1α expression in the serum of patients with UC.

Methods: We observed 25 patients with UC. Among them 14 patients had a mild degree and 11 patients had a disease of moderate degree of activity. The production of TNF-α and IL-1α in the serum was determined by ELISA. In control group 10 healthy donors were included.

Results: In the serum of patients with UC of the stage of aggravation there was observed an increasing the TNF-α and IL-1α levels in comparison with the level in healthy donors. In the patients with UC of light degree the TNF-α level composed 19.4 ± 1.6 pg/ml, in the patients of average degree of gravity - 32.3 ± 2.4 pg/ml vs 6.2 ± 0.9 pg/ml in control. In the patients with UC of light degree the IL-1α level composed 43.1 ± 3.5 pg/ml, in the patients of average degree of gravity - 71.9 ± 5.6 pg/ml vs 24.8 ± 2.6 pg/ml in control. In this case the straight correlation of both cytokines' levels was fixed with the degree of activity of inflammatory process. The strongest correlative connections were marked in TNF-α.

Conclusions: Cytokines TNF-α and IL-1α play an important role in the pathogenesis of UC. These cytokines can be considered as the markers of the activity of the inflammatory process under UC.
Pancreatic autoantibodies in Greek patients with inflammatory bowel disease

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Background: Pancreatic autoantibodies (PAbs) have been suggested as a specific but not sensitive marker for CD. The aim of the present study, was the evaluation of the diagnostic value of PAB in Greek IBD patients.

Methods: Sera were collected from 150 patients with IBD (73 with UC and 77 with CD) and 104 healthy controls. Determination of PAbs was performed by a standard indirect immunofluorescence technique. The relationship of these antibodies with clinical parameters of UC and CD was assessed.

Results: PAbs were detected in 18 of 73 (24.7%) samples from UC patients and in 32 of 77 (41.6%) samples from CD patients. The prevalence of positive PAbs was significantly higher in CD than in UC (p = 0.04). None of the 104 samples from healthy controls had detectable PAbs. Both UC and CD had significantly higher prevalence of positive PAbs compared with healthy controls (p < 0.0001). Sensitivity, specificity, positive predictive value, and negative predictive value of the PAbs test were 41%, 85%, 64%, 69% in CD patients, 25%, 50%, 36%, 65% in UC patients and 33%, 100%, 100%, 51% as overall values for diagnosing IBD respectively. A significant association of PAbs with stenotic CD was also found (p = 0.02).

Conclusions: The prevalence of PABs in Greek CD patients was found to be similar to previous reports. In contrast to these studies we found also increased prevalence of PABs in UC patients. These findings suggest that PAbs should be considered as a specific marker for IBD rather than for CD.
Long-term follow-up in pediatric patients affected by Crohn's disease treated with autologous erythrocytes loaded with dexamethasone 21-phosphate

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We previously described a new treatment with autologous erythrocytes loaded with dexamethasone 21-phosphate in pediatric patients with Crohn's disease.

Aim of our study was to demonstrate the efficacy of this treatment and its long-term safety in a greater number of patients with a longer follow up.

We studied 11 patients, (7F, 4M; mean age 16.3 yrs ± 3.9) affected by CD. Inclusion criterium for treatment with autologous erythrocytes loaded with dexamethasone 21-phosphate was corticoiddependence with severe steroid induced side effects. At the beginning of treatment three patients were in an active phase of the disease (mean PCDAI 58); six patients in a moderate phase (mean PCDAI 15) and two were in complete remission (mean PCDAI 5).

A total of 277 infusions (one every three week) were performed with a mean 25 infusions per patient (range 12-39). Mean follow-up was 72 weeks (range 36-117). All patients could stop and did not need to start again conventional steroid treatment either oral or e.v. Mean PCDAI decreased from 25.2 to 11.5. In particular the patient with an active or moderately active disease went into remission and the other maintained remission.

None of our patients showed any of the typical steroid side effect (moon face, hypertension, stria rubre ect) and in half of them in which we performed a DEXA-MOC at the beginning of treatment and six months afterwards there was no change in their Z-score. We showed that periodic treatment with autologous erythrocytes loaded with dexamethasone 21-phosphate in pediatric patients with CD is effective and safe.
The usage of antiprotozoal medications at complex treatment for colitis associated with enteric blastocystosis

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The one of the etiological factors of colitis is parasitic invasions, enteric blastocystosis in particular. In view of it the purpose of our work is optimization of complex treatment for colitis blastocysts infected patients.

Methods: 89 colitis patients were examined, 85 of them (95.5%) were blastocysts infested. All the patients were divided into 4 groups. During the therapeutic complex for the patients from Group 1 (22 people) tinidazole antiprotozoal medication was used, for the patients from Group 2 (21 people) - metronidazole, for the patients from Group 3 (23 people) - ornidazole. The patients from Group 4 (19 people) didn't receive any antiprotozoal medications.

Results: The patients who had received the antiprotozoal therapy had higher remission index. In 4 weeks in Group 1 it was 91% against 64%, in Group 2 - 89% against 67%, in Group 3 - 78% against 70%. The induction of clinical and endoscopic remission was achieved by all the patients who had received the antiprotozoal medications in comparison with the patients who hadn't received those medications. The colitis patients who were receiving tinidazole, metronidazole and ornidazole had less relapses at remission stage. Preservation of remission during 12 months had been observed at 68% of the patients.

Conclusion: Antiprotozoal medications efficiently induce and preserve remission at colitis associated with enteric blastocystosis patients that permits to recommend the usage of the it for complex treatment for this disease.
Tacrolimus microparticles mitigate experimental colitis in rats with minor nephrotoxic adverse effects

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Tacrolimus has proven a distinct effect in mitigating inflammatory bowel disease risking, however, severe adverse effects. Subsequently, a more selective delivery to the site of inflammation may further improve efficiency and tolerability. Eudragit P-4135F as pH-sensitive polymer for colonic delivery was applied to prepare tacrolimus microspheres (MS) using an oil/water emulsification technique. MS were found to keep drug leakage at pH 6.8 lower than 10% within 6 hours. At pH 7.4, nearly immediate release (within 30 min) was observed. Tacrolimus MS providing pH-sensitive colonic drug delivery were tested for their therapeutic efficiency in a trinitrobenzenesulfonic acid colitis model induced to male Wistar rats with daily drug administrations for 10 consecutive days. The MS formulations proved to be as efficient in mitigating the experimental colitis as the subcutaneously injected drug solution on the basis of the myeloperoxidase activity (MS: 9.64 ± 6.6 U/mg tissue; parenteral 7.48 ± 6.96 U/mg) and to be superior to drug solution given by oral route (oral: 12.66 ± 5.46 U/mg; control: 21.88 ± 4.12 U/mg). Colon/body weight index and histological damage score showed similar results. The group receiving subcutaneously injected tacrolimus exhibited a high level of adverse effect, whereas the tacrolimus MS group proved their potential to retain the drug from systemic absorption as evidenced by significantly reduced blood urea nitrogen, creatinine clearance, and calcineurin kidney level. The development of this selective delivery system for tacrolimus should be given particular consideration in the treatment of inflammatory bowel disease since it allows to profit from tacrolimus’ high immune suppressive effect with a simultaneously reduced nephrotoxicity.
Saccharomyces boulardii activates expression of peroxisome proliferator-activated receptor-γ through suppression of NF-κB in HT-29 cell

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Background/Aims: Saccharomyces boulardii was known to be beneficial in the treatment of inflammatory bowel disease and decreased IL-8 proinflammatory secretion via inhibition of the NF-κB, however, little is known about their mechanisms of action. The peroxisome proliferator-activated receptor-γ (PPAR-γ) is nuclear receptor that is expressed mainly in adipose tissue and which have a role in lipid metabolism and insulin sensitization. New sites of PPAR-γ expression have been described, especially in the intestinal tract. PPAR-γ is recently found to regulate inflammation in intestinal epithelial cell. We hypothesized that the anti-inflammatory effects of Saccharomyces boulardii are mediated, in part, through PPAR-γ. To test this hypothesis, we examined the ability of Saccharomyces boulardii to modulate the expression of PPAR-γ and suppress NF-κB activation in human colon cells.

Methods: Effects of Saccharomyces boulardii on survival and proliferation of HT-29 human colon cells were assessed by MTT and [3H]thymidine Incorporation assays. PPAR-γ expression was assessed by Western blot and RT-PCR. Induction of IL-8 expression by tumor necrosis factor-α (TNF-α), Interleukin-1β (IL-1β), or lipopolysaccharide (LPS) was assessed by RT-PCR. Nuclear translocation of NF-κB was assessed by Western blot.

Results: Saccharomyces boulardii did not affect viability and proliferation of HT-29 cell. Saccharomyces boulardii up-regulated PPAR-γ expression at both mRNA and protein levels. Pretreatment of HT-29 cells with Saccharomyces boulardii blocked PPAR-γ down-regulation by TNF-α, IL-1β, or LPS, whereas it ameliorated IL-8 response to these proinflammatory factors. TNF-α-induced suppression of PPAR-γ was eliminated by p38 and NF-κB inhibitor. Saccharomyces boulardii blocked TNF-α-induced nuclear translocation of NF-κB.

Conclusion: Saccharomyces boulardii stimulates PPAR-γ expression and reduces response of human colon cells to proinflammatory cytokines. Saccharomyces boulardii may activate PPAR-γ expression through suppression of NF-κB.

Key words: Saccharomyces boulardii, PPAR-γ, NF-κB, HT-29
Dendritic cells in the peripheral blood in patients with ulcerative colitis and Crohn’s disease

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Background: The etiopathogenesis of ulcerative colitis (UC), and Crohn’s disease (CD) is still largely unknown. Dendritic cells (DCs) are thought to play a crucial role in the regulation of immunity of the gut. Disturbances in the number and function of DCs may therefore be involved in the initiation, and maintenance of the inflammatory response in these diseases.

The aim of the study was to determine the quantity of myeloid (BDCA1+) and lymphoid (BDCA2+) dendritic cells from peripheral blood in patients with UC and CD.

Methods: Peripheral blood was obtained from 20 patients with UC, 16 patients with CD and 35 healthy controls. The cells were collected using a FACSCalibur flow cytometer. Myeloid DCs were identified as BDCA-1 positive and CD19 negative cells, whereas lymphoid DCs were identified as double BDCA-2 and CD 123 positive cells. The count of DCs were definned as the percentage of mononuclear cells. Wilcoxon and U Mann-Whitney non parametric tests were applied to statistical comparison. Results are presented as the mean value ± standard deviation and p value of < 0.05 was considered as significant.

Results: The percentage of myeloid DCs in peripheral blood was significantly lowered in patients with ulcerative colitis (UC) and Crohn’s disease (CD) as compared to healthy subjects (p = 0.026 and p = 0.012 respectively). Lymphoid DCs were also significantly decreased in patients with UC (p = 0.034). The patients with UC showed lower values compared to CD ones but the difference appeared not significant.

Conclusion: Lowered percentage of myeloid and lymphoid DCs observed in peripheral blood of patients with UC and CD may play an important role in the pathogenesis of the inflammatory bowel diseases.
Crohn’s disease associated with asymptomatic celiac disease. Case report

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Very few cases of association between Crohn’s disease and symptomatic celiac disease have been reported. The case reported herein is probably the first describing an association between Crohn’s disease and asymptomatic celiac disease.

Case report:
A twenty six old woman with Crohn’s colitis has presented three acute flares within the two years following the diagnosis. Each acute flare treatment with sulphasalazine and corticoid enemas has been effective. Because of last remission short duration, UC-like Crohn’s colitis was suspected. Maintenance therapy was initiated and pANCA testing was performed to support this hypothesis. By chance, immunological studies included antiendomysial and anti gladin antibodies research which were positive. Celiac disease was confirmed by duodenal biopsy showing villous atrophy and increased number of lymphocytes epithelium infiltration. Gluten-free diet was associated to Crohn’s disease maintenance therapy. With a four year follow-up, our patient is still asymptomatic. Through this case report, the authors discussed pathogenic aspects and emphasize diagnosis particularities.
Perinuclear antineutrophil cytoplasmic antibody as predictor for pouchitis after colectomy with ileal pouch-anal anastomosis in ulcerative colitis patients

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Introduction: Pouchitis is a complication frequently reported in patients with ulcerative colitis underwent total colectomy with ileal pouch-anal anastomosis (IPAA). The aim of our prospective study is to evaluate preoperative perinuclear antineutrophil cytoplasmic antibody (pANCA) expression in order to determine its predictor role in developing pouchitis.

Patients and methods: We included in this study 33 patients with median age 37 years between January 1997 and December 2004. Before the operation we analyzed pANCA from serum samples by ELISA and indirect immunofluorescence technique. Using this variable, we included patients in two groups: group A with high levels of pANCA (more than 100 UI/ml) and group B with low level (under 100 UI/ml). After the operation we assessed all patients clinically and endoscopically in order to determine the inflammation of ileal pouch.

Results: There were 21 antibody-positives patients. The median follow-up was 24 months and, after this period, 10 patients (23.80%) developed pouchitis: 3 patients with acute and 7 with chronic evolution. We discover no significant difference between two groups in developing acute pouchitis, but we find that the incidence of pouchitis was higher in group A comparing with group B or pANCA-negative patients.

Conclusions:

1. High level pANCA is associated with development of chronic pouchitis; so we can assume that this may be a good predictor for the disease.
2. There are no correlations between level of pANCA and development of acute pouchitis.

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Long-term oral cyclosporine therapy in severe, steroid-refractory ulcerative colitis with a daily dose of 4 mg/kg - Result of the one-year follow-up

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Cyclosporine therapy has proven to be an alternative to emergency colectomy in steroid-refractory ulcerative colitis. Oral cyclosporine has less toxic side effect than intravenous treatment, but therapeutic ability, optimal dosage, the long-term efficacy and safety of this formulation is not well studied.

The aim of this study was to investigate the clinical outcome of all patients treated with Sandimmune® Neoral® (Novartis) orally at a daily dose of 4 mg/kg for a year.

Patients and methods: 16 of the 290 regularly controlled ulcerative colitis patients were treated with cyclosporine because of severe active colitis (12 female, 4 male; the extent of inflammation: 15 pancolitis, 1 left-side colitis; clinical course: 5 continuous activity, 7 intermittent activity and 4 first attack). All patients were treated with oral microemulsion cyclosporine as a first line therapy, and the administration of the drug was continuous for a year. The dose of corticosteroid was gradually reduced, and 2 mg/bw/kg dose of azathioprine was initiated during the cyclosporine treatment. Disease activity, and blood level of cyclosporine were followed by using of a two-point sampling times to evaluate efficacy and safety of therapy. Primary objectives were the induction of remission, the frequency of relapse during the next twelve month and colectomy-free survival.

Results: All patient improved within 14 days and complete remission was achieved in 14/16 patients after 1 month. 13/16 patients have remained in remission during the one year of cyclosporine therapy. 1/16 patient was operated after an reversible hepatotoxic side effect, while 2/16 after a second relapse.

Discussion: Oral cyclosporine seems to be effective in the treatment of severe steroid refractory ulcerative colitis not only for the induction but - in combination with azathioprine - also in the maintenance of remission. Colectomy can be avoided in most of the patients with prolonged use of oral cyclosporine. Therapeutic drug monitoring by using of a two-point sampling times is the guarantee of the safety during a long-term oral cyclosporine therapy.
The safety and efficacy of granulocyte and monocyte absorption apheresis (GCAP), and leukocytapheresis (LCAP) in patients with refractory ulcerative colitis (UC)

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Background & Aims: Systemic corticosteroids are used for the treatment of severe and moderately severe UC, and approximately 30-40% of patients with severe UC require additional therapy such as intravenous cyclosporine A. We report our experience with cytapheresis in the treatment of refractory UC.

Methods: Thirty patients with active UC refractory to corticosteroids, or having corticosteroid-related complications, were treated either with GCAP (18 patients) or with LCAP (12 patients). Venous blood was drained and circulated through a cellulose acetate bead column (GCAP) or a polyethylene fiber column (LCAP) once or twice a week for 5 consecutive weeks, without increasing their dose of corticosteroids, mesalazine, or immunosuppressants.

Results: Twenty patients were corticosteroid-dependent, 10 were intolerant to corticosteroids because of complications such as osteoporosis, diabetes mellitus, cataracts, or glaucoma, and 24 patients were refractory to corticosteroid therapy. Nineteen of 24 patients with refractory UC (79%), and 4 of 6 with non-refractory UC (83%) showed clinical improvement. Cytapheresis was not effective with massive ulcers (n = 1), but deep ulcers improved in 7 of 11 patients (64%), and shallow ulcers improved in 12 of 12 patients (100%), when examined endoscopically after 5 weeks of treatment. No severe adverse effects were noted.

Conclusions: GCAP and LCAP are safe and effective treatments for active UC, especially UC refractory to corticosteroids.
The prevalence of inflammatory bowel disease in Turkish patients with primary sclerosing cholangitis

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Background: Few reports document the prevalence of primary sclerosing cholangitis (PSC) in Turkish patients with inflammatory bowel disease (IBD). However, lack of data exists about the prevalence of IBD in Turkish patients with PSC.

Aims: To determine the prevalence of IBD in Turkish patients with PSC, and to compare the clinical features of patients with PSC coexisting IBD (Group A) or not (Group B).

Study: We reviewed the patients diagnosed as sclerosing cholangitis by endoscopic retrograde cholangiopancreatography and/or liver biopsy in our department between 2000 and 2004. Patients with secondary sclerosing cholangitis (SSC) were excluded. Patients with PSC were divided into two groups according to the presence (Group A) or absence (Group B) of IBD. Clinical features were compared between two groups.

Results: There have been 46 patients with sclerosing cholangitis consisting of 30 patients with PSC and 16 patients with SSC. The mean age at diagnosis of 30 patients with PSC was 38.2 years (range: 16-57 years) with a male-to-female ratio of 17:13. Group A was consisted of 13 patients (ulcerative colitis: 13, Crohn's disease: 0). Prevalence of IBD in patients with PSC was found to be 43.3% (13/30). Liver transplantation was performed in 8 patients (Group A: 4, Group B: 4) because of recurrent cholangitis. No characteristic difference was found between group A and group B.

Conclusions: Prevalence of IBD in Turkish patients with PSC is similar to results of western origin studies. Presence of IBD does not affect the clinical features of Turkish patients with PSC.
Amelioration of ulcerative colitis by peroxisome proliferator-activated receptor-gamma in rats. Role of proinflammatory cytokines, nitric oxide synthase and cyclooxygenase pathways


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Introduction: Peroxisome proliferator-activated receptor-gamma (PPARgamma) is a ligand-dependent transcription factor that plays a pivotal role in the resolution of inflammation. Little is known about the effect of PPARgamma ligand on the time-course of healing of colonic mucosa in the experimental ulcerative colitis.

Aims & Methods: We have studied the effect of treatment with vehicle and pioglitazone (5-40 mg/kg), a specific PPARgamma ligand, on the colonic damage induced in male Wistar rats by the administration of 2,4,6-trinitrobenzenesulfonic acid (TNBS, 10 mg/kg intrarectally) with or without A) suppression of prostaglandins synthesis by indomethacin (5 mg/kg i.p.) and B) inhibition of NO-synthase with L-NNA (20 mg/kg i.p.), applied with or without vehicle or pioglitazone. 3, 7, 10 and 14 days upon the TNBS treatment, the distal 8 cm of the colon was removed. Area of colonic lesions measured and the activity of myeloperoxidase (MPO) was determined. The plasma IL-1beta and TNFalpha levels were determined by RIA and ELISA. The PPARgamma mRNA and protein were analyzed by RT-PCR and Western Blot.

Results: Administration of TNBS resulted in macroscopic lesions that peaked at day 3, being accompanied by an increase in tissue weight, the fall in the CBF, the 4-5-fold increase in the MPO activity and the rise in plasma IL-1beta and TNFalpha levels. Concomittant with healing of these lesions at day 7, 10 and 14, a significant decrease in these parameters were observed. Pioglitazone (5-40 mg/kg) dose-dependently attenuated the area of colonic lesions, by 50% (ED50 ) and this was accompanied by the dramatic fall in tissue weight index, MPO activity and plasma IL-1beta and TNFalpha levels. Pioglitazone (20 mg/kg) downregulated COX-2 and iNOS mRNAs but failed to influence those for COX-1 and cNOS.

Conclusion:

1. Pioglitazone accelerates the healing process of ulcerative colitis due to its anti-inflammatory action involving the suppression of IL-1beta, TNFalpha, COX-2 and iNOS at the site of colonic inflammation;
2. PPARgamma-ligands may be useful as the potential therapeutic agents in the treatment of ulcerative colitis.
Association of CARD15 gene variants with pediatric inflammatory bowel disease

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Three major polymorphisms of CARD15 gene (R702W, G908R, L1007fsinsC) have been associated with Crohn’s disease (CD), but not with ulcerative colitis (UC), in different Caucasian adult populations. We analyzed the three variants in 208 Italian patients affected by inflammatory bowel disease (IBD), including 116 with CD and 92 with UC, whose age at onset was ≤ 18 years. As a control group, 101 unaffected individuals also were analyzed. Comparison of allele frequencies between patients and controls demonstrated an independent association for all three variants with CD, but not with UC. After combining the three polymorphisms together, 38.5% of CD patients carried at least one CARD15 variant compared to 5% of controls (p < 10^{-8}; OR = 12.04; 95% CI = 4.52-32.02). Eleven CD children (10.1%), but only one UC and no control subjects carried two CARD15 variants (homozygotes or compound heterozygotes). The combined frequency of CARD15 variants was higher also in UC children compared to controls (13.1% vs 5%), but this difference was at limits of significance (p = 0.045; OR = 2.89, 95% CI = 0.96-8.69). Analysis of genotype-phenotype correlation did not find any significant clinical difference between CARD15 positive and negative patients in both CD and UC groups. The present study shows that the major CARD15 variants are strongly associated with pediatric onset CD in Italy. It indicates also a possible role for these polymorphisms in pediatric UC; however this association needs to be confirmed in larger cohorts. CARD15 genotypes do not seem to be useful to predict the clinical outcome in pediatric IBD patients.
Aspirin and its nitric oxide (NO) derivative in the healing of the colonic damage in the experimental model of ulcerative colitis

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The new NO-releasing derivative aspirin (ASA), has been shown to exhibit lower gastrointestinal toxicity than parent aspirin and to spare the gastrointestinal tract even when administered repeatedly for several weeks but its anti-inflammatory effects in the lower gut have been little studied. In this study we compared the effects of vehicle, ASA and NO-ASA applied intragastrically (i.g.) in a dose of 2.5-40 mg/kg on colonic damage induced in male Wistar rats by the administration of 2,4,6-Trinitrobenzenesulfonic acid (TNBS, 10 mg/kg intrarectally) with or without inactivation of sensory nerves by capsaicin (125 mg/kg s.c.). At 2 weeks upon the TNBS treatment, the distal 8 cm of the colon was removed for the area of colonic lesions measured by planimetry, the tissue weight index and the tissue myeloperoxidase (MPO) activity. The colonic blood flow (CBF) was assessed by H₂-gas clearance technique and blood was withdrawn for the measurement of plasma cytokine IL-1β and TNF-α levels (ELISA). Administration of TNBS resulted in macroscopic lesions accompanied by increase in tissue weight and 4-5-fold increase in the MPO activity. ASA (40 mg/kg s.c.) significantly aggravated the area of colonic lesions and produced the significant increase in tissue weight index and significantly enhanced MPO activity. In contrast, NO-ASA (40 mg/kg i.g.) failed to delay the colonic ulcer healing and this action of this NO derivative of ASA was accompanied by the significant rise in the CBF (by 25%) and the significant fall in the plasma IL-1β and TNF-α levels. Capsaicin-deactivation of sensory nerves attenuated significantly the NO-ASA-induced increase in the healing of these lesions and colonic hyperemia. We conclude that NO-ASA exerted opposite effect to that of classic ASA on healing of ulcerative colitis and that this beneficial action of NO-ASA may involve hyperemia probably mediated by NO and sensory nerves acting via brain-gut axis.
Introduction: Iron deficiency is an ordinary situation in IBD due to chronic bleeding. Nevertheless fact of iron overload (IO) is not rare.

The aim was to indicate the reason of iron overload in IBD in children - iron hyperabsorption in hemochromatosis associated with IBD.

Method: we observe 5 patients with chronic sideremia among 60 patients with IBD. Three of them suffer from ulcerative colitis (UC), 2 - from Crohn's disease (CD), 12-17 years aged, 2 girls, 3 boys.

Results: Mean serum iron was 33.5 ± 1.2 mmol/l. Ferritin, transferrin were normal in all cases, transferring saturation was 50.2 ± 3.7%. All of patients had 3-5 symptoms evidenced abnormal myoelectrical conduction: seek sinus syndrome, bradycardia, gastroesophageal and duodenogastral reflexes, gallbladder dysfunctions. The genotypic tests showed heterozygous H63D mutations of hereditary haemochromatosis (HFE). Three patients had sings of primary sclerosing cholangitis (PSC) as complication of UC. The symptoms of IO included symptoms of chronic intoxication (5 patients), liver enlargement (3 patients), abdominal pain syndrome (5 patients) both in remission and exacerbation of IBD. Three patients with hemosiderosis associated with PSC have manifestations of heart disease: congestive heart failure and cardiac arrhythmia (two patients have hard bradyarrhythmia, two atrioventricular conduction damage, one -ventricular extrasystole (bigeminy).

Conclusions: Heterozygous H63D of HFE penetrate in patients with IBD, especially complicated PSC. Iron overload mechanism in IBD patients can be explained as by primary and secondary reasons - hereditary prediction, poor back regulation of iron absorption and PSC.
Videocapsule endoscopy for diagnosis IBD in children

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Objective: Videocapsule endoscopy (VCE) is a recent diagnostic option for imaging the small intestine not available for push endoscopy.

Aim: To evaluate the small bowel mucosa in children with inflammatory bowel diseases and assess diagnostic capability of VCE.

Methods: We performed videocapsule endoscopy in 22 children (17 boys, 5 girls, aged 7-18 years) with IBD. All patients before VCE were performed laboratory blood tests, colonoscopy and histological examinations of biopsy specimens. According this date before VCE in 14 children was diagnosed ulcerative colitis (UC) and in 8 children Crohn's disease (CD). All patients had no strictures of digestive tract and age above 7 years.

Results: According VCE date we funded out in 14 patients from 22 patients (64%) inflammatory changes in small intestine. Jejunum damage was seen in 3 patients (14%), it was seen edema, hyperemia of mucus, erosions and fissure ulcers with detritus. Damaged areas had segmental manner with areas of normal mucosa. In one patients was found out jejuno-jejunale fistulae. Ileum damage was seen in 11 patients (50%) with erosions and ulcers in all cases, 3 patients had pseudopolyps. According VCE date in 6 patients diagnosis UC was changed to CD.

Conclusions: Videocapsule endoscopy allowed to establish CD with small intestine damage in 64% children with IBD and change diagnosis from UC to CD in 6 children.
The diagnostic value of disclosing blastocysts at colitis patients

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Colitis is often followed by enteric infections and invasions. In view of it the purpose of work is to determine the diagnostic value of disclosing blastocysts at colitis patients at acute condition and remission period.

Methods: 89 colitis patients received the endoscopic and parasitologic checkup of intestines at acute condition and remission period of the disease. For comparison of the results 45 people in practically good health were examined.

Results: At acute condition blastocysts were disclosed at 85 patients out of 89 (95.5%). The endoscopic state was characterized by mucous tunic thickening of the rectum and the colon. Goblet cells abruptly decreased in number, crypts had an awkward shape. Lamina propria was in hydropic state and infiltrated by lymphocytes, neutrophils and eosinophils, had vascular stases and numerous hemorrhages. At remission period had been performed sizeable rehabilitation of structural characteristics of the intestines was observed. It was followed by decreasing of the number of blastocysts inside the intestines. So at remission period the number of the blastocysts infested patients halved (48.3%). At the comparison examination group that index didn't exceed 3.5%.

Conclusion: Exacerbation of colitis was followed by high blastocysts intestines invasion and reduction of this index at remission period that permits to use the method of disclosing blastocysts for the purpose of exacerbation prediction.
Endoscopic diagnosis versus histopathologic diagnosis in inflammatory bowel disease (IBD)

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Introduction: We consider that the endoscopy is the most important diagnostic tool in IBD. The aim was to correlate the endoscopic description with histopathology.

Material and methods: We performed a retrospective study, including 170 patients with active IBD (endoscopic diagnosis), examined during 2000-2003 in our Department. There were 3 groups of patients:
Group UC: 99 cases with an endoscopy suggestive of ulcerative colitis.
Group IC: 6 patients with non-specific description (indeterminate colitis).
All patients included performed colonoscopy, with multiple mucosal biopsies.

Results: on the description of an expert histopathologist, we found 6 categories of biopsies: suggestive of UC, suggestive of CD, non-specific (chronic active inflammatory infiltrate without any specificity), suggestive of acute microbial colitis (AMC), other diagnosis (other), normal. This description was applied to the 3 patients groups: see table.

<table>
<thead>
<tr>
<th>Patients group</th>
<th>Type of biopsy</th>
<th>UC</th>
<th>CD</th>
<th>Non-specific</th>
<th>AMC</th>
<th>Other</th>
<th>Normal</th>
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<tbody>
<tr>
<td>CD</td>
<td>5</td>
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<td>38</td>
<td>6</td>
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<tr>
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<td>23</td>
<td>1</td>
<td>1</td>
<td>6</td>
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</tr>
<tr>
<td>IC</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

Conclusions:

– in patients with endoscopy suggestive of CD, biopsy findings are most often non-specific (58.5%), while in 7.7% suggests UC and in 9.23% AMC.
– in patients with endoscopic ulcerative colitis, the biopsy is concordant with the endoscopy in 68.7%, only 23.2% have non-specific findings.
– cases with endoscopic indeterminate colitis have bioptic findings of UC in 50%, while in 50% are non-specific.
– mucosal biopsies seem more important for differential diagnosis, rather than for positive diagnosis.
Prevalence and significance of anti-neutrophil antibodies (pANCA) in patients with Crohn's disease (CD) and ulcerative colitis (UC) in Romania

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Introduction: ANCA are known as a serologic marker of immune disturbances in IBD (more specific are pANCA). The aim of this study was to investigate their significance in IBD in Romania.

Material and methods: A prospective longitudinal study, including all the patients admitted in our Center in 2000 with UC (33 patients) - UC group or with CD (40 patients) - CD group. The control group (C) included 22 healthy individuals, with similar age and sex distribution. Blinded serum was sent for serologic assay (ELISA) at Leuven University.

Results: ANCA prevalence in CU group was 12/33 (36.4%), in CD group was 6/40 (15%), while in the C group all sera tested negative (0%), p-value = 0.004. All ANCA antibodies in patients with IBD were perinuclear. In CU group, the prevalence of pANCA was higher among females comparing to men (52.9% versus 16.7%; p = 0.04). In CU group, the phenotype pANCA+ didn't correlate with the disease extension, the severity, the evolutive form or complications. In CD group, the phenotype pANCA+ was more frequently found in colonic extension, but p-value insignificant (0.52), there was also a tendency for non-obstructive non-fistulizing forms to associate with pANCA + (p = 0.59). Higher severity of CD correlated well with higher pANCA titers (p = 0.05).

Conclusions: pANCA prevalence in UC in Romania was lower comparing with other studies from literature (36.4% versus 50-80%), with a higher prevalence among females with UC. In CD, pANCA+ is associated with a higher severity. pANCA determination stays as a research tool, it is necessary to enlarge the investigation.
Lactose intolerance in children with inflammatory bowel diseases

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Objective: Lactase deficiency is recently described in patients with inflammatory bowel disease (IBD), especially in Crohn's disease (CD), however results of researches vary between scientific publications.

Goal of this research was to investigate susceptibility for lactose intolerance in children with both types of IBD in our region.

Method: There were 33 (15 females and 18 males, aged 13-18; mean 16 years) IBD patients identified in period from January 2001 to December 2004 among children who were admitted to Gastroenterology Unit in University Children's Hospital in Katowice. The patients were divided in 2 groups: 11 had CD, 22 had ulcerative colitis (UC). All children were diagnosed to IBD according to a clinical picture, endoscopic image, small and large bowel pathological examination and laboratory and immune tests. In all children we investigated lactose malabsorption using the hydrogen breath test after ingestion of lactose (1.75 g per 1 kg of body mass maximum 50 g per dose). Hydrogen expiration was measured with Bedford Gastrolyzer. As a proof of hypolactasia we assumed the minimum 20 ppm hydrogen increase in breath air. The H₂ breath test results were compared to 30 healthy volunteers who underwent only H₂ breath test.

Results: The analysis revealed hypolactasia in 5 of 22 UC patients (22.7%) and in 3 of 11 CD children (27.3%) and in 7 of 30 (23.3%) healthy volunteers.

Conclusion: The lactase deficiency rate was similar in each group, so it seems there is no differences in lactose intolerance between IBD and general population.
Disease-free interval following strictureplasty for Crohn's disease

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Introduction: Strictureplasty is now well-established as a bowel-sparing alternative in the surgical treatment of complicated Crohn's disease. However, in patients with a single focus of disease, limited resection is still preferred, as subsequent re-operation rates are low. This study investigates whether reconstructive surgery may confer extended disease-free states in patients with uncomplicated Crohn's disease.

Methods: A retrospective review was undertaken of 26 patients who underwent surgery for small bowel Crohn's disease at our institution between 1996 and 2004. A total of 96 small bowel strictureplasties were performed. 19 patients had strictureplasties performed in isolation, while the remaining 7 patients had strictureplasty with concomitant limited resection. 3 strictureplasties involved the ileo-caecal junction. 14 strictureplasties were performed at previous sites of surgery. The mean number of strictureplasties carried out per patient was 3.1.

Results: There was no operative mortality. Median follow-up was 41 months. Four patients developed complications, requiring re-operation. 73.3% of patients undergoing strictureplasty alone and 79.7% undergoing strictureplasty with concomitant resection were disease-free at 41 months. If the follow-up were continued, the same proportion of patients remaining disease-free would be observed at an interval of 70 months or more. Four patients developed further recrudescence disease, and required additional surgery. 25% of these patients were disease-free at 41 months.

Discussion: Our results show that strictureplasty alone or with concomitant resection can confer disease-free periods of 41 months or more in 73.3% of patients, suggesting that strictureplasty can be utilised as an alternative to limited resection in uncomplicated Crohn's disease.
Strictureplasty for active Crohn's disease

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Background: Studies carried out over the last twenty years have confirmed the safety and efficacy of strictureplasty in the treatment of obstructive Crohn's Disease. However, most of these studies use strictureplasty to treat fibrotic strictures while limited resection is usually preferred to treat active disease strictures. This study investigated the complication and recrudescence rates, together with the disease-free intervals in patients undergoing strictureplasty for active disease strictures.

Methods: A retrospective review was undertaken of 14 patients who underwent surgery for active small bowel Crohn's disease between 1996 and 2004. Surgery involved strictureplasty alone or combined with limited resection. A total of 73 strictureplasties were carried out. The mean number of strictureplasties carried out per patient was 5.2

Results: There was no operative mortality. The median follow-up was 41 months. One patient (7.1%) developed complications requiring further surgery. Three patients developed further recrudescence disease and required surgery. Overall, 73.8% of patients undergoing strictureplasty were disease-free at 41 months. Extrapolating the disease-free curve further, if an extended follow-up interval were observed, the same proportion of patients would remain disease-free at 70 months or more.

Conclusions: Our results show that the use of strictureplasty in active disease strictures is safe, well tolerated, and has similar, if not better, complication rates when compared with limited resection in patients with similar disease profiles. Additionally, reconstructive surgery in 73.8% of these patients confers significant clinically disease-free intervals of three and a half years or more, comparing favourably with disease-free intervals reported following small bowel resection.
Thrombosis and Crohn's disease

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The risk of thrombosis is increased during inflammatory bowel disease (IBD). To illustrate this association, we bring back the observation of five patients having a Crohn's disease and a vascular thrombosis often without other etiology than IBD.

The patients were 2 males and 3 females with a mean age of 35.6 years. Thrombotic complication consisted in phlebitis of the lower member in four cases and an ischemic vascular accident (AVC) in a case.

In the setting of balance etiology, a deficit in C protein and in III antithrombin has been noted in a case, an essential thrombocytemia is recovered in a 2nd case. The evolution under anticoagulant treatment was favourable in all any cases. At the patient having a deficit in C protein and III antithrombin, a treatment by anti agrégant plaquettaire has been instituted to the long course.
Pathogenical aspects of the questions of classification of gastrointestinal tuberculosis

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The clinico-pathogenic variants of gastrointestinal tuberculosis have been studied at 62 patients since 1995. The diagnosis was verified in 89% morphologically (3544 autopsies, 131,380 lifetime biopsies), in 2.4% bacteriologically (Koch's bacilli in feces in the presence of ulcers in the distal sections of large intestine), in 8.6% clinically and thanks to the test of therapia exyvantibus. The diagnosis of tuberculosis of such localizations is very difficult because of the absence of clinical diagnostical important criterions and bases mainly on the morphological picture

According to the modern condition of the problem and own observations offer the working classification of the digestive organs - gastrointestinal tuberculosis.

Infectious period:
- primary
- secondary.

Involving of other systems:
- isolated (without the lesions of other systems);
- combined (with the lesions of other systems).

Prevalence:
- limited (single organ of the abdominal cavity);
- extended (two and more organs of the abdominal cavity).

Morphological manifestations:
- mainly the productive type of inflammation;
- mainly the exudato-alterative type of inflammation;
- mixed type of inflammation.

Pathogenesis:
- sputagenic;
- hematogenic;
- lymphogenic;
- lymphohematogenic;
- contact (by extent).
Localization:
- tuberculosis of esophagus;
- tuberculosis of stomach;
- tuberculosis of duodenum;
- tuberculosis of liver;
- tuberculosis of cholecyst;
- tuberculosis of pancreas;
- tuberculosis of spleen;
- tuberculosis of omentum;
- tuberculosis of peritoneum;
- tuberculosis of small intestine;
- tuberculosis of large intestine;
- tuberculosis of mesenteric lymph nodes.

Phase of process:
- active;
- inactive.
Granulomatous diseases of digestive apparatus

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The group of the granulomatous illnesses have made: tuberculosis of digestive apparatus (n = 62) - 0.05% (I group); Crohn's disease (n = 18) - 0.01% (II group); sarcoidosis with involving a liver and mesenteric lymph nodes (n = 8) - 0.006% (III group).

I group. The tuberculosis of digestive system was mono- and mainly poliorganal with the following structure: tubercular colitis at 39 (62.9%); ileocecal zone at 18 (29%); mesenteric lymph nodes at 48 (77.4%); peritoneum at 19 (30.6%); omentum at 2 (3.2%); stomach at 8 (12.9%); gullet at 3 (4.8%); liver and spleen at 21 (33.9%); cholecyst at 1 (1.6%); pancreas at 5 (8.1%). Took place the cachexia, fever, anemia, acceleration of SSE, lymphopenia, abdominal pain, diarrhea, hematoschizis, rare - arthritis, a combination to pulmonary tuberculosis in 72% cases.

II group. Clinic: anemia, acceleration of ESR, abdominal pain, diarrhea, weight loss, rare - hepatites, arthritis, purulent pararectal fistulas.

III group. Clinic: abdominal pain, hepatomegaly, ascites, intrathoracic lymphadenopathy, accompanied with pains in the breast, cough, proved with Ro.

68% of patients have died in I group, in II group - 22.2% of patients.

The epithelio-cellular granuloma was revealed morphologically at the patients of all groups.

In I group, in all struck organs on the different depth, in all layers of the hollow organs and on all thickness of the parenchyma of the liver, spleen, pancreas were found out specific granulomae with the lymph elements, Pirogov-Largengans's cells and caseous necrosis in the centre.

In II group, granulomae without Pirogov-Largengans's cells and without caseous necrosis settled down deeply, in submucous layer of the gut.

In III group granulomae in liver, intramesenteric lymph nodes with the prevalence over the lymph elements, individual Pirogov-Largengans's cells and without caseous necrosis.
Gastrointestinal tuberculosis in the structure of the tuberculosis: The modern status of the problem

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The number of cases of tuberculosis annually increases on 3.8-12.9% in the Russian federation since 1995. The level of morbidity with the extrapulmonary tuberculosis of different localizations is 3,572-3,876 on 100,000 population what is evidence of the inadequate diagnostics

Especially complicated diagnostic dilemma is about gastrointestinal tuberculosis (GIT), which is registered by official statistics as 3 localizations - intestines, peritoneum, mesenteric lymph nodes.

According to our data, the morbidity of GIT in the Ulyanovsk region is 0.365-0.648 and it's presented by monorganal and poliorganal specific lesions.

The basic diagnostic methods are morphological and bacteriological.

The structure of tuberculosis has been studied according to the materials of 3,544 autopsies and 131,380 lifetime biopsies for the period time 1995-2003

During the lifetime pulmonary and/or extrapulmonary tuberculosis was diagnosed in 0.39-0.43% of biopsy materials annually, more often meets in branches of surgery, urology, hematology of which pulmonary tuberculosis and extrapulmonary localizations make 92.63-7.37% cases conformably.

Under the analysis of autopsies a share of tuberculosis annually forms 2.92-5.6% of all dissections of which extrapulmonary forms make up to 14.74%.

The acute poliorganal hemato-disseminated tuberculosis (Landusy's sepsis) is verified at 2.11% died.

The structure of the extrapulmonary forms of tuberculosis is following: mesenteric lymph nodes - 4.8%; intestines - 4.21%; liver, spleen - 3.16%; peritoneum - 2.1%; esophagus, stomach - 0.1%; omentum - 0.03%; meninges - 2.11%; kidneys - 2.11%, peripheral lymphadenitis - 1.05%; osteoarticular - 1.05%. GIT is classified by morpho- and pathogenesis, localization, prevalence.

At 3.16% died the pulmonary tuberculosis was combined with malignant tumors: with pulmonary cancer in 2.11%, with hepatic cancer - initial hepatocellularis carcinoma - in 1.05%.
MDR1 and MRP1 expression in peripheral mononuclear cells in patients with inflammatory bowel disease

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Background: Most current drugs to treat inflammatory bowel disease (IBD) including corticosteroids, azathioprine, cyclosporine are substrates of ABC-MDR transporters. These proteins significantly alter intracellular drug availability and thus efficacy. Our aim was to determine the activity of these proteins in peripheral blood mononuclear cells, to screen individual transporter status and to determine the "THERANOSTIC" potential of testing MDR activity for personalized therapy of IBD.

Patients & Methods: twenty seven patients were included in the study: 18 patients had Crohn’s disease and 9 patients had ulcerative colitis. 33% of patients were non-responder, 41% of them were on current steroid therapy, 33% were in remission on steroid at the time of testing. Functional MDR assays were performed based on the Calcein-AM method by FACS. Lymphocytes were labeled by anti-human CD3, CD4, CD8, CD19, CD45 and monocytes by anti-human CD14 antibodies. In all cases MDR1 and MRP1 activity was assessed as described in the original assay (http://www.solvobiotech.com).

Results: MDR1 and MRP1 activity in patients with IBD was high in 81% of patients. Using a cut-off level of 35 > MAF for MRP1 activity in the CD8 positive subpopulation, none of the patients without history of steroid therapy was found positive compared to 14% of those with previous steroids. 22% of resistant cases were CD8+/MRP1 positive by MAF > 35 compared to 6% in clinical remission.

Conclusion: CD8+/MRP1 activity MAF > 35 confers a 3.67x risk for corticosteroid resistance. Testing MDR-function before starting steroids to induce remission in patients with a history of previous steroid therapy can help to select patients for an early aggressive approach. Controlled clinical studies should assess the THERANOSTIC potential of MDR-activity-testing to enable personalized therapy of IBD patients.
Peculiarities of extraintestinal manifestations of ulcerative colitis

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Purpose: To study peculiarities of clinical course of ulcerative colitis (UC) complicated with extraintestinal manifestations and to improve the results of treatment.

Methodology: 380 patients with relapses of ulcerative colitis (age from 18 to 65 years, 170 - males, 210 - females) were under observation. Clinical, X-ray, endoscopic, morphological, coprological, biochemical, immunological, microbiological, ultrasound methods were used. The frequency of extraintestinal manifestations of disease was analyzed. The level of catalase, superoxidodysmutase, histamine, ceruloplasmin, cathepsin D, seromucoids, general protein, erythrocytes resistance to peroxide action, amylase, and activity of fibrinogen degradation products in blood sera were determined.

Results: Pathology of hepatopancreobiliary system (cholecystitis, hepatitis, cholangitis, hepatosis, pancreatitis) were observed in 44.7% patients, pathology of upper part of gastrointestinal tract (oesophagitis, gastritis, duodenitis) - in 26.5%, stomatitis - in 9.2%, arthritis - in 5.8%, conjunctivitis - in 3.7%, skin changes (erythema nodosum, pyoderma gangrenosum) - in 3.2%. Extraintestinal manifestations of UC had correlations with severity, form, duration from the beginning of disease, length of colon lesion. Increase of peroxide oxidation of lipids and decrease of antioxidant defense promoted to high activity of inflammatory reaction and chronization of disease. Increase of histamine, cathepsin D, seromucoids and decrease of ceruloplasmin, catalase was determined. The treatment included Salofalk®, glycocorticoids, hepatoprotectors, enzymes, antioxidants. The performed treatment led to decrease of inflammation activity, improvement of endoscopic and morphological picture of colon mucosa, tendency to normalization of biochemical and immunological indices, disappearing of extraintestinal manifestations of UC.

Conclusions:

1. Extraintestinal manifestations were developed in patients with severe forms of UC, with duration of disease more than 10 years, with total and subtotal lesion of colon.
2. The most frequent extraintestinal manifestations of UC is hepatopancreobiliary pathology, which promote to metabolic intoxication syndrome, to changes of some biochemical indices and equilibrium in peroxide oxidation of lipids and antioxidant protection.
3. As addition to basic therapy of UC with extraintestinal manifestations it's reasonable to include hepatoprotectors, enzymes and antioxidants.
Evaluation of the effect of diagnostic criteria on initial and final diagnosis in follow-up of inflammatory bowel disease

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Purpose: Patients with a diagnosis of inflammatory bowel disease (IBD) on their initial visits can get a different diagnosis in their follow-up. Therefore, by observing a group of patients for a period of 1-3 years, we aimed (i) to prospectively evaluate parameters that contribute to determine the diagnosis of IBD, and (ii) to evaluate contribution of these parameters to the final diagnosis.

Method: Among 97 patients with preliminary diagnosis of chronic diarrhea and IBD, 69 of them (25 female, 44 male, average age 42.34) were clinically diagnosed as ulcerative colitis (UC) by microbiology, radiology, histopathology, and endoscopy. Their regular visits and surveys were prospectively examined.

Symptoms: For 13 of the 69 patients with UC, five diagnostic criteria did not overlap with each other. Colonoscopic and histopathologic diagnoses of these patients are shown in the table below. Out of 9 patients with infectious colitis (IC) as their initial diagnosis, 6 were found to be UC in control biopsy after their treatment. In 3 of these 6 patients, E. histolytica trophozooids were found in their initial diagnosis and they were diagnosed as IC in their histopathologic evaluation. However, the same patients, after amebiasis treatment, received an absolute diagnosis of UC in their follow-up histopathologic and endoscopic evaluation. In the second evaluation after follow-up and treatment of the 13 patients, 9 of them received the diagnosis of UC, 3 of them received the diagnosis of IC, and the other received gluten induced enteropathy as their final diagnosis. At the end, there was a change of 5.7% in the final diagnosis of 4 patients whom we discharged with a diagnosis of UC from the hospital.

In UC, colonoscopy had a sensitivity of 100%, a specificity of 75%, a positive predictive measure of 98%, a negative predictive measure of 100%. Also in UC, histopathology had a sensitivity of 86%, a specificity of 100%, a positive predictive measure 98%, a negative predictive measure of 30%.

Conclusion: Endoscopic and histopathologic evaluation alone is not sufficient for IBD diagnosis, and all criteria must be filled out for an absolute diagnosis. In the case of suspicion, by assigning a diagnosis of indeterminate colitis we can prevent incorrect diagnosis and treatment of the patients in the future if they present with similar symptoms to other centers. Since histopathologic IC in the initial diagnosis causes confusion with IBD, it must be re-evaluated after the treatment. Cases with amebiasis do not rule out the diagnosis of IBD. For EC cases with a clinical presentation of IBD, endoscopic and histopathologic control after the treatment must be performed to assure an absolute diagnosis.
<table>
<thead>
<tr>
<th>Ulcerative Colitis (UC)</th>
<th>Initial Diagnosis</th>
<th>Absolute Diagnosis</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UC</td>
<td>IC</td>
<td>Kr</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>10</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Histopathology</td>
<td>-</td>
<td>9</td>
<td>3</td>
</tr>
</tbody>
</table>

- UC: Ulcerative Colitis
- IC: Interfaceitis Colitis
- Kr: Karypectosis
- N: Normal
Efficacy of Saccharomyces boulardii on enterocolitis induced by indomethacin in the rat

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Background and aim: The aim of this study was to determine efficacy of SB on enterocolitis induced by indomethacin in rats.

Methods: Thirty two male Wistar albino rats were obtained from local experimental research laboratory. Enterocolitis was induced by the administration of indomethacin (7.5 mg/kg SC for 2 days) in all rats. Rats were randomly divided into 4 groups (Table).

<table>
<thead>
<tr>
<th>Group 1 (control) n=8</th>
<th>Group 2 n=8</th>
<th>Group 3 n=8</th>
<th>Group 4 n=8</th>
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<td>Saline N/G tube and/or SC</td>
<td>SB 1 mg/kg/d via N/G tube, 2x1</td>
<td>prednisolone 1 mg/kg/d, SC</td>
<td>SB 1 mg/kg/d, N/G tube, 2x1 and prednisolone 1 mg/kg/d, SC</td>
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SB: Saccharomyces boulardii, N/G: Nasogastric

Saline was given the same dose and by the same route as SB or prednisolone in group 1 (control group). All medications were given from the second day of administration of indomethacin for a period of 7 days. Rats were killed at the end of this time. The intestine and colon of rats were macroscopically and microscopically assessed according to the scoring systems and proliferating cell nuclear antigen (PCNA) ratio was measured. The tissue TNF-α, plasma IL-1beta, the tissue and plasma total sulphydryl (-SH) and the tissue and erythrocyte malondialdehyde (MDA) levels were determined.

Results: Macroscopic and microscopic pathologic scores, PCNA scores, weight loss, the tissue TNF-α, plasma IL-1beta, erythrocyte MDA, plasma and tissue –SH levels were not different between groups.

Discussion: There was no effect of prednisolone and/or SB on the enterocolitis induced by indomethacin in rats.
Implication of mast cells and neuronal structures in the etiopathogenesis of Crohn's disease

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Crohn's disease is a chronic form of intestinal inflammation, which is segmental, transmural, and granulomatous, and affects any part of the intestine, but most commonly it occurs in the distal ileum and proximal part of the colon. Over the past decade, attention has been paid to the role of neuronal structures and mast cells in regulating the inflammatory and immune responses in inflammatory bowel diseases. This study was aimed to investigate the chemical coding of neurons and neuronal fibres, as well as the distribution of mast cells in the intestine of patients with Crohn's disease.

Specimens from five patients with histologically confirmed Crohn's disease were investigated with immunocytochemical techniques for detection of substance P (SP), vasoactive intestinal polypeptide (VIP), and tryptase. Normal intestinal tissue, taken from three patients operated on for rectal carcinoma was used as a control. A significant increase in the number of tryptase positive mast cells was observed in all layers of the intestine with Crohn's disease with prevalence in the mucosa. The number of SP- and VIP-immunoreactive neurons was higher than in the controls. In addition, there was a chaotic display of nerve fibres containing the neuroactive substances VIP and SP with high frequency of enlarge varicosities in the circular muscle layer and in the submucosal and the serosa layer.

These results show quantitative and qualitative changes in the neurochemical composition of enteric nerve fibres and nerve cell bodies, and a significant increase in the number of mast cells in Crohn's ileum. These findings suggest that mast cells activation and nerve-immune interactions may have a significant role in the process of the inflammatory changes in Crohn's ileitis.

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The true extent of ulcerative colitis: Comparison of colonoscopy and histology from segmental biopsies

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Objective: To compare and correlate disease extent of ulcerative colitis on the basis of colonoscopy and histology from segmental colorectal biopsies.

Methods: Retrospective review of all patients with a diagnosis of ulcerative colitis made at a single tertiary level hospital from 1984-2003, who had colonoscopy with segmental colorectal biopsies. Diagnosis of UC was based on a clinical history of passing blood and mucus per rectum with diarrhoea, and confirmed by typical appearances on colonoscopy and histology, and response to therapy. Signs of disease on colonoscopy were erythema, loss of vascular pattern, mucosal edema, friability, granularity and ulceration. Histological assessment was made for chronic inflammation extending beyond the crypts, crypt destruction, epithelial regeneration, goblet cell depletion, metaplasia and atrophy.

Results: 572 colonoscopies and segmental biopsies on 477 patients were evaluated. On the basis of colonoscopy 37.6% had proctosigmoiditis, 26.7% had left sided disease and 35.7% had extensive disease and on histology only 25.2% had proctosigmoiditis, 25.7% had left sided disease and 49.1% had extensive disease. Colonoscopic extent was further than histological extent in 2.79% while the reverse was true in 22.55%. Agreement was noted in 74.66% of patients only and the kappa statistic used to compare the two was 0.617.

Conclusions: This study reveals discrepancies between endoscopic and histological assessment of extent of inflammation. Histological assessment increases the extent in more than a fifth of cases. This has prognostic importance with regards to treatment strategies, colectomy and risk of cancer.
Morphologic and clinical activity of Crohn's disease: Comparison with imaging

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**Purpose:** To compare enteroclysis, sonography and AgAb scintigraphy in diagnosing early and late ileocecal Crohn's disease (CD) and in assessing activity.

**Method:** Retrospective analysis of the studies of 54 patients (30 females, 24 males, 18-71 years) with verified CD (operation: 8, biopsy: 50 cases) located in the ileocecal region. All patients had enteroclysis, sonography with superior mesenteric artery flow measurement (SMA) and 45 of them underwent 99mTc AgAb immunoscintigraphy with scintigraphic activity index (ScAI) calculation. Activity was determined by 1) CDAI questionnaire and, 2) the presence of ulcerations or fistulas on enteroclysis. The results were compared.

**Results:** Overall sensitivity of enteroclysis, sonography, and immunoscintigraphy was 100%/89%/71%. In early Crohn's disease (12 cases) the sensitivities were 100%/75%/40%. I): No correlations with SMA-CDAI, ScAI-CDAI or SMA-ScAI were found. II): In detecting morphologically active disease immunoscintigraphy had 70%/33%, increased SMA flow 76%/100%, while wall thickening (> 3 mm) 92%/33% (sensitivity/specificity). Using combined sonographic criteria (presence of destroyed wall stratification, or detection of fistulas or abscesses, or increased SMA flow) 96%/100% (sensitivity/ specificity) could be obtained. Surgical indications (fistulas, abscesses, severe stenosis) were detected in 6, 8, and 1 case respectively by both enteroclysis and sonography.

**Conclusion:** Although the sensitivity of sonography in early CD is not sufficient for detecting suspected CD, for follow-up in advanced cases sonography could replace enteroclysis. Clinical activity may not be substituted by SMA flow or ScAI, but new combined sonographic criteria give excellent correlation with morphologic activity determined by enteroclysis. Sensitivity for detecting abscesses might compensate for missed fistulas.
Diagnosis, extent and CDAI in patients with Crohn's disease at presentation

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A retrospective study of 28 patients of our clinic with Crohn's disease was performed with regards to the method of diagnosis, extent of the disease, extraintestinal manifestations and CDAI at presentation.

Of the 28 patients, 17 were women (60%) and 11 - men (40%), with mean age 39.2 years (40.3 for women, 37.4 for men) and overall peak of incidence 20-29 years (26% of the patients), for women - also 20-29 years (29.4%), for men - 30-39 years (30%).

The diagnosis was established by endoscopy with or without histological examination in 81% of the patients and intraoperatively - in 19% of the patients. The diagnosis was confirmed by histology in 89% of the patients.

The extent of the disease was as follows: mouth - 1/27 (3.7%), esophagus - 0, stomach - 0, duodenum - 0, jejunum - 2/27 (7.5%), ileum - 12/27 (44%), caecum - 8/27 (30%), ascending colon - 5/27 (19%), transverse colon - 9/27 (33%), descending colon - 13/27 (48%), sigmoid colon - 17/27 (63%), rectum - 8/27 (30%).

Extraintestinal manifestations were registered in 9/24 patients (38%) and 1 of 24 patients had primary sclerosing cholangitis.

The CDAI at presentation was below 140 in 3 of 16 patients (19%), between 140 and 280 in 8 of 16 patients (50%) and above 280 in 5 of 16 patients (31%).

Key words: diagnosis, extent, presentation
Errors in diagnosis of colitic syndrome of noninfectious etiology in infection clinics

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The Grodno State Medical University, Republic of Belarus

Aim of study: Evaluation of errors in diagnosis of colitic syndrome (CS) of noninfectious etiology in patients treated at infection hospitals.

Materials and methods: From 2002 through 2003 1536 patients (aged 15-75) were admitted to the in-patient department with the diarrhea syndrome (DS). In 152 of them (9.9%) DS of infectious etiology has been ruled out upon admission at the reception ward. In 165 patients (10.7%) the diagnosis of DS of noninfectious etiology was made (80 males and 85 females).

Results obtained: Colitic syndrome (CS; colitis, enterocolitis, gastroenterocolitis) was diagnosed in 105 (63.6%) out of total 165 patients with DS of noninfectious etiology. Medium and old age patients with exacerbation of chronic diseases of gastrointestinal tract comprised the main study group (49.5%). Stool frequency in them did not exceed 3-5 times a day and no fever was noted. In 26.7% of cases surgical pathology has been diagnosed, i.e. acute appendicitis (4 patients), acute pancreatitis (8), acute intestinal obstruction (4), strangulated hernia (1), rectal cancer (5), suppurated ovarian cyst (2) and mesenteric ischemia (4). In these patients painful syndrome prevailed upon the DS. In 12.4% of patients colitic syndrome was caused by intestinal disbiosis and in 11.4% - helminthiasis.

60 patients with primary false diagnosis of DS of noninfectious etiology were later on diagnosed to have low quality alcohol-induced poisoning (13 patients), acute pyelonephritis (5), urolithiasis (3) acute respiratory infection (13), bronchitis (7), pneumonia (10), pulmonary tuberculosis (5), sepsis (2), hypertension stroke (2).

Conclusion: The results obtained speak in favor of hyper diagnosis of DS of infectious etiology in non-infectious patients, of high incidence of colitic syndrome in non-infectious patients. One should analyze not only separate symptoms and syndromes but their totality, rate of intensity as well as consistency in each individual patient. Errare humanum est, but needs to learn how to accept one's own errors in order not to make them again.
Pulmonary function test, high-resolution computed tomography findings and inflammatory bowel disease

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Aim: The association between inflammatory bowel disease and pulmonary involvement has not been well emphasized. The aim of this prospective study was to define features of pulmonary function test and high resolution computed tomography in inflammatory bowel disease patients and relation of these with disease activity.

Method: Fifty-two patients with inflammatory bowel disease (20 with Crohn’s disease and 32 with ulcerative colitis) were enrolled. The standard pulmonary function test and thorax high resolution computed tomography findings were investigated with respect to inflammatory bowel disease activity. Crohn’s disease activity index and Rachmilewitz endoscopic activity index for ulcerative colitis were used to assess disease activity. Medications used and smoking habit rate were also documented.

Results: A total of 6.25% of the subjects with ulcerative colitis and 25% of the subjects with Crohn’s disease showed an obstructive and/or restrictive ventilatory defect. A total of 50% of the subjects with ulcerative colitis and 60% of the subjects with Crohn’s disease showed abnormal findings in high resolution computed tomography. Pulmonary function test and high resolution computed tomography abnormalities were not significantly different between Crohn’s disease and ulcerative colitis. No significant difference related with inflammatory bowel disease activity was found (P > 0.05).

Conclusion: Findings of high resolution computed tomography and pulmonary function test were not different between ulcerative colitis and Crohn’s disease. Bowel disease activity did not seem to affect these measurements.

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Soluble RANKL/osteoprotegerin relationship to calcaneal quantitative ultrasonography in patients with inflammatory bowel disease

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Background/Aim: Inflammatory bowel disease (IBD) is frequently associated with metabolic bone disease and increased risk of fragile fractures. We hypothesized that low bone mineral density (BMD) in patients with IBD might be mediated through the osteoclastogenic factor RANKL (the ligand for receptor activator of NFkB), produced by activated T-lymphocytes. We further hypothesized that imbalance in RANKL/osteoprotegerin (OPG) regulation system might favour increased bone resorption. The aim of the present study was to evaluate plasma RANKL/OPG in relation to calcaneal quantitative ultrasonography.

Patients and Methods: Thirty-one patients with different stages of IBD (Crohn’s disease n = 20, ulcerative colitis n = 10, intermediate syn. n = 1; median age 33 yrs., range 18-63) and 20 healthy controls were recruited. The study examined calcaneal bone strength by using quantitative ultrasonography (QUS) measurement of the speed of sound (SOS) and broadband ultrasound attenuation (BUA). Immunoassay was performed to estimate sRANKL and OPG levels.

Results: IBD patients had significantly lower BUA (64 ± 14 vs 81 ± 20 dB/MHz, p = 0.007) and lower SOS (1524 ± 28 vs 1565 ± 37 m/sec, p = 0.0003) than controls. Calcaneal BUA was significantly but inversely associated with OPG measured in IBD group (r = -0.46, p = 0.009), whereas the relationship to total sRANKL/OPG complex was absent. In the whole study group, however, there was negative correlation between sRANKL and OPG (r = -0.39, p = 0.0047). A cut-off level of 61 dB/MHz for calcaneal BUA discriminated patients (n = 10) with t-score < -2.5, lower BMD (0.323 ± 0.06 vs 0.480 ± 0.07 g/cm²), and less of sRANKL/OPG complex (12.3 ± 5 vs 14.6 ± 5 pmol/l).

Conclusion: IBD patients had lower BUA and SOS than control group confirming osteopenia and osteoporosis as complications of IBD. This pilot study illustrates the importance of the relative abundance of RANKL compared with the levels of OPG for the low BMD.
Hyperbaric oxygen therapy as a part of treatment of ulcerative colitis

A. Uzunova, M. Karkamov, H. Uzunov, Z. Kirvicov
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The ulcerative colitis is difficult for treatment, with long duration and recidives, with many complications and invalidation. Hyperbaric oxygen therapy is up-to-date. The curative effect of hyperbaric oxygen therapy is a very important of tissue's hypoxia and compensates organ's reaction.

There were examined 64 patients with exacerbation's ulcerative colitis. All patients were treated by Salofalk® - 4 x 500 mg, enemas by Salofalk® and additional hyperbaric oxygen therapy.

The other group of patients with ulcerative colitis - /18/ we treated with hyperbaric oxygen therapy only.

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

There were made clinical retrace for: number of defecation, blood in faeces etc.

We have found endoscopical and clinical remission after treatment with Salofalk®, curative enemas and addition hyperbaric oxygen therapy in 81% of patients.

Hyperbaric oxygen therapy is useful as a part of treatment of ulcerative colitis in 81% of patients with ulcerative colitis, but hyperbaric oxygen therapy as only therapy is useful in 60% of patients with light's forms.
Changes in the upper part of alimentary tract in children with colitis

Sabina Wiecek, Urszula Grzybowska-Chlebowczyk, Maciej Kajor, Halina Wos
Department of Pediatrics, Silesian Medical University, Katowice, Poland

Introduction: The group of Inflammatory Bowel Disease comprises of ulcerative colitis, Lesniowski-Crohn’s disease and indetermined colitis. The common feature is unknown primary cause. In the course of these diseases inflammatory change can refer the various part of the alimentary tract.

The aim of study: The aim of the study was evaluation of macroscopic changes and histopathological in the upper part of the alimentary tract in children with various forms of colitis.

Materials and methods: We examined 84 children (41 boys - 48.8% and 43 girls - 51.2%), at the age between 2 years and 18 years (mean age- 14 years), in which on the base clinical picture, results of laboratory test, colonoscopy and histopathological examinations the colitis was diagnosed:
- in 12 children (14.3%) Lesniowski-Crohn’s disease
- in 23 children (27.4%) ulcerative colitis
- in 19 children (22.6%) colitis in the course of food allergy
- in 30 children (35.7%) indetermined colitis.
In all patients we did endoscopy of the upper part of alimentary tract with taking biopsy to histopathological examinations. The indication to do panendoscopy were: abdominal pain, suspicion of food allergy and/or malabsorption syndrome.

Results: Inflammatory changes in esophagus we found in 22 children (26%), stomach - in 53 patients (63%), however in duodenum in 47 children (56%). The most common change in the upper part of the alimentary tract we observed in children with Lesniowski-Crohn’s disease. In this group macroscopic esophagitis we found in 33%, gastritis 83.3%, however duodenitis in 33% of patients. In the histopathological examination the most often gastritis chronica superficialis was diagnosed and in 8/12 (66%) of children we observed partial atrophy of villi of small intestine. In patient with ulcerative colitis changes in the upper part of the alimentary tract occurred more rare, however in 60% of children gastritis was diagnosed, in the most confirmed by histopathological examination.

The similar often (in 2/3 examined) we observed inflammatory changes of stomach and duodenum in patients with colitis in the course of food allergy. In about 50% histopathological examination shown present of eosinophilic infiltrations in duodenum. The most little abnormalities in the upper part of the alimentary tract we found in patients with indetermined colitis. In all group of patients infection of Helicobacter pylori was observed in 8 children (8/84-9.5%) and in 10 children (12%) gastroesophageal reflux was diagnosed.

Conclusions: In all children with colitis it seems be purposeful doing endoscopy of upper part the alimentary tract with intake biopsy to histopathological examination with consideration on the large frequency occurring of inflammatory change. This examination can facilitate the establish the final diagnose and treatment.
The clinical course of lymphocytic colitis in children

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Introduction: Lymphocytic colitis is a rare disease, which together with collagenous colitis belong to microscopic inflammations of the large intestine. Its etiology is not clear. Mostly it is diagnosed in the sixth decade of life and very rarely in young people. With regard to an uncharacteristic clinical picture and normal macroscopic picture in colonoscopy diagnostic difficulties are frequent. The histopathological examinations of the large intestine biotopates is a conclusive examination.

The aim of the study was evaluation of clinical course of lymphocytic colitis in children.

Materials and methods: The analysis included 6 children (4 girls and 2 boys) aged 6-17 years (mean: 13.5 years). The diagnosis of lymphocytic colitis in these patients was based on clinical symptoms, the results of laboratory tests, the macroscopic picture in colonoscopy and, first of all, the histopathological examination of the large intestine.

Results: The majority of analysed patients were over 10 years old, only 1 child was under this age (6 years). In the clinical picture abdominal pains localized in the hypogastrium were predominant; diarrhea without any blood admixture and slight loss of body weight were also observed. Only in 1 case the deficiency of body weight was present (body weight 3-10 pc). In all children laboratory markers of the inflammatory process were negative. In 3 children colonoscopy did not reveal any abnormalities. In the rest of children there were small changes in the form of unclear blood vessels markings. In all patients the diagnosis of lymphocytic colitis was based on the result of the histopathological examination. Additionally, in 2 patients (33%) lactose intolerance was found. In 2 patients food allergy (to cow milk proteins and wheat) with accompanying eosinophilic infiltration within the small intestine were observed. In 2 patients the histopathological examination of the small intestine revealed the atrophy of intestinal villi - 3 A (according to Marsh), however, the immunological tests for celiac disease were negative. Treatment included: 5-ASA preparations, metronidazole, medicines regulating motor activity of the intestines, probiotics and, in selected cases, elimination diet. The improvement of ailments was achieved. The patients are the subjects of the Gastroenterological Outpatient Clinic.

Summary: In this report we would like to pay attention to a relatively rare disease, lymphocytic colitis in children. In all our patients this disease had a comparatively mild course. The clinical improvement was achieved after pharmacological and dietetic treatment. The crucial role of histopathological examination for a definite diagnosis should be stressed.
Experimental colitis and carcinogenesis in rats

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Background: There are some clinical studies showed connections between carcinoma and ulcerative colitis. Studies are related to experimental oncology.

Aim of the study was to test the risk of cancer development in experimental colitis in rats. The important value has especially adenoma to carcinoma sequence histologically proved. Additionally the dysplasia lesions (high and low grade) were evaluated as well.

Methods: 40 two months old inbred Wistar rats were used. The experiment consisted of two parts. First the colitis was developed and histologically proved. 2 cm of 4% acetic acid was used to rectal administration to create colitis. Six weekly series of acetic acid were given. The second part was carcinogenesis in two groups of animals. First group suffered from colitis the second were healthy subjects. As a carcinogen the AOM (azoxymethane) was used given intraperitoneally. Six series of weekly injections were used. The dosis was 15 mg/kg body weight.

Results: In both groups of carcinogen administration we achieve colonic adenocarcinoma (adequate 30% and 20%). Histological changes were more dynamic (including metastases to the liver) in group with colitis developed rats. Dysplastic lesions low and high grade coexisted with histologically proved carcinoma. The rectum and descendens colon was affected.

Conclusions:

1. Histologically proved adenocarcinoma coexisted with dysplastic lesions in experimental carcinogenesis.
2. Dysplasia precides carcinoma lesions.

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Recurrent nephrotic syndrome complicated with renal insufficiency following aminosalicylates in ulcerative colitis: A case report

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Background: In addition to more frequently seen interstitial nephritis, nephrotic syndrome due to minimal change disease have been reported in few patients with UC on mesalazine or sulphasalazine.

Case report: In December 2002 a 27-old woman with left sided UC diagnosed one year before and remission maintained with sulphasalazine was admitted to a district hospital with generalised oedemas accompanied with hypertension and a diagnosis of nephritic syndrome was made. Sulphasalazine was discontinued and proteinuria resolved. Due to colitis symptoms recurrence topical mesalazine was prescribed at discharge. One month later the patient was readmitted due to nephrotic syndrome recurrence complicated with renal insufficiency. Repeated haemodialysis was necessary and renal biopsy revealed minimal changes glomerulonephritis. Prednisone was introduced and topical mesalazine maintained. The next, mild nephrotic syndrome episode was observed in March 2003 and mesalazine was definitively discontinued. No recurrence of proteinuria has been observed since then.

She has been our patient since December 2003 when a severe ulcerative colitis attack occurred following discontinuation of steroids. Azathioprine was introduced and complete remission achieved.

Conclusion: This is the report on three nephrotic syndrome episodes timely related to oral and then topical treatment of sulphasalazine and mesalazine, respectively. This along with a follow up of 21 months without nephrotic syndrome recurrence indicates that both drugs were involved in glomerulonephritis development.
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