Inflammation in the Intestinal Tract: Pathogenesis and Treatment

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Abstracts
Poster Abstracts
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INFLAMMATION IN THE INTESTINAL TRACT: PATHOGENESIS AND TREATMENT

Kiev (Ukraine)
May 15 – 16, 2009

Scientific Organization:
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Session I

Pathogenesis of inflammatory bowel disease
Genetic basis of inflammatory bowel disease

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Family studies, especially concordance studies in twins, strongly suggested that both Crohn’s disease and ulcerative colitis were partly determined by genetic factors, with genetic influence being strongest in Crohn’s disease. In the 1990s, it became possible to link each disease to specific sites within the genome by studying the inheritance of microsatellites (repeat sequences of nucleotides found throughout the genome which are inherited like alleles) within multiply affected families. These studies suggested that some genes were common to both diseases but that there were also genes specific to Crohn’s disease and others that were specific to ulcerative colitis. Within the last 5 years, genome-wide association studies in which up to 500,000 single nucleotide polymorphisms are typed in very large cohorts of patients and controls have confirmed this hypothesis. Over 30 genes are now known to play a role but they are not all specifically identified. Nevertheless, for Crohn’s disease, several mutations have been described in genes encoding proteins that are involved in bacterial recognition whether via the adaptive immune system, the innate immune system or the process by which antigen and microbial organisms are degraded within the cell. This latter process is known as autophagy, is present in all cells and is primarily involved in the turnover of intracellular organelles. Thus, NOD2, ATG16L1 and IRGM, genes which are strongly associated with Crohn’s disease, are all involved in the autophagy pathway which supports the hypothesis that the disease represents an interaction between host genetic susceptibility and bacteria. In addition, there is increasing evidence that mutations in genes involved in the IL12–IL23 pathway are also associated with Crohn’s disease which may therefore imply differences in T cell function in patients with these mutations.
Clinical implications of genetic findings in inflammatory bowel disease

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

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

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

Genome-wide linkage analysis has demonstrated eight confirmed susceptibility regions with the one on chromosome 16 being most consistent between different populations. In 2001 three coding variations in the NOD2 gene were identified that are highly associated with development of the disease. All variants affect a part of the gene that codes for the leucin rich part of the protein that appears to be involved in bacteria induced activation of NFκB in macrophages and epithelial cells. Interestingly, the three diseases associated SNPs are never found on the same haplotype. In compound heterozygotes or homozygotes they result in a RR of > 35 to develop Crohn’s disease as an adult. A particular subphenotype with localization of the disease in the ileocecal region is highly associated with the variants in the NOD2 gene.

Variants in the NOD2 gene by far not explain the genetic risk for Crohn’s disease. DLG-5 is the example of a low-risk susceptibility gene with a modest associated odds ratio (1.2–1.5). Interestingly, the association signal appears to be confined to young males.
With the advent of high-density, genome wide association studies enormous progress has been made to discover the remaining disease genes. More than 35 disease genes have been identified unto today, which however still explain less than 30% of the total genetic risk. In addition to innate immune genes, cytokine response genes (e.g. IL-23R, IL12B, STAT3) and autophagy related genes (e.g. ATG16L1, IRGM) have been identified.

In ulcerative colitis GWAS studies are just at the beginning. The first two published studies pointed among several cytokine and macrophage function related genes point to a locus in the 3’ end of the IL10 gene. In this regard the IL-10 knockout mouse becomes interesting again that in its phenotype is closer to ulcerative colitis than Crohn’s disease.

The further exploration of Crohn’s disease and ulcerative colitis will result in genetic risk maps that are presently completed with amazing speed. The creation of a medical systems biology of disease will lead to new models and eventually new therapies. However, before a comprehensive view of the genetic risk map is reached etiologic discoveries remain interesting but are not yet helpful new tools for the clinician.
Mechanisms and functional implications of intestinal barrier defects

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Intestinal epithelial barrier defects, or increased paracellular permeability, were first reported in patients with Crohn’s disease (CD) over 25 years ago. The observations that increased permeability may herald disease relapse in patients with inactive disease suggests that impaired barrier function may contribute to disease progression. However, limited understanding of the mechanisms that create barrier defects in CD have made it impossible to determine whether increased permeability is a cause or effect of disease. It is now clear that inflammatory cytokines trigger intestinal barrier defects acutely, by cytoskeletal contraction, or chronically, via modulation of tight junction protein expression. Both mechanisms cause barrier dysfunction, but their effects on size- and charge-selectivity of the induced paracellular leak differ; the clinical ramifications of this distinction are not yet clear. Recent data using in vivo models demonstrate that cytoskeletally-mediated barrier dysfunction is sufficient to activate innate and adaptive components of mucosal immunity. Consistent with the presence of increased permeability in some healthy first-degree relatives of CD patients, these barrier defects are insufficient to cause disease in the absence of other stimuli. However, cytoskeletally-mediated barrier defects are sufficient to accelerate onset and increase severity of experimental inflammatory bowel disease. Thus, inflammatory cytokines can cause barrier defects and, conversely, barrier defects can activate the mucosal immune system. This raises the possibility that restoration of barrier function may be therapeutic in CD. Consistent with this hypothesis, emerging data indicate that inhibition of cytoskeletally-mediated barrier dysfunction may be able to prevent disease progression. In the future, barrier restoration may provide a non-immunosuppressive approach to maintaining clinical remission.
Therapeutic options to modulate barrier defects

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In IBD, epithelial barrier function is impaired contributing to diarrhea by a leak flux-mechanism and perpetuating inflammation by an increased luminal antigen uptake. The barrier is composed of the apical enterocyte membrane and the epithelial tight junction and can be affected by tight junction alterations, induction of epithelial apoptoses and gross lesions as well as by accelerated transcytotic antigen uptake. Tight junction strands are reduced in IBD and strand breaks appear. Several of the 24 claudins can be affected in IBD. Epithelial apoptotic rate has also been shown to be elevated causing focal lesions, e.g. already in early stages of UC. As far as regulation is concerned Th1-cytokines like TNFα and interferon-γ are important for Crohn’s disease, while Th2 responses are dominated by IL-13 and TNFα in UC. TNFα is known to induce tight junction alterations via different pathways including IP3/p-AKT and can also induce apoptosis. IL-13 does stimulate epithelial apoptosis as well and up-regulates claudin-2. Together with an IL-13 dependent restitution arrest this may explain why ulcer lesions are seen already early in ulcerative colitis but only in advanced stages of Crohn’s disease. Luminal antigen uptake occurs via tight junction discontinuities, epithelial gross lesions and endocytotically. The latter can be stimulated by interferon-γ. Therapeutically, anti-inflammatory remedies as e.g. TNFα-antibodies improve active IBD and in parallel repair barrier function. Again, this is assumed to be due to reduced cytokine release in active IBD, as result of immune cell apoptosis. Glucocorticoids can also affect immune cells in the mucosa and consequently interfere with tight junction regulation and apoptosis induction, as a result of which barrier dysfunction is improved in IBD. This action is usually interpreted to be the direct result of the anti-inflammatory influence. However, glucocorticoids can also influence gene expression in favor of anti-diarrheal actions. So far, there is no final evidence for a beneficial barrier role of glutamine in IBD, although it is an important metabolic fuel for enterocytes. In contrast, butyrate directly regulates claudin-2 expression and intensifies glucocorticoid effects supporting their beneficial role in IBD. Furthermore, nutritional food components can strengthen the epithelial barrier as e.g. flavonoids, since claudin-4 has e.g. been shown to be by up-regulation by quercetin. Finally, traditional drugs possess barrier protective effects as e.g. berberine. However, the inherent mechanisms are less well understood and may include inference with different intracellular signaling pathways of inflammation.
Immunoregulatory disturbances in IBD

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Over the past decade a major hypothesis has emerged for the etiopathogenesis of Inflammatory Bowel Disease (IBD). This hypothesis proposes that IBD represents a dysregulated mucosal immune response to antigens derived from the commensal microbiota in a genetically susceptible host, leading to proinflammatory cytokine (T helper 1, T helper 2, and T helper 17 cytokines) production over and above the response that is normally associated with tolerance and immunoregulation. Given that the genetic predisposition has increasingly been recognized to affect the regulation of innate and adaptive immunity, intestinal epithelial cell physiologic barrier function and the potential inappropriate access of antigens to the mucosal immune system through this dysfunctional barrier function, a key point in understanding IBD pathophysiology is to understand the immunoregulatory pathways associated with the intestinal immune system as they apply to IBD.

Inflammation that derives from an immune response involves a sequential cascade of events that start with the recognition of an antigen as foreign. Antigens which are derived from the subcellular fractions of host or microbial origin are detected and sampled by antigen-presenting cells (mediators of innate immunity), which present antigen breakdown products to T lymphocytes (mediators of adaptive immunity). This cross talk between a professional (dendritic cell, macrophage or B cell) or nonprofessional (intestinal epithelial cell) antigen presenting cell (APC) leads to the secretion of a variety of soluble mediators and an up-regulation of cell surface molecules in both the APC and T cell. These soluble mediators, the majority of which are called cytokines (for example tumor necrosis factor, interferon gamma, interleukin 13, interleukin 17) lead to the activation of a wide variety of cell types within tissues such as other leukocytes, epithelial cells, stromal cells and endothelial cells. Activation of endothelial cells leads to the recruitment (homing) of additional immune cells resulting in tissue infiltration, the production of inflammatory mediators and ultimately tissue injury.

The core of the origin of the immune response is therefore the relationship between antigen, APC and T cells. With regards to the antigen, it has several properties. Certain antigens especially those from microbes have the ability to bind directly to a variety of cell surface receptors on the APC resulting in their activation. These intact antigen structures which were primarily derived from microbes consist of bacterial DNA, bacterial proteins such as heat shock proteins, bacterial glycoproteins such as peptidoglycan, glycolipids such as lipopolysaccharide or bacterial proteins such as flagellin. Such intact bacterial antigens have the unique property of containing patterns that are repetitive and therefore hard-wired to bind receptors on the cell surface of professional and non professional of APCs; so called pattern recognition receptors (PRR). These PRRs are part of the innate immune response and their ligation leads to the activation of the APC. Examples of PRRs involved in innate immune responses on professional and non-professional APCs include toll-like receptors (TLR), NOD2 and others. Ligation of PRRs causes an up-regulation of a variety of cell surface receptors on the APC as well as the secretion of cytokines that foster and amplify the adaptive immune response. Thus cytokines derived from innate immunity mold subsequent adaptive immune responses.
Adaptive immune responses require a second characteristic from antigens. Certain bacterial antigens have additional properties. Upon ingestion by the professional or non-professional APC, some antigens such as polypeptide antigens, glycolipid antigens, glycoproteins or polysaccharides of bacteria can be processed, that is, broken up into smaller subunits. These smaller subunits which are largely degraded in endolysosomes and other specific intracellular compartments represent the so-called nominal antigens that are associated with adaptive immunity. They are nominal in that they derive from a larger, more complex antigen. For example in the case of a polypeptide, a polypeptide chain of several hundred amino acids can be broken into nine amino acid fragments for presentation by major histocompatibility complex class 1 molecules (HLA-A, B or C) or ten to twenty amino acid structures that bind MHC class 2 molecules (HLA-DR, DP or DQ). Presentation of these nominal microbial structures by antigen-presenting cells to T lymphocytes is associated with the initiation of the process associated with adaptive (acquired or specific) immunity associated with T cells and B cells. T cells secrete cytokines and provide killer function whereas B cells secrete immunoglobulins.

Innate immunity that is initiated by the interaction between specific types of antigens and PRRs, and adaptive immunity interact with one another with different outcomes depending on the type of antigen and the cells involved in the initial response. For instance, the factors that are induced by APC by PRR ligation (such as ligation of TLR-4 with lipopolysaccharide) lead to the secretion of cytokines such as interleukin-12 and IL-23 which amplify adaptive immune responses associated with T helper 1 (interferon gamma) and T helper 17 (interleukin-17) that characterize Crohn’s disease. On the other hand, other innate immune elements may lead to dendritic cell activation that fosters development of T helper 2 – like cells (e.g. natural killer T cells) that secrete cytokines such as IL-5 and IL-13 that foster the development of T helper 2 associated inflammation as seems to be characterized in ulcerative colitis. Still other cytokines secreted by APC such as tumor growth factor beta drive T regulatory cells which inhibit inflammation derived from T helper 1, T helper 2 and T helper 17 cells.

Therefore, immunogenetic pathways associated with innate and adaptive immunity, the cytokines secreted by innate and adaptive immune cells, the epithelial factors and leukocyte factors that are associated with inflammation and structures on the endothelium that regulate the recruitment of leukocytes defined potential pathways that are amenable to therapeutic manipulation in IBD.
Targeted therapies in IBD

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The pathogenesis of inflammatory bowel disease (IBD) is still not completely understood. However, the ongoing research of the last decade is allowing the hypothesis that in genetically predisposed individuals distinct environmental factors result in a dysregulation of the mucosal immune system and thus IBD. Until today the majority of patients are being treated with rather unspecific medications exerting suppressive effects on the mucosal immune system. Nevertheless, these substances including azathioprine and steroids have proven excellent efficacy for defined subgroups of patients.

However, the better understanding of the underlying pathogenesis resulted in the clinical development of novel therapeutic strategies with specific targets. The most prominent example being antibodies targeting tumor necrosis factor-α which are routinely administered in patients suffering from either Crohn’s disease or ulcerative colitis. A second strategy is targeting the protein subunit p40 which heterodimerizes either with p35 resulting in the pro-inflammatory cytokine IL-12 or with p19 thus forming the pro-inflammatory IL 23. Experimental data suggest a crucial role for both cytokines in experimental colitis. Various antibodies against p40 are currently in clinical trials for patients with Crohn’s disease. In areas of inflammation, the blood vessel endothelial cells up-regulate adhesion molecules resulting in the infiltration of leukocytes into the respective area. Natalizumab is blocking these adhesion molecules. Treatment with Natalizumab was associated with clinical improvement in patients with Crohn’s disease and has been approved in the US.

In summary, several therapeutic targets have already entered our clinical routine and have for some patients resulted in significant changes of the disease course.
Session II

Diagnostic approach in IBD
Mucosal healing: Impact on the natural course or therapeutic strategies

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Introduction: Mucosal healing (MH) is an important treatment goal in various gastrointestinal disorders, such as peptic ulcer and other chronic diseases. After the introduction of biologic treatment in Crohn’s disease (CD)\(^1\,^2\), MH was observed in a substantial number of patients, leading to the question if MH could be a general predictor of disease course or a main end point of efficacy in clinical trials\(^3\).

Impact on the natural course of IBD: In a prospectively followed incidence cohort\(^4\) of CD (n = 160) and ulcerative colitis (UC) (n = 410) patients in Norway, MH after one year of individual treatment, could be significantly associated with a subsequent low risk of colectomy in UC after 5 years and reduced risk of resections in CD after 10 years. In both groups, less inflammation and decreased steroid treatment was observed at 5 years. These observations may provide evidence for the use of endoscopic evaluation in clinical practice. Since this study was performed prior to the introduction of biologics, the results may indicate that MH may be obtained in a proportion of the patients even with conventional treatment, both in UC and CD.

Impact on therapeutic strategies: Although studies with conventional treatment, including immunosuppressants, have shown MH in a proportion of patients\(^4\,^5\), the lack of documentation of MH after treatment with systemic glucocorticosteroids, has not given reason to use this parameter as an ultimate goal of acute treatment in IBD, in spite of an obvious effect on global disease activity. This situation changed dramatically by the introduction of biologic treatment.

In the ACCENT I trial\(^1\), a significantly higher number of patients showed MH after scheduled treatment compared with episodic treatment with Infliximab\(^6\), suggesting a role for MH as a monitoring parameter during follow up. Moreover, patients with MH showed less demands for hospitalization and surgery\(^7\).

Recent investigations seem to indicate long term healing of the bowel mucosa can be achieved with immunosuppressives and anti-TNF treatment even beyond one year of scheduled treatment. Some studies in children also seem to support effect on MH up to one year after initiation of anti-TNF therapy, in at least 50% of the patients\(^8\).

Conclusion: UC and CD are chronic intermittently active diseases, and although MH may seem to be an important sign of efficacy in the acute stage, long term healing may be difficult to predict in each individual case. We do not completely know which additional factors besides drugs that are influencing on the healing process and which factors that are responsible for the maintenance of healing over time, and also, why in a substantial number of patients the mucosa does not heal. Nevertheless, our recent experience, based on follow up of population based cohorts and clinical trials, give reason to suggest MH as a sign of early response to treatment, as well as an indication for sustained medical treatment with immunosuppressives or biologics in. MH seems to be an important prognostic marker associated with reduced frequency of surgeries, hospitalizations and cost of health care in IBD, and implies an early top down strategy with potent drugs for subgroups of patients.
Moreover, it is not clear if MH in CD in general, may be a prognostic important sign regarding disease course and response to treatment. A prerequisite for the study of MH in CD, in general, would be to be able to perform a prospective follow up of a population based endoscopic study. We also wanted to study the prognostic impact of established healing after one year of treatment on the subsequent outcome of disease.

References:


Diagnostic approach to small bowel involvement in IBD: View of the endoscopist

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Traditionally small bowel (SB) Crohn’s disease (CD) has been diagnosed with radiological studies, namely an upper GI series with SB follow through (SBFT). Recent advances in endoscopic techniques have revolutionized the diagnostic approach of patients with suspected CD of the SB and in patients with known IBD.

Wireless capsule endoscopy (WCE) has become an important diagnostic tool for the evaluation of suspected CD of the SB or in patients with known IBD to rule out SB involvement. The greatest utility of WCE has been observed in cases of suspected CD, where the initial evaluation with upper and lower endoscopy and traditional radiographic techniques has failed to establish the diagnosis. WCE can detect SB involvement in CD, particularly early lesions that can be overlooked by traditional radiological studies. The sensitivity of diagnosing SB CD by WCE is superior to other endoscopic or radiological methods such as push enteroscopy, computed tomography or magnetic resonance enteroclysis. The utility of WCE in patients with known CD, indeterminate colitis and a select group of patients with ulcerative colitis can help to better define the diagnosis and extent of the disease and may lead to reclassification of IBD from UC/IC to definitive CD. In addition, previously diagnosed patients with CD may be found to have a more significant burden of SB disease. Taken together, this information may facilitate more targeted and effective therapies and potentially lead to better patient outcomes. A disadvantage of WCE is that it has a low specificity and the device may be retained in a strictured area of the SB.

Therapeutic balloon-assisted enteroscopy (BAE) using either the single or double balloon enteroscopy technique (which has essentially replaced push enteroscopy) have been successfully used to treat CD strictures, obtain biopsies from areas of SB involvement and even retrieving a retained capsule.
Diagnostic approach to small bowel involvement in IBD: View of the radiologist

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Small bowel imaging
Radiologic evaluation of patients with suspected as well as proven inflammatory bowel disease is a key element in managing the patient with special respect to determine surgical or non-surgical treatment options. The radiologic imaging modalities that are based on projection radiography are almost replaced by state-of-the-art cross sectional imaging, represented by computer tomography (CT) and magnetic resonance imaging (MRI). Cross sectional imaging has several important advantages over the classic radiologic procedures (Sellink enteroklysma). Cross sectional imaging is a very fast and investigator independent modality that is suitable for evaluation of the gastro-intestinal tract as well as extraintestinal complications (abscess, fistula, lymph node enlargement).

Recent advances in imaging technology have led to a significant improvement in diagnostic accuracy. Both time and spatial resolution have undergone extraordinary changes that have led to completely new implementations in abdominal imaging. Isotropic data acquisition in multislice CT allows for true 3-dimensional datasets from which multiple applications benefit: multiplanar reformats in virtually any plane without loss of resolution, multiphasic imaging for assessment of dynamic processes, and new applications such as virtual reconstructions that carry the potential to replace conventional radiography. MRI, on the other hand, can meanwhile assess not only morphologic changes in the abdomen, but it also allows for dynamic assessment of organ perfusion and even bowel motions. Both CT and MRI provide spatial resolution in the range of 1 mm, setting a new standard in abdominal imaging.

This lecture will illustrate the latest advances in imaging technology as well as their clinical usefulness in imaging the small bowel in inflammatory bowel disease. Furthermore, special attention will be given to staging the disease and detection of relevant complications.
Experience of capsule endoscopy in intestinal pathology

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**Background and aims:** Capsule endoscopy (CE) is a major advance in the investigation of small bowel diseases. This technology allows noninvasive visualization of the small bowel. The main indications for CE include obscure gastrointestinal bleeding, Crohn's disease, celiac disease, abnormal small bowel radiology, polyposis syndrome, chronic abdominal pain, malabsorption etc. At least the indications for CE are constantly expanding, currently there are very limited data evaluating the impact of CE findings on the clinical management of patients. The aim of this study was to examine how CE findings influences on following management of patients in terms of diagnostic and treatment strategy.

**Methods:** Physicians requesting CE were contacted before the examination and asked what their management recommendations would be if CE were not available. These responses were compared with management recommendations by the same requesting physician after CE. The end points assessed were change in overall management and specific change in diagnostic and treatment strategy.

**Results:** Responses were obtained from physicians before and after CE in 58 patients. Requesting physicians (n = 12) were composed of gastroenterologists (75%), surgeons (17%) and internists (8%). Physicians changed post-CE overall management plans in 43 (74.1%) of patients. Of this physicians, 9 (75%) did so as a result of CE findings. Post-CE diagnostic strategy was changed in 35 (60.3%) of patients; the diagnostic strategy was changed to less complex or decreased risk associated in 18 (51.4%) of patients and a more complex strategy in 4 (11.4%) of cases. Of those requesting physicians who changed their diagnostic strategy, 10 (83.3%) did so as a result of CE. Post-CE treatment strategy was changed in 18 (31%) of patients. This involved a less complex strategy in 4 (22.2%) of cases and a more complex strategy in 3 (16.6%) of cases.

**Conclusions:** Patients requesting CE changed management in the majority of patients on the basis of CE findings. Diagnostic strategy was changed in the majority of patients, and often a less complex approach was pursued. Treatment strategy wasn't changed in the majority of patients.
Significance of abdominal ultrasound in IBD

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Transabdominal ultrasound is most commonly used to examine the liver, hepatobiliary-pancreatic and urogenital tract. Its utility for imaging the intestinal tract was less well established in the past and considered more difficult. Improvements of technology and increasing experience with sonographic findings in a variety of intestinal diseases including inflammatory bowel disease (IBD), however, have contributed to firmly establish the role of ultrasound as a clinically important, non-invasive and widely available imaging modality. In addition, newer techniques such as Harmonic Imaging and contrast-enhanced ultrasound (CEUS) also have recently gained increasing attention.

Transabdominal ultrasound is clinically useful in detecting inflammatory bowel disease (initial diagnosis) by evaluating bowel wall thickness and surrounding structures including periintestinal inflammatory reaction, extent and localization of involved bowel segments and detection of extraluminal complications such as fistula, abscesses, carcinoma and ileus.

Transabdominal ultrasound presently is accepted as a clinically important first line tool in assessing patients with Crohn’s disease irrespective of their clinical symptoms and/or disease activity. It helps to better characterize the disease course in individual patients and can guide therapeutic decisions.

The topic of this review will provide an updated overview of the role of transabdominal ultrasound in IBD including Crohn’s disease, ulcerative colitis, tuberculosis and neutropenic colitis while summarizing the results of recent studies with special reference to sensitivity/specificity in detecting the disease and sonomorphologic features to evaluate disease activity and its luminal and extraluminal complications.
Session III

Differential diagnosis of chronic diarrhea
Celiac disease (cd) is a common inflammatory disorder of the small intestine (prevalence 1:70–1:200), characterized by destruction of the resorptive villi, which can lead to severe diarrhea and malabsorption. cd is triggered by the storage proteins (gluten) of wheat, barley or rye. The only available treatment is a life-long strict gluten-free diet. Nowadays, the majority (> 80%) of screening-detected celiacs shows no, minor or non-diarrhea associated clinical symptoms (clinically silent, oligosymptomatic or atypical cd). Oligosymptomatic cd is associated with anemia, osteoporosis and an often compromised wellbeing and quality of life. Atypical cd can manifest itself as peripheral neuropathy or ataxia, aphthous stomatitis, arthritis, infertility, hypertransaminasemia, and even liver failure. cd is frequently found in conjunction with classical autoimmune diseases, such as type 1 diabetes, autoimmune thyroiditis, autoimmune hepatitis, dermatitis herpetiformis and autoimmune alopecia. Patients with long-standing undetected and untreated cd are at risk to develop (diet) refractory cd, enteropathy associated T cell lymphoma, small bowel adenocarcinoma and other cancers of the gastrointestinal tract.

The enzyme tissue transglutaminase (tTG) has been identified as the autoantigen of cd. It is the main antigen of endomysial autoantibodies. IgA anti-tTG is an excellent predictor of cd in untreated patients, reaching sensitivities and specificities well above 95%, even in a setting of population screening. Together with a test for autoantibodies against deamidated gliadin peptides, these numbers approach 100%. Cd is the best defined human lymphocyte antigen (HLA)-linked disorder: (i) the trigger is well defined: at least fifty defined 9–13 amino acid long gluten peptides (gluten is the storage protein of wheat that comprises > 50 different gliadins and several structurally more distantly related glutenins); (ii) gluten peptides are presented via HLA-DQ2 or -DQ8 on macrophages, monocytes, dendritic cells and B cells to Th1 T cells that cause mucosal destruction; (iii) the autoantigen tTG deamidation certain glutamines in the gluten peptides and thus increases their affinity to HLA-DQ2 or DQ8.

In addition, another class of gluten peptides can fuel innate (immediate, pathogen-directed) immunity that triggers and maintains the adaptive (HLA-DQ2/DQ8-Th1 T cell-mediated) immune response or activates cytotoxic T lymphocytes. Different gluten peptides may stimulate innate immunity in intestinal epithelial cells or macrophages/dendritic cells.

Based on our increasing knowledge of cd pathogenesis, non-dietary therapies have become feasible. These are based on: (i) degradation of immunodominant gliadin peptides that resist intestinal proteases by use of prolyl-endopeptidases and germinating wheat or barley proteases; (ii) Decrease of intestinal permeability by blockade of the putative zonulin receptor with the octapeptide AT-1001; (iii) Inhibition of intestinal tTG activity by specific tTG-inhibitors; (iv) Inhibition of gluten-specific T-cell stimulation by peptides that only bind to HLA-DQ2 or -DQ8 but not to the gluten-specific T cell receptors; (v) Induction of oral tolerance to gluten; and (vi) Modulation or inhibition of proinflammatory cytokines in refractory cd or intestinal T cell lymphoma, e.g., by inhibition of the T cell intestinal homing receptor CCR9, or of IL-15.
Chronic diarrhea syndrome as high risk factor of gluten enteropathy

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Celiac disease (CD) is a small intestinal enteropathy resulted by disrupted immune response to wheat proteins (gliadins) and characterized of complete life-long gluten intolerance. There are no studies examined the prevalence and clinical features of CD in Ukraine, especially among adults. In our study 2761 adult gastroenterological patients inspected in the clinic of Internal Medicine Department №1, O. Bogomoletz National Medical University (Kyiv, Ukraine) within 2003–2008 years were observed. Mean age of pts was 35.43 years (range 15–75 years); female put together – 1525; male – 1236 persons. Clinical, laboratory and histological features of CD were evaluated.

The inclusion criteria comprised chronic diarrhea syndrome (23%), abdominal distension (16%), recurring abdominal pain without clear localization (13%), irritable bowel syndrome (15%); loss of weight or failure to thrive (13%) followed by fatigue (16%); chronic anemia, repeated skin eruptions; cereal intolerance, chronic fatigue, infertility and family history of CD.

All enrolled pts were randomized into the 3 groups according to the method of serological screening. Thereby serum antibodies to gliadin (AGA IgA), tissue transglutaminase (TTG IgA) and newly developed IgA and IgG antibodies to synthetic, deamidated gliadin-derived peptides and human tissue transglutaminase (DGP/hTTG) in human serum measured by ELISA were used. In the group 1 (AGA-screening) we found 183 seropositive (SP) cases. Mean titer of AGA was 63.14 (range 15.1–581.4) U/ml (figure greater than 15 U/ml considered positive). In group 2 (TTG – positive, with results greater than 12 U/ml) were detected 277 SP-pts with mean figure 47.32 (range 12–599.2) U/ml. In the third group (DGP/hTTG – screening) we detected 14 SP-cases (titers greater then 30 U/ml) with mean result 75.7 (range 34–157.5) U/ml. Female to male ratio composed 1.3. Mean age of SP-pts was 36.01 years. Small intestinal biopsy revealed that 56.7% of AGA-seropositive pts (n = 30) had typical lesion (types 2–3) according to the Marsh classification; 66.7% – in TTG – group (n = 30) and 92.3% in DGP/hTTG – group (n = 13). It is apparent that AGA and TTG give a high number of false positive results.

We performed that prevalence of CD in Ukraine is common among the pts with chronic diarrhea syndrome as predominant that should be kept in mind. Seroprevalence of CD depends on serological methods and commercial kits. Most accurate laboratory analysis – DGP/hTTG IgA and IgG – should be conducted in cases when biopsy cannot be performed.
Whipple's disease

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Whipple’s disease is a rare systemic infectious disorder caused by the actinomycete *Tropheryma whipplei*. This chronic disease, first described by Whipple as “intestinal lipodystrophy”, affects preferentially middle-aged white men who may present with weight loss, diarrhea, abdominal pain and arthralgia. Thus, it represents an important differential diagnosis of chronic diarrhea. A variety of other clinical patterns, such as involvement of the heart, lung, or central nervous system (CNS), are frequent. In addition, individuals with isolated heart valve involvement or asymptomatic carriers may be observed. The diagnosis often is established by small bowel biopsy, which is characterized by periodic acid-Schiff (PAS)-positive inclusions representing the causative bacteria. *T. whipplei* can be detected by specific polymerase chain reaction (PCR), immunohistochemistry or electron microscopy and has been cultured few years ago. Several studies show that subtle defects of the cell-mediated immunity exist in active and inactive Whipple’s disease which may predispose individuals with a certain HLA type to a clinical manifestation of *T. whipplei* infection. As confirmed in a recent controlled trial, most patients respond well to a prolonged antibiotic treatment, but some patients with relapsing disease or CNS manifestation may have a poor prognosis. In the presentation, the relevance of Whipple’s disease in the differential diagnosis of chronic diarrhea and the new findings of this enigmatic rare disorder will be discussed.
Microscopic colitis

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Microscopic colitis has been regarded as rare disease but has now emerged as a quite common cause of chronic non-bloody diarrhea, particularly in elderlies. Most common forms of microscopic colitis are collagenous (CC) and lymphocytic colitis (LC). Recent epidemiological evidence suggest an incidence of microscopic colitis similar to ulcerative colitis, and an incidence of CC and LC each comparable to Crohn’s disease. The clinical presentation of microscopic colitis is well described and includes chronic or recurrent watery diarrhea, nocturnal diarrhea, abdominal pain, weight loss, fatigue and fecal incontinence. Quality of life is substantially reduced in microscopic colitis. Clinical symptoms of microscopic colitis may overlap with those of diarrhea-predominant irritable bowel syndrome suggesting a potential rate of mis- or underdiagnosis of microscopic colitis.

CC and LC cannot be distinguished on clinical or endoscopic grounds, the macroscopic appearance of the colonic mucosa is usually normal. Thus, the diagnosis of CC and LC relies on the histological examination of multiple biopsies from the entire colon. In both CC and LC, there is chronic inflammation in the lamina propria. The histopathological hallmark of CC is a thickening of the subepithelial collagenous layer of ≥ 10 µm while the diagnosis of LC is based on increased number of intraepithelial lymphocytes (IEL) which should exceed 20 IEL/100 surface epithelial cells. The aetiology of microscopic colitis is largely unknown and likely multifactorial. Potential factors include genetics, infections, bile acids, drugs and autoimmunity.

Budesonide is currently the best documented treatment in both CC and LC. Three randomized placebo-controlled trials in CC and one in LC have shown that budesonide 9 mg daily significantly improves the patient’s clinical symptoms and quality of life. After withdrawal of treatment, many patients will suffer from clinical relapses. In these cases, recurrent treatment or prolonged maintenance treatment is usually required. Two randomized placebo-controlled trials have recently shown, that budesonide 6 mg daily effectively maintains clinical remission in the majority of patients. Controlled studies are also available for bismuth subsalicylate, prednisolone, Boswellia serrata extract and probiotics, however, results were either negative or inconclusive. Antidiarrheals, sulfasalazine, mesalazine or immunosuppressives have also been used but never been tested in controlled trials. Therefore, budesonide represents the treatment of choice in patients who are in need for effective therapy. Important tasks for the future will be to establish well-balanced long-term treatment strategies and to increase the awareness of microscopic colitis among clinicians and pathologists.
Session IV

Clinical manifestations of IBD
Arthritis in inflammatory bowel disease

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An extraintestinal manifestation (EIM) very often occurs in inflammatory bowel disease (IBD) patients. EIM modified natural course of ulcerative colitis (UC) and Crohn’s disease (CD), decreased quality of life in UC and CD patients. Joints lesions consist near one third of all EIM in IBD patients.

Aim of study to analyze clinical and laboratorial findings in IBD patients with joint’s EIM.

319 UC patients and 96 CD were examined. Among UC patients were 131 (41.1%) patients with distal UC, 102 (32.0%) patients suffered from left-side UC and 86 (26.9%) patients had total UC. 95 (29.8%) UC patients and 34 (35.4%) CD patients had joint’s EIM. Arthritis correlated with prevalence forms of IBD, more often were determined in patients with left-side and total UC (36 (35.3%) and 29 (33.7%) respectively). Arthralgia was prevalence sign of joint’s EIM in patients with distal UC.

Phenotypic signs of genetic predispositions to joints damage are connective tissue dysplasia (CTD), colon microbiocenosis and mucus barrier by a lectin histochemical test, quantitative and qualitative characteristic of stool culture, short chain fatty acids levels in stool of IBD patients were analyzed. Cytokines status with privilege cytokines profile changes was investigated. Following interleukins levels in blood were analyzed: IL-1, 2, 4, 6, 8, 10 and TNF.

CTD could be one of the main predisposed genetic factors have an influence on joints EIM in IBD. Modification of collagen synthesis in IBD patients could lead to important changes of connective tissue structure and function that affect on course and progress of disease. In IBD patients with arthritis more than 3 signs of CTD were found significantly often than in IBD patients without EIM (77.9% and 53.2% respectively p < 0.05)

In all IBD patients microbiocenosis modifications with decreasing quantity of Bifidobacteria, Lactobacilli and total E. coli, but increasing of facultative flora levels were found. At the same time in IBD patients with arthritis association of facultative flora were observed. In these patients Staphylococcus, Enterobacter in stool culture were found more often. These associations correlated with modification of short chain fatty acids level in stool and violations of colonocytes cells receptor’s condition with decreasing of staining intensity by lectins.

In all IBD patients cytokines imbalance with increasing of pro-inflammatory and decreasing of anti-inflammatory cytokines were found. Privilege cytokines profile changes in IBD patients with joints EIM were analyzed. Maximal increasing of IL-1 and TNF with decreasing IL-10 in plasma in patients with joints and EIM were observed.

Conclusions: 29.8% of UC patients and 35.4% CD patients had joints EIM and they had clinical microbiological and immunological peculiarities.
Joint involvement associated with IBD

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Joint involvement associated with IBD belongs to the concept of spondylarthritides (SpA) and includes two types of arthritis: a peripheral arthritis characterized by the presence of pauciarticular asymmetrical arthritis affecting preferentially joints of lower extremities and an axial arthropathy including inflammatory back pain, sacroiliitis and ankylosing spondylitis (AS). Prevalences of peripheral arthritis varies between 10% and 20%, inflammatory back pain between 20% and 30%, radiologic evidence of sacroiliitis around 30% and full diagnosis of ankylosing spondylitis according to Rome criteria around 4%.

Treatment of arthritis includes a short-term use of NSAIDs associated with optimised treatment of gut inflammation. Safety concerns mean that long-term treatment with NSAIDs is best avoided if possible. Salazopyrine can be recommended for treatment of peripheral arthritis. Methotrexate and azathioprine are generally ineffective. Finally efficacy of anti-TNF therapy (Infliximab and Adalimumab) is well established. However, use of Etanercept is not recommended because of the increased risk for intestinal disease relapse.

Pathogenesis of gut-joint interopathy is not elucidated. Both inflammations are tightly related as suggested by human evidence of gut inflammation in patients with other forms of spondylarthritides and animal evidence of gut and joint inflammation in HLAB27/human β2-microglobulin transgenic rat model and TNFΔARE mice. Several clues for the linkage between gut and joint inflammation have been put forwards including an altered recognition and handling of bacterial antigens, an aberrant trafficking of CD8+ T cells with an impaired Thelper type 1 cytokine profile and expression of αEb7 integrin, an altered trafficking of macrophages expressing CD163 and evidence of an increased angiogenesis. A transcriptome analysis of mucosal biopsies identified a set of 95 genes that are differentially expressed in both CD and SpA as compared with healthy controls suggesting common pathways*

TNF plays a key role in the pathogenesis of various arthritic diseases and IBD. Mesenchymal/myofibroblast-like cells may represent the local primary targets of TNF in the induction of gut and joint pathology. Selective expression of TNFRI on these cells seems to be sufficient to orchestrate the complete development of SpA-related pathologies at least in TNFDARE mice**.

Finally genetic susceptibility is probably required to develop these pathologies. Genotyping of AS patients provided evidence for an important overlap between determinants of inherited predisposition to CD and AS. The best documented common association is with an IL23R polymorphism although the exact role remains unexplored. In addition, evidence suggests that a number of recently identified CD-susceptibility loci are associated with AS.
Literature:


Can we modulate the clinical course of IBD by our current treatment strategies?

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Ulcerative colitis and Crohn’s disease are chronic disabling long-life diseases, diagnosed usually in very young people, disconcerting in their evolution, which may be disturbed by severe flares and anatomical complications requiring surgery. Until the very last years there was no clear indication that treatment was able to modify the long term natural history of the disease. In particular, there are no data demonstrating a clear improvement through the period 1950–2000 in disease activity, occurrence of complications and need for surgery, in spite of an increased use of immunosuppressants since the nineties. However, in both IBD, thiopurines and methotrexate are very efficient in about half the patients and in responders, may heal the mucosa and decrease the need for surgery. The apparent lack of effect of these immunosuppressants may be related to the fact that in the past, they were used too late in the course of the disease. Their early use in selected patients may have an impact on occurrence of severe flares and complications, and need for surgery. Moreover, anti-TNF now used for ten years in Crohn’s disease and for five years in ulcerative colitis demonstrated in two thirds of the patients a remarkable anatomic effect, healing the mucosa, closing fistulæ and preventing strictures. Infliximab does prevent endoscopic recurrence following ileal resection for Crohn’s disease. In a randomized trial including patients with recently diagnosed Crohn’s disease, early use of anti-TNF was associated with a lesser use of steroids and a better endoscopic result at two years but did not demonstrate a clear effect on disease activity when compared to the current step-up strategy. Actually because irreversible anatomical damage may develop during the first years of disease, there is a need to classify early in the course of the disease patients into three groups, those needing a major therapy (anti-TNF), those requiring classical immunosuppressants, and those with a benign disease. There is the need in the next few years to better define these subgroups and to compare different strategies within each group through randomized interventional studies.
In 2001 we observed male patient K., 25 years old, which suffered from primary sclerosing cholangitis (PSC) complicated with bacterial cholangitis and secondary biliary cirrhosis of the liver. 7 years ago there was made a diagnosis of non-specific ulcerative colitis (NUC) with predominant affection of sigmoid colon and rectum with minimal activity of the disease. During patient’s stay in the clinic NUC was in remission. Applied treatment using cephalosporins of III generation, metronidazole and ursodeoxycholic acid was ineffective. Anemia of mixed etiology (hemolytic and iron-deficient) grown progressively worse; additional symptoms appeared: significant arthralgia and myalgia, severe malabsorption. The patient died due to sepsis developed on the background of multiple abscesses of the liver.

Patient K. had brother (patient B.). They were monozygotic twins. Patient B. had NUC developed at the age of 16 years and its clinical course was more severe than in brother K.: exacerbations were more frequent, with significant bleeding; colonoscopy showed involvement of entire left half of the large intestine. Patient B. hadn’t clinical signs of PSC in 2001. In view of significant immunogenetic predisposition to PSC both brothers underwent immunogenotypic analysis, which revealed allele DR B1*1301. Biochemistry of patient B. showed elevation of ALP – 7 norms, GGT – 6 norms, ALT – 1.7 norms on the background of normal bilirubin level. At the time of the first examination patient B. had NUC in remission phase. Both brothers had p-ANCA in blood. Patient B. underwent liver biopsy twice – in 2001 and 2005. Results of the first biopsy: sclerosis and proliferation of bile duct epithelium, large cellular infiltrates around ducts. ERCP: sclerosing cholangiopancreatitis. Diagnosis of PSC in combination with NUC was produced. Starting from 2001 patient B. receives the follow treatment: Ursofalk® – 20 mg/kg constantly, Salofalk® – 1 g/day in courses of 6–7 months with interruptions for 2–3 months, Budenofalk® 6 mg/day constantly. Taking into account steatorrhea patient B. constantly takes Creon 120000 U F.I.P. per day. Results of the second biopsy: there was no PSC progression, but infiltration around ducts even decreased. There were no exacerbations of NUC during last 3 years.

Conclusion. It is necessary to study near relatives of patients with PSC especially in case if patient has monozygotic twin. In our clinic timely diagnosed PSC in one of the co-twins let us to improve course of the disease and to avoid complications.
Session V

Treatment algorithms in IBD (1)
The past decade has brought significant changes to the medical management of Crohn’s disease. At the same time that there has been a world-wide increase in the incidence and prevalence of Crohn’s disease there has been an evolution in the management, similar to therapeutic changes in other immune-mediated inflammatory disorders, towards individualized medicine with selection of patients for “early-aggressive” immune-directed therapies, including biologic therapies targeting tumor necrosis factor α. It should also be recognized that Crohn’s disease is a chronic condition requiring sequential therapy to induce and, then, maintain clinical remissions. The level of therapy needed to induce remissions will determine the effective maintenance strategies. Our end-points for therapy remain clinical although the ability to induce mucosal healing and modify the long-term course of Crohn’s disease offer future goals of therapy.

Despite debate regarding “top down” vs. “step-up” management approaches, it is most appropriate to consider the prognosis of patients based upon their presentation before determining a therapeutic approach. Approximately 50% of patients in population series have mild presentations of Crohn’s disease and never require corticosteroid therapy. In contrast patients presenting; at young ages, those with extensive disease, extraintestinal or transmural complications (i.e. fistulae), smokers, and patients who require systemic corticosteroids early in their course should be treated aggressively with early intervention with immunosuppressives or biologics.

Patients presenting with mild-moderate symptoms, without systemic complications, can be treated with aminosalicylates or non-systemic steroids. Antibiotics such as metronidazole or ciprofloxacin are appropriate for patients with uncomplicated perianal fistulae. If patients respond to aminosalicylates they can continue at the same dose for long-term maintenance. Patients who are treated successfully with budesonide-induction can be treated long-term with low-dose budesonide with monitoring for steroid-toxicity.

Individuals who fail to respond to therapy for mild-moderate disease or those presenting with moderate-severe disease require combination therapies to induce and maintain remission. There is strong evidence for either corticosteroid + thiopurines, corticosteroids + methotrexate, corticosteroids + infliximab, or infliximab + a thiopurine or methotrexate for induction therapy. The goal is long-term control without corticosteroids. Patients who fail steroid-weaning despite optimal dosing of a thiopurine or methotrexate should be treated with an anti-TNF agent and the immunosuppressant can be discontinued. While combination therapy has been demonstrated to be the most efficacious means of inducing remissions, monotherapy for maintenance therapy will minimize risks of long-term toxicities. (1–3)
References:


A number of factors have to be considered to choose the optimal therapy for a patient suffering from ulcerative colitis (UC). Similar to Crohn’s disease (CD) the disease activity and the severity of the flare are crucial factors for the appropriate choice of medication. Also the duration of the symptoms, the preceding therapy(ies), the disease history as well as the individual symptoms influence the therapy decision. In addition, the extent of the colitis should be taken into consideration. However, many patients may not receive the most effective therapy and their disease may remain active, leading to uncontrolled inflammation and potentially the development of complications.

The role and efficacy of topical therapy is frequently underestimated, or even ignored. A distal or left-sided UC with mild to moderate activity should be first treated topically. Rectally administrated steroids are superior as compared to placebo, however, 5-aminosalicylic acid (5-ASA) suppositories or enemas have been proven to be superior to topical steroids. First line treatment for mild to moderate-active left-sided colitis therefore is 5-ASA foam or enema. Due to their higher volume enemas usually are less well tolerated by the patients. In ulcerative proctitis 5-ASA suppositories should be used.

If the colitis extends beyond the left flexure the topical therapy should be combined with an oral 5-ASA preparation. The recommended duration of treatment is at least four weeks.

Upon failure of the topical therapy systemic steroids are used. A severe flare or manifestation of distal UC should be initially treated with oral systemic steroids if possible in combination with topical use of 5-ASA.

In pancolitis ulcerosa with mild to moderate activity oral 5-ASA should be given. 4 g 5-ASA are superior to 2 g. Recent studies suggest that the total dose can be taken at one time (e.g. in the morning). For severe colitis or in case of a lack of response to oral 5-ASA, systemic steroids given orally or intravenously are the treatment of choice (dosage 1 mg/kg body weight or 60 mg prednisolone equivalent). There is no generally accepted protocol for the tapering of oral steroid medication after patients achieve remission.

Patients with severe UC or toxic megacolon need to be hospitalized. Treatment should be discussed interdisciplinary between gastroenterologists and surgeons. A conservative approach is only acceptable if no indication for surgery exists. The basis of treatment in those cases is liquid and electrolyte substitution as well as parenteral nutrition – if necessary. Treatment options include intravenous steroids (e.g. 4 x 100 mg hydrocortisone i.v.), cyclosporine A (cyclosporine A: 2 mg/kg body weight, i.v. continuously over 24 hrs) or Infliximab (5 mg/kg body weight as initial dose, repeated applications after 2 and 6 weeks). Approx. 60–80% of the patients will have a benefit initially. However, on a long-term basis only for 40–50% of the patients a colectomy can be avoided.
In case of severe, chronically active UC the option of a colectomy should always be discussed with the patient. Immunosuppression with azathioprine/6-mercaptopurine (2–2.5 mg/kg body weight or 1–1.5 mg/kg body weight respectively) has been shown to be effective. Infliximab can be given, if a fast induction of remission is desired.

Whether relief or absence of clinical symptoms or mucosal healing should be our treatment goal will hopefully be answered by future studies.
Diagnostic and treatment algorithms of ulcerative colitis in Ukraine

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Standards of diagnostics and treatment of ulcerative colitis (UC) in Ukraine are based on world generally accepted approaches and include differentiated stage prescription of preparations in dependence on spreading of pathological process and character of the course of the disease. The promising trend in UC treatment is cytoprotectors using, which leading to the increase of resistance of mucosal epithelial cells of the bowels. Rebamipide is a novel agent with action like stimulation of mucosal epithelial cell regeneration by increasing the expression of epithelial growth factor.

25 patients with the average heavy course of the UC (the index of clinical activity 6–12; endoscopic index – 4 according to Rachmilewitz, 1989) divided into 3 groups depending on curative complexes: group I (n = 9) – mesalazine (tablets) 3 g/day and budesonide 9 mg/day for three taking; group II (n = 8) – mesalazine (granules) 3 g/day and budesonide 9 mg/day for one taking; group III (n = 8) – mesalazine (granules) 3 g/day and budesonide 9 mg/day for one taking and rebamipide 300 mg/day.

Clinical, endoscopic assessments were made at baseline and the end of the study and symptoms were recorded daily on a diary card. The primary end point was introduction of clinical remission and clinical improvement was also measured by the UC disease activity index.

The biggest number of patients at phase of clinical remission after 8 – weeks therapy were recorded in group III – 6 (75%), II – 5 (62.5%), I – 5 (55.6%). The duration of the clinical remission were in group I was 24.7 ± 1.4 days, II – 27.5 ± 1.7 days, III – 30.7 ± 1.8 days (p > 0.05). Endoscopic remission were detected in 3 (33.3%) patients of the group I, 4 (50%) of the group II, 5 (62.5%) of the group III.

The rise of concentration of N-acetylneuraminic acid (NANA) was detected from the patients of all the groups as well as decreasing in 1.8 times of the level of blood fucose connected with albumin. The prescription of curative complexes leads to reduction of NANA and fucose increasing in blood, what is significantly expressed in the group III.

Thus, optimization of the curative complexes with the substitution of the mesalazine in tablets on granules, especially with additional rebamipide prescription, in one time daily taking of budesonide leads to rising of the effectiveness of treatment and improvement of life spending quality in UC patients.
Infection with cytomegalovirus in patients with inflammatory bowel disease: Prevalence and clinical significance

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Despite frequent use of immunosuppressive drugs in patients with inflammatory bowel disease (IBD) and reports of cytomegalovirus (CMV) infection following post-transplant immunosuppression, data on the frequency and clinical significance of CMV in patients with IBD are scant.

Thirty patients with left-sided ulcerative colitis with moderate activity were evaluated for CMV using serology (IgM, IgG antibodies), PCR for CMV DNA in colonic biopsy and serum, histological assessment of haematoxylin and eosin-stained colonic biopsy.

Positive result in any test was considered as CMV infection. Various parameters associated with CMV infection were analysed using univariate and multivariate analysis.

Twenty of 30 (66%) patients (age 39.2 ± 10.8 years) were infected with CMV. Ten of 20 patients with CMV infection used immunosuppressive therapy.

Patients with CMV infection were more often female (13/20 vs. 4/10), had histological activity (15/20 vs. 5/10) and used immunosuppressive therapy (5/10 vs. 3/10). On multivariate analysis, female gender and histological activity were the independent factors associated with infection. PCR of colon biopsy was the most sensitive method of detection followed by IgM antibody for diagnosis.
Therapy and non-therapy-dependent infectious complications in IBD

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Patients with inflammatory bowel disease (IBD) are susceptible to infections. IBD may predispose to infectious complications independent from concurrent immunomodulatory therapy. Thus, the incidence of C. difficile infection is increased in IBD patients, and a significant proportion of these patients seems to develop C. difficile infection without precedent antibiotic use. Cytomegalievirus infection has been reported in corticosteroid-naive patients with ulcerative colitis and infectious gastroenteritis has been linked to initiation and exacerbation of IBD. Finally, in Crohn’s disease there is a substantial risk for abscess formation, and urinary tract infections occur more frequent than in a non-IBD control population. Apart from the disease process itself, factors that predispose to infectious complications in IBD are malnutrition, advanced age, immunosuppressive medications, leukopenia from immunosuppressive medications and surgery. However, the main risk for infections is clearly related to immunosuppressive therapy. Immunosuppressive medications commonly prescribed for treatment of IBD include corticosteroids, azathioprine, methotrexate, cyclosporine, and TNF-blocking biologicals like infliximab. A wide spectrum of infectious complications has been reported for IBD- and non-IBD patients using these medications, including viral (e.g. CMV, VZV, EBV), bacterial (e.g. Mycobacteria, Listeria, Staphylococci, E. coli) fungal (e.g. P. jiroveci, Aspergillus, Candida, Cryptococcus) and protozoal (Toxoplasma) pathogens. The greatest risks obviously relates to the combined use of immunomodulating agents rather than to individual drugs. The risk of infections is also aggravated by an insufficient immunization status as frequently observed in patients with IBD. Physicians treating patients with IBD must be aware of the risks for infectious complications in these patients as well as of strategies to minimize them.
Session VI

**Treatment algorithms in IBD (2)**
Surgical treatment of Crohn’s disease

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Aim of the study: to evaluate results of surgical treatment of Crohn’s disease in the specialized department.

Materials and methods: In the State Scientific Center of Coloproctology, between 2000–2008 years there were 372 patients with Crohn’s disease (CD) of different parts of the bowels: small intestine 71 (19.1%) patients, large intestine 130 (34.9%) patients, combined lesion of small and large intestines 171 (46.0%) patients. Out of them 126 (33.9%) patients were operated for lesion of the small intestine 52 patients, the large intestine 48 and 26 for combined lesion of the small and large intestines.

The indications for operation for CD of small intestine were strictures of the intestine in 22 cases (42.3%), internal fistulas in 19 (36.6%) cases, external fistulas of the small intestine in 11 (21.1%) cases. One stage resection of the affected part of the small intestine with the formation of primary anastomosis was performed in 24 (46.2%) patients. The existence of fistulas with leakage and perifocal inflammation, intestinal permeability impairment in 17 (32.7%) cases demanded to divide surgery in two stages. During the first stage the ileocecal segment was resected with formation of ileo- and ascendostomas. The reconstructive anastomoses were created within 2 after 4 months. The presence of interne and extern fistulas, extensive inflammation, and intestinal occlusion in 11 (21.1%) patients required to divide surgery into three stages. The first stage consists of defunction by loop ileostomy, the second stage performed after the reduction of inflammation in the period of 2–8 months and included ileocecal resection. The third stage was closure of ileostomy between 1–3 months after the second stage. The presence of perianal lesions was also the indication for the three stage surgery. Post-operative complications were developed in three cases: fluid collection in 1 case and ileus into 2 cases. All complication resolved conservatively. There was no mortality.

In cases of the lesions of the large intestine the indications for surgery were formation of intestinal strictures n = 2 (4.2%), internal and external fistulas of the colon n = 4 (8.3%), perianal lesions in 14 (29.2%) patients, toxic colitis with the development of severe metabolic disorders combined with fistulas and strictures of the large intestine.

Patients with strictures were undergone, in one case to the stricturoplasty, in the other resection of the left flexure of colon was used. In cases of surgery of the colon with fistulas, one operation was the two-way ileostoma with the subsequent resection of the affected section, 3 patients underwent single-stage operation of the resection of the affected colon section. In perianal cases patients underwent the so called operations of “switching off” and (if necessary) plastic operations on perineum with the subsequent closure of the ileostoma.

Patients with toxic colitis combined with lesions (n = 18) more often has multi-stage treatment. At the first stage, the defunctioning ileostomy with the subsequent resection of affected segment of the colon and of ileostomy closure. Ten patients had colon resection of the Mikulitch or Hartman type of surgery. After the reduction of inflammation it was possible to restore anal defecation in 18 patients; in 10 cases it was necessary to remove rectum and create permanent colostomy. The overall 70.9% of patients after CD surgery of the colon restored anal defecation.
In this group 9 patients had complications which were the lengthy period of operational wounds healing due to the low level of reparative processes. There was no mortality in this group of patients.

For treating of patients with combined lesions of small and large intestines the conservative methods were preferable. The indication for surgery was only in 20.6% of cases: 15 patients with perianal lesions, 4 patients with fistulas, 7 patients with strictures. The resection of affected bowel segments with formation of primary anastomosis was done in 10 patients, with formation of side anastomosis in 2 patients, resection with the formation of colostomy in 5 patients, with formation of ileostomy and colostomy in 9 patients. It was possible to regain anal defecations only in 16 (61%) cases of this group of patients.

Azathioprine 2 mg/kg and 5-aminosalicylic acid follow up period of 3–24 months. Recurrence of the disease after the resection of the small intestine was developed in 7 (13.5%) patients. The conservative therapy was effective in all patients and there was no need for surgery. In cases of large intestine lesions the recurrence of the disease was detected in 4 (8.3%) patients. One case necessitated a new ileostoma, another case required subtotal resection of colon and formation of stoma, in two cases conservative treatment was effective.

Thus, the indications for surgical treatment of the Crohn’s disease are complications of the disease, including perianal lesions.

Therefore the actual task is the search of adequate surgical tactics in cases of toxic colitis (Crohn’s disease), which also includes the preservance of anal defecation. Suggested surgical management and prophylaxis of recurrence alloy to minimize the recurrence of the disease in small intestine and colon as well.
Treatment algorithms in case of perianal complications of Crohn’s disease

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The aim of the study is to construct the algorithm of the treatment tactics, which would include modern conservative and surgical methods.

Materials and methods: Endoscopy under anesthesia, endorectal ultrasonography, histological and radiological examinations, MRT. During the last 22 years 310 patients with Crohn’s disease were treated in our clinic, and 144 of them had perianal complications. Among them 60 patients had fissura, 52 patients had fistula, and in 61 cases was observed perianal abscess. In 29 patients perianal abscess developed on the ground of fistulas and fissures.

Results: The treatment of perianal abscesses is opening and drainage, following by conservative treatment (local and systemic). Using conservative treatment for patients with fissura, clinical remission was attained in 45 (75%) of them; other 15 patients (25%) were operated by Maslyak’s method. We haven’t conducted surgical treatment of fissures in the last 5 years. On the basis of our experience we have used the following clinical tactic for the treatment of the patients with Crohn’s disease and perianal fistulas: phase I – general anti-inflammatory treatment by prednisolone, Salofalk®, metronidazole; local treatment by Salofalk® (rectal suspensions, suppositories) and dioxizol (emulsion); phase II – surgical treatment; phase III – general anti-inflammatory treatment using Salofalk®, azathioprine, metronidazole and ciprofloxacin, local treatment included usage of dioxizol, Salofalk® (suppositorium and foam) posterizan forte (unguent), metronidazole (gel). The 51 patients with fistulas were operated. When the malignization was confirmed, we conducted extirpation of rectum or colproctectomy. Recurrence of Crohn’s disease was observed in 65 patients (45.1%) during the first 2 years after the beginning of treatment, and in 128 patients (88.9%) – during 5 years. CDAI varied from 150 to 450. PCDAI was in the range of 5–20.

Conclusions:
1. Planned surgical treatment of the perianal complications requires complex examination of the gastrointestinal tract.
2. The fissures and the pararectal fistulas should be operated in the period of complete remission (clinical and endoscopic).
3. Surgical treatment of perianal complication should be microinvasive: noncutting seton, fistulotomy and advancement flap.
4. It is rational to use anti-TNF drugs, such as infliximab.
5. Incontinence and decrease of life quality appears due to aggressive local surgical treatment.
6. Colostomia and enterostomia in combination with systemic and local treatment is an effective method to achieve remission and decrease the frequency of recurrences in perianal Crohn’s disease.
Indications for surgical therapy in ulcerative colitis, results and complications

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Medical treatment, generally with medications taken orally or rectally, is the first therapeutic option for patients with ulcerative colitis. However, about 25–40% of patients with ulcerative colitis will require surgery during the course of their disease. It should be avoided to prolong every medical since they lead frequently to secondary infections and increase perioperative complications. Some people elect to have surgery if they experience chronic severe symptoms or if medical therapy fails to adequately control symptoms. Surgery may also become necessary if complications arise. Complications of ulcerative colitis which can require emergency surgical intervention include: perforation of the colon; massive bleeding in the colon; sudden, severe ulcerative colitis; toxic megacolon (in which the muscle wall of the colon dilates and bacteria and gases build up inside the colon).

The standard surgical procedure for ulcerative colitis is proctocolectomy. Unlike Crohn's disease, which can recur after surgery, ulcerative colitis is cured once the colon is removed. For many years, proctocolectomy has been performed along with an ileostomy. This procedure is still widely performed. However, about 20 years ago, a modification was made to eliminate the need for a continuous ostomy. The newer procedure, called ileoanal pouch anal anastomosis (IPAA) or restorative proctocolectomy, allows to remain continence for the patient. This procedure has become the most commonly performed surgical procedure for ulcerative colitis and is an attractive alternative for many patients. Most of these procedures can be performed laparoscopically. This reduces the invasiveness of the procedure and leads to faster postoperative recovery.

The restorative proctocolectomy is usually performed in two stages. In the first operation, the colon and rectum are removed, preserving the sphincter. The ileum is fashioned into a J-pouch and pulled down and connected to the anus. Because the newly formed pouch needs time to heal, a temporary ileostomy is also performed. Ten to twelve weeks after the initial surgery, the temporary ileostomy is closed. After the surgery, most people have on average six bowel movements per day. The two most common complications of restorative proctocolectomy are pouchitis and small bowel obstruction. About 8–10% of patients will have pouch failure, which requires removal of the pouch and conversion to a permanent ileostomy.

Contraindications to ileal pouch-anal procedures in patients with ulcerative colitis are few. An absolute contraindication is anal sphincter dysfunction. Preexisting incontinence due to neurologic impairment or other causes makes reservoir construction unnecessary and ileoanal pull-through inadvisable. Other contraindications include suspected Crohn’s disease. The diagnosis of ulcerative colitis must be certain before an ileal pouch reservoir is created in a patient with inflammatory bowel disease. The need for pelvic radiation is also a contraindication to pelvic reservoir construction. If rectal cancer is found at the time of exploration, end ileostomy should be performed in anticipation of postoperative pelvic irradiation. Radiation leads to pouch fibrosis and noncompliance, with resultant loss of reservoir function.
Laparoscopic management of IBD

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Laparoscopic treatment of Crohn’s disease

Introduction: The goal of the surgical treatment of Crohn’s disease is to improve quality of life. Surgery is generally reserved for patients who develop complications of the disease such as strictures and fistulas or who are unresponsive to or develop complications from aggressive medical therapy. Markedly thickened bowel loops, thickened and friable mesentery, inflammatory phlegmons, fistulas, abscesses, and adhesions from previous surgeries pose a surgical challenge to the laparoscopic approach.

Results: In 1996, Reissman et al. reported their early experience of laparoscopy in 29 patients with terminal ileitis [1]. A mean length of the hospital stay was 5.2 days and an overall morbidity rate was 10%. Further study of Reissman et al. assessed a series of 51 patients with Crohn’s disease [2]. The mean length of hospital stay was 5.1 days. The overall conversion and complication rates were 14% each, and there was no mortality. Alabaz et al. retrospectively compared the safety, outcome, and feasibility of laparoscopic assisted and conventional laparotomy for ileocolic resection in Crohn’s disease [3]. The length of hospitalization was significantly longer in the laparotomy group (9.6 vs. 7 days) with no difference in the morbidity rate (16.7% vs. 15.3%) and conversion (11%). Patients in the laparoscopically assisted group returned to work faster (3.7 weeks) compared with 8.2 weeks in the laparotomy group, had better cosmetic results and improved social and sexual lives. Hamel et al. showed the feasibility and safety of laparoscopically assisted subtotal colectomy in patients with Crohn’s disease compared to ileocolic resection [4]. Although there were more intraoperative complications in the subtotal colectomy group (29% vs. 7%), the hospital stay was similar (8.8 days) and the postoperative complication rate was not significantly different (29% and 18%, respectively). Laparoscopic management of Crohn’s disease is complicated by fistulas, abscess, or strictures and is therefore especially challenging. Watanabe and co-workers reviewed 25 laparoscopic operations in 20 patients with a total of 31 intestinal fistulas [5]. The complication and conversion rates were 16% each. The median hospital stay was 8 days. Duepree et al. compared 21 patients who had a laparoscopic ileocolic resection with 24 patients who had an open resection [6]. The median length of hospital stay was significantly shorter in the laparoscopic group compared to the open group (3 and 5 days, respectively). Resumption of oral intake and intestinal function were faster in the laparoscopic group and there was no difference in the complication rate between the groups (14.3% and 16.7%, respectively). Benoist and colleagues compared the postoperative outcome of 24 laparoscopic ileocolic resections with 32 open cases [7]. There were no significant differences between the two groups in the morbidity and mortality rates, operative time, resumption of bowel function, hospital stay, and postoperative morphine requirement.
Young-Fadok et al. matched 33 cases of laparoscopic ileocolic resections with 33 open resections [7]. They found significantly shorter length of hospital stay, a shorter period of narcotic use, and reduced time to regular diet in the laparoscopic group compared to the laparotomy group without any significant differences in the complication rates.

Long-term outcomes following laparoscopic ileocolic resections were assessed in several studies. Alabaz et al. reported significantly more symptomatic bowel obstructions in the laparotomy group compared to the laparoscopic group in a mean follow-up of 30 months (31% vs. 8%, respectively) [3]. Bergamaschi et al. compared 39 patients who underwent laparoscopic ileocolic resection with 53 patients who had previously undergone open resection by the same surgeons at the same institution in terms of small bowel obstruction and recurrence rates at a follow-up of 5 years [3]. They reported a significantly lower rate of small bowel obstruction following laparoscopy (11.1% vs. 35.4% following laparotomy) with no differences in the recurrence rates (27.7% and 29.1%, respectively).

Milsom et al. compared the short-term outcome of 31 patients in the laparoscopic group versus 29 in the laparotomy group [8]. They found a significantly faster recovery of pulmonary function and fewer minor complications in the laparoscopic group compared to the laparotomy group (13% and 28%, respectively). However, there were no significant differences in the amount of morphine used, return of bowel function parameters, or the median length of stay between the two groups.

Thaler et al. showed that long-term quality of life is significantly reduced in patients with CD at long-term follow-up after both laparoscopic and open surgery and lower than in the general healthy population [8]. Irrespective of the surgical procedure, recurrence was the single significant predictor of quality of life in this study.

Several studies have conducted economic analysis of surgery for ileocolic Crohn’s disease. Duepree et al. demonstrated significantly lower direct cost per case for the laparoscopic group compared to the open group [6]. Young-Fadok et al. showed significantly lower direct and indirect costs in the laparoscopic group compared to the laparotomy group [9].

Laparoscopic experience has improved over recent years. However, Hamel et al. showed no differences in either morbidity or conversion between the earlier and the latter time periods of the experience, suggesting maintenance of a plateau after the initial experience [10].

**Summary:** The laparoscopic approach to terminal ileal Crohn’s disease is feasible and safe even in cases complicated by fistulas or in patients with previous abdominal surgery or recurrent disease. This approach is associated with an increased operative time compared to laparotomy, however, offers significant advantages over open ileocolic resection in terms of pulmonary function, length of hospital stay, duration of postoperative ileus, cosmesis, postoperative small bowel obstruction, and early postoperative complications. Laparoscopy is also associated with decreased overall hospitalization costs and improved patient satisfaction. Therefore, the laparoscopic approach for patients with Crohn’s disease should be considered as the preferred operative approach.
Laparoscopic surgery for ulcerative colitis and familial adenomatous polyposis

The surgical approach to the treatment of mucosal ulcerative colitis (MUC) and familial adenomatous polyposis (FAP) has dramatically evolved, restorative proctocolectomy with the construction of an ileal reservoir emerged as the treatment of choice to manage these conditions [11, 12]. In the case of MUC, procedures like appendicostomy and ileostomy, aimed to decompress the colon, were followed by safe treatment options like subtotal colectomy and completion proctectomy [11]. For decades FAP, a condition with a 100% risk of colorectal cancer in untreated individuals, was managed with total proctocolectomy and permanent stoma, the only efficacious treatment to lower cancer mortality and morbidity [13]. However, living with a permanent stoma was not an attractive option for many of these patients and diverse attempts to avoid a permanent stoma were undertaken. Procedures like straight ileoanal anastomosis were performed in the mid 20th century but with poor functional outcomes [11, 14]. In 1976, Sir Alan Parks described the technique of ileal reservoir-anal anastomosis after total proctocolectomy in 8 patients with MUC, obtaining satisfactory results in 4 out of 5 patients available to follow up by the time of publication [12, 15]. During the last 30 years, restorative proctocolectomy with ileal pouch-anal anastomosis has become the standard surgical treatment for patients with MUC and FAP [11–13, 16–21] and several modifications to the original technique have been advocated including changes to the shape of the pouch itself [12, 13]. In the original technique, a transanal mucosectomy followed by a pouch-anal handsewn anastomosis was performed [12, 15]. Alternatively, closure of the rectum with a stapler and completion of the anastomosis with a circular stapler placed through the staple line – the so called double-stapling technique – was described by Knight and Griffen and was intended to preserve the anal transition zone (ATZ) hence achieving better functional results [11–13, 22]. Temporary diverting loop ileostomy has been routinely used as a protective measure. However, several studies have proposed the single stage pouch as a safe alternative [18, 23–25].

Laparoscopic surgery was originally introduced by gynecologists mainly with diagnostic purposes. General surgeons adopted this technique [26] and virtually all abdominal procedures have been successfully completed laparoscopically. Laparoscopic colectomy and ileal pouch-anal anastomosis (Lap-IPAA) for the treatment of MUC and FAP was intended to take advantage of the benefits of laparoscopy such as early bowel function recovery, decreased pain, less adhesions, shorter hospital stay and better cosmesis [13]. However, these benefits were not as obvious with such a complex and technically demanding undertaking. In 1992, Wexner et al [26], published the results of a prospective trial in which they compared the results of 5 patients who underwent open versus 5 patients who underwent laparoscopic assisted total abdominal colectomy. In this short, early series, parameters like length of surgery, length of ileus and hospital stay were longer for the laparoscopic group; no morbidity or mortality were seen. In another study by the same author [27], in which 5 patients with MUC were treated using the laparoscopic approach, operative time was significantly longer and only a shorter length of incision but no recognizable advantages in terms of morbidity or hospital length of stay were observed. Schmitt et al [28] compared duration of ileus and of hospitalization in 22 patients who underwent laparoscopic assisted colectomy and 20 age, gender, and diagnosis-matched controls who underwent standard colectomy and they found that neither the length of time for ileus resolution nor the length of hospitalization were...
reduced in the laparoscopic group concluding that laparoscopic-assisted IPAA failed to provide any of the theoretical advantages described for other laparoscopic procedures. Other series of patients with MUC or FAP treated with laparoscopic TPC + IPAA are listed in Table 1 [17, 18, 29–34]. Marcello et al [35] compared laparoscopic versus open restorative proctocolectomy by using a case-matched design that included 40 patients, 20 consecutive laparoscopic cases (13 mucosal ulcerative colitis, 7 familial adenomatous polyposis) and 20 open cases (13 mucosal ulcerative colitis, 7 familial adenomatous polyposis) and found that operative time was significantly longer but bowel function returned more quickly and the length of stay was shorter in laparoscopic cases. Dunker et al [16] matched sixteen patients who underwent a lap-assisted IPAA with 19 patients who had a conventional IPAA. No differences were found in functional outcome and quality of life and satisfaction with the cosmetic result of the scar was significantly higher in the laparoscopic-assisted group compared with the conventional group. They found that neither functional outcome nor quality of life of laparoscopic-assisted ileal pouch-anal anastomosis were different from conventional ileal pouch-anal anastomosis. In the long-term, better cosmesis was the most important advantage after laparoscopic surgery. In a case-control study, Marcello et al [36] published results in which 19 patients who underwent laparoscopic total colectomy were compared to 29 patients who underwent open total colectomy for acute colitis. This study aimed to determine the safety and efficacy of laparoscopic colectomy in patients in the acute setting when compared with those individuals undergoing conventional urgent colectomy. The authors found that operative times were significantly longer in the laparoscopic group but bowel function returned more quickly and the length of stay was shorter and therefore concluded that the technique was feasible and safe in patients with acute nonfulminant colitis and could lead to a faster recovery than conventional resection. Ky et al [18] addressed the issue of the feasibility of a one-stage laparoscopic-assisted restorative proctocolectomy in patients with MUC and FAP; 32 (29 MUC and 3 FAP) patients who underwent such a procedure over a 24-month period were followed up prospectively for short-term and long-term complications and functional outcome. The 11 postoperative complications included were 1 pelvic abscess, and 1 pouch leak requiring reoperation (1 temporary ileostomy and 1 transpouch drainage). In this study it was concluded that one-stage laparoscopic-assisted restorative proctocolectomy could be performed effectively and safely. In 2005 Larson et al [20] published the results of a study designed to assess the operative, functional, and quality of life outcomes in patients with MUC or FAP with a minimum of one year follow up after undergoing lap-assisted IPAA vs. open IPAA. Patients were matched by age, gender, body mass index, and indication. Postoperative morbidity occurred in 6% of the laparoscopic cases and 12% of the open cases. Functional outcome after a minimum of one year revealed equivalent median day and median nocturnal number of stools and quality of life was equivalent as well. It was concluded that the function and quality of life outcomes for patients undergoing laparoscopic-assisted ileal pouch-anal anastomosis seemed to be equivalent to the open experience. Also, in 2006 Larson et al [19] released their results on a study in which 100 Lap-IPAA patients were case matched to 200 open IPAA patients by age, operation, gender, date of operation, and body mass index and operative and postoperative outcomes at 90 days were compared. The laparoscopic conversion rate was 6%. Median operative time was longer for the Lap-IPAA group. Lap-IPAA patients had shorter median time to regular diet, time to ileostomy output, length of stay, and decreased IV narcotic use. Postoperative morbidity was
equivalent and readmission rates were equal. Authors concluded that LAP-IPAA is equivalent to open IPAA in terms of safety and feasibility. In addition, LAP-IPAA provided significant improvements in short-term recovery outcomes. Other series of patients with MUC or FAP treated with laparoscopic TPC + IPAA vs. open TPC + IPAA are grouped in Table 2 [28, 37, 38]. All of these studies have the common denominator of a highly skilled surgical team operating on very carefully selected patients.

Among the proved benefits of laparoscopic assisted restorative proctocolectomy and ileal pouch anal anastomosis for the treatment of mucosal ulcerative colitis and familial adenomatous polyposis are shorter length of hospital stay with shorter ileus and faster recovery and milder postoperative pain. In addition, a better cosmesis is attributable to this approach. On the other hand, significantly longer operative times have to be expected. However, due to the complexity of this procedure, a steep and longer learning curve is expected before it can be routinely and safely undertaken. Prospective randomized studies are optimal before this complex procedure can be considered the best option for the surgical management of these diseases.

Table 1

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N of pts</th>
<th>Mean OR time</th>
<th>Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tucker [34]</td>
<td>1995</td>
<td>4</td>
<td>5 h, 27 min</td>
<td>Not stated</td>
</tr>
<tr>
<td>Liu [31]</td>
<td>1995</td>
<td>5</td>
<td>8 h</td>
<td>20%</td>
</tr>
<tr>
<td>Hildebrandt [30]</td>
<td>1998</td>
<td>5</td>
<td>6 h</td>
<td>0</td>
</tr>
<tr>
<td>Santoro [33]</td>
<td>1999</td>
<td>5</td>
<td>6 h, 4 min</td>
<td>0</td>
</tr>
<tr>
<td>Pace [32]</td>
<td>2002</td>
<td>13</td>
<td>4 h, 25 min</td>
<td>46%</td>
</tr>
<tr>
<td>Hasegawa [29]</td>
<td>2002</td>
<td>18</td>
<td>6 h</td>
<td>33.3%</td>
</tr>
<tr>
<td>Ky [18]</td>
<td>2002</td>
<td>32</td>
<td>5 h, 15 min</td>
<td>34%</td>
</tr>
<tr>
<td>Kienle [17]</td>
<td>2003</td>
<td>59</td>
<td>5 h, 20 min</td>
<td>18%</td>
</tr>
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</table>
Table 2
TPC + IPAA
Laparoscopic vs. open. Other series

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Surgery</th>
<th>n</th>
<th>MUC/FAP</th>
<th>Op time</th>
<th>Morbidity %</th>
<th>Hosp Stay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schmitt</td>
<td>1994</td>
<td>Lap</td>
<td>22</td>
<td>16/6</td>
<td>240</td>
<td>68</td>
<td>8.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Open</td>
<td>20</td>
<td>15/5</td>
<td>120</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Araki</td>
<td>2001</td>
<td>Lap</td>
<td>21</td>
<td>21</td>
<td>215</td>
<td>33.3</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Open</td>
<td>11</td>
<td>11</td>
<td>198</td>
<td>45.5</td>
<td></td>
</tr>
<tr>
<td>Hashimoto</td>
<td>2001</td>
<td>Lap</td>
<td>11</td>
<td>6/5</td>
<td>443</td>
<td>64%</td>
<td>24.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Open</td>
<td>13</td>
<td>38%</td>
<td>422</td>
<td></td>
<td>31.3</td>
</tr>
</tbody>
</table>

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Session VII

Malignant transformation in IBD: Prevention – surveillance – treatment
Basic mechanisms of malignant transformation in intestinal inflammation

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A causal link between inflammation and cancer has been suspected for a long time but only over the recent years some of the basic underlying molecular mechanisms have been discovered. One of the main signaling pathways responsible for linking inflammation and cancer is the classical NF-κB activation pathway (Karin and Greten, 2005). NF-κB plays a dual role in inflammation-associated tumorigenesis: it can either directly control the survival of tumorigenic cells or indirectly in immune cells it regulates the transcription of a variety of pro-inflammatory cytokines, which in turn act in a paracrine manner on tumor cells thereby stimulating their growth (Greten et al., 2004). One of these NF-κB regulated and by immune cells secreted pro-inflammatory cytokines is IL-6. Therefore, we hypothesized that gp130-mediated activation of Stat3 in tumorigenic cells could be responsible for the pro-proliferative effects of IL-6. Using loss-of-function and gain-of-function mouse models in an inflammation-associated tumor model, we could demonstrate that IL-6 family cytokines indeed control Stat3 induced transcription of a variety of genes important for cell survival and proliferation of tumorigenic cells (Bollrath et al., 2009). Thus, Stat3 and NF-κB comprise the central signaling nodes in inflammation-associated cancers.

References:


Patients with inflammatory bowel disease (IBD) are at an increased risk for developing cancers of the gastrointestinal tract, particularly colorectal cancer (CRC). Because of the relative rarity of IBD in the general population, it has been difficult to quantify this risk; nonetheless, within particular subsets of IBD patients, the cumulative risk of developing neoplasia and CRC may be substantial. Nowadays, it is considered as an established fact that patients with longstanding ulcerative colitis (UC) are at an increased risk of developing colorectal cancer (CRC). Although data for CRC risk in Crohn's disease (CD) are not as extensive, it has been suggested that the risks are comparable to UC. Current strategies for the prevention and early detection of cancer in this high risk population are based on the concept of an inflammation-neoplasia-carcinoma sequence. To reduce CRC mortality in IBD, colonoscopic surveillance with random and targeted biopsies were recommended to detect early neoplasia. The success of a surveillance program depends on the identification of patients with neoplasia and timely referral for colectomy. A number of issues might counteract a surveillance system achieving its maximal effect (less than ideal agreement in the interpretation of biopsy specimens, sampling error by endoscopists, delays in referral to surgery, and patient drop-out among others). In survey studies in the US, UK and Germany it was shown that surveillance colonoscopy frequency and biopsy protocols have varied widely. One study suggested that at least 33 biopsies were required to maximise neoplasia discovery, but this has never been revisited. To encounter the problem of time and expense incurred with 30 or more biopsies novel endoscopic techniques emerged as a means to target biopsies and otherwise minimise random multiple biopsies. The introduction of chromoendoscopy, narrow band imaging or confocal endomicroscopy to facilitate targeted biopsies has become increasingly associated with enhanced neoplasia surveillance. However, there is only indirect evidence that such surveillance strategies are likely to be effective at reducing the risk of death from IBD-associated colorectal cancer. Further, new data revealed that surveillance strategies largely based upon disease duration delayed or missed a substantial number of patients with early CRC. Therefore, actual surveillance guidelines seem to be insufficient and need to be restructured.
New techniques in endoscopy

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Patients with a long-standing history of ulcerative colitis (> 8 years in pancolitis, > 15 years in left-sided colitis) have a significant risk for the development of colon cancer. To these patients at least one colonoscopy per year should be offered according to the national surveillance guidelines in patients with inflammatory bowel disease. In patients with long-standing Crohn’s disease and a history of inflammatory activity also in the colon the risk of colon cancer development is less documented. However, following the results of large meta-analysis these patients should also enter surveillance programs. During a surveillance colonoscopy with no or mild disease activity 4 tissue samples each 10 cm should be taken.

Beside high-resolution videoendoscopy the application of dyes applied via a spraying catheter are of additional diagnostic value with a factor 3–4 higher detection rate of intraepithelial neoplasia (IEN). We can differentiate absorptive dyes (methylene blue 0.1–0.5%, cresyl violet 0.2%) from contrast dyes (indigo carmine 0.2–0.4%). In daily practice classical panchromoeendoscopy is not widely accepted due to a relatively high time exposure for the procedure. It is under current evaluation if the use of computerized virtual chromoendoscopy techniques (NBI, FICE, High Line/HD+) has the same diagnostic output compared to classical spraying techniques. First data in a limited number of patients are promising and will potentially recognize a certain comparability of both methods.

The detection rate of IEN can be further improved by using in-vivo histology techniques. A combination of chromoendoscopy with confocal laser endomicroscopy (CLE) can detect 5-fold higher rates of IEN compared with random biopsy protocols. CLE is possible after injecting 2.5–5 ml fluorescein 10% intravenously. A confocal miniaturized laser with a defined wave-length of 488 nm generates in-vivo histology images up to a 1000-fold magnification. During ongoing endoscopy single cellular and subcellular tissue analysis from 0–250 µm in depth are visible (Pentax, Japan). In patients with ulcerative colitis targeted biopsies of mucosal areas suspicious of IEN can be identified directly while performing the colonoscopy.

An alternative technique to CLE is the miniprobe confocal laser microscopy. After the miniprobe is pleaded through a 2.8 mm working channel of any standard video endoscope the laser unit generates a confocal image with a high frame rate per second. Special attention towards this technology (Mauna Kea Technologies, France) has raised up since the company has developed a high resolution miniprobe device. However, comparable studies with the other techniques are under current evaluation.

Up to now, classical high resolution endoscopy with chromoendoscopy is evidence-based and should be used for routine surveillance colonoscopy. The detection rates of intraepithelial neoplasia can be further improved by using virtual chromoendoscopy and confocal laser endomicroscopy.
Diagnostic standards in pathology

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Inflammatory bowel disease (IBD) is associated with an increased risk for the development of colorectal adenocarcinoma. There is a strong relationship between the presence of dysplasia in patients with ulcerative colitis (UC) or Crohn’s disease (CD) and colon cancer. Thus, the differentiation between biopsies with reactive atypia, atypia indefinite for dysplasia, low-grade dysplasia and high-grade dysplasia is of great importance. Furthermore, distinction between dysplasia-associated lesions or masses (DALMs) and sporadic adenomas is crucial. Various features e.g. localization of the lesion, architecture, inflammation and immunohistochemical evaluation of additional markers e.g. p53, Ki-67 and beta-catenin may be helpful to solve this issue. Microsatellite instability (MSI) can be screened for by immunohistochemical labeling against mismatch repair gene products MLH1, MSH2 and MSH6 in cases of interest. In advanced colorectal cancer, molecular genetic analysis of colorectal cancer after dissection of tumor tissue yields best results regarding K-ras mutation status important the assessment of treatment response to monoclonal antibody therapy directed against the epidermal growth factor receptor (Cetuximab). Finally, the use of modern immunosuppressive therapies may go along with an increased susceptibility towards infections e.g. CMV colitis or Epstein-Barr-Virus (EBV) induced lymphoproliferative disorders and a high degree of awareness by clinicians and pathologists is required in order not to miss these life threatening complications of IBD.
Making sense of the endoscopic modalities for colitis-associated dysplasia and cancer

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Long-standing ulcerative colitis (UC) is well known to have risk factor for developing UC-associated cancer (UCAC) and dysplasia. Therefore, in high-risk patients with pancolitis or left-sided colitis, surveillance with colonoscopy is essential. Histologically diagnosed dysplasia from biopsied specimen has not merely been regarded as a precancerous lesion, but rather as a marker suggesting the existence of cancer cells at the other site of colonic mucosa. Thus, conventional surveillance guidelines in UC recommend random biopsy at multiple sites in colon. In this procedure, however, even 30 to 40 biopsy sites would sample less than 1% of the colonic mucosa regardless of a tremendous amount of time and effort. Furthermore, its detection rate is low with an estimate of at least 200,000 dollars required to detect 1 case of UCAC.

Here we analyzed the clinical features and macroscopic (endoscopic) findings including mucosal color of 43 cases (71 lesions) of UCAC and dysplasia diagnosed from target-biopsied specimen with retrospective follow-up in our hospital. Twenty six cases of 43 (60.1%) were in clinical active stage and all of 71 lesions had severely or moderately active inflammation around them. Fifty three lesions (74.6%) were located in the rectum and sigmoid colon. In 53 lesions of early UCAC and dysplasia, 42 lesions (79%) were protruded type, 11 lesions (21%) were superficial type, such as flat and/or depressed type. Most of lesions, especially in superficial type, were identified as red color shape.

Taking into consideration the problems with conventional surveillance, the Ministry of Health, Labor and Welfare requested a prospective study to evaluate detailed colonoscopy for surveillance. Eighteen institutions participated in the trial, and a total of 341 patients with either left-sided or total colitis more than 7 years of history underwent surveillance. (Inflamm Bowel Dis. 2008; 14: 259–264). Target biopsy specimens were taken during surveillance by conventional colonoscopy and chromoendoscopy. The mean number of biopsy specimens taken during surveillance was 4.5. UCAC/dysplasia was found in fourteen patients (4.1%). The detection rate of UCAC/dysplasia was almost comparable with the results from Western countries, which use Step biopsy during surveillance. Thus chromoendoscopy can be useful in detecting alterations in mucosal color and texture from the surrounding mucosa. This is important in identifying areas for targeted biopsy.

Colonoscopic surveillance in UC has been primarily targeted for detecting polypoid lesions. To further detect flat lesions, dye spraying is necessary to detect alterations in mucosal color and surface structure from the surrounding mucosa. Furthermore, new endoscopic techniques including magnifying endoscopy would have the key role for diagnosing UCAC/dysplasia in longstanding UC patients.
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POSTER ABSTRACTS

Poster Numbers 1 – 65

Author Index to Poster Abstracts
The effect of desferrioxamine as supplement to cefotaxime in the treatment of spontaneous bacterial peritonitis

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Aim: To assess the efficacy of the iron chelating agent desferrioxamine supplemented to the antibiotic therapy in the treatment of spontaneous bacterial peritonitis (SBP) in cirrhotic patients.

Patients and methods: Thirty patients admitted in In-patient units of the tropical disease department of Ain Shams University Hospitals and Tanta University Hospitals. During the period of October 2006 to October 2007 divided into two groups: Group I (n = 15) with SBP and receiving cefotaxime (1 g IV every 12 hours) alone and Group II (n = 15) with SBP receiving cefotaxime (1 g IV every 12 hours) with desferrioxamine (500 mg IM twice daily). All patients were monitored for seven days, their vital organs were screened and their ascitic fluid was assessed completely including microbiological investigations.

Results: The concomitant administration of desferrioxamine with cefotaxime significantly at \( p < 0.001 \) and \( p < 0.01 \) improved the therapeutic outcome and the cure rate after 5 days of treatment as compared to patients using cefotaxime only.

Conclusions: Desferrioxamine can improve the therapeutic outcome through reduction of the time required for complete cure (defined as resolution or disappearance of all signs and symptoms of SBP, detection of no bacteria in the peritoneal fluid, normalization of polymorphonuclear count) by preventing iron-induced organ damage and inhibiting bacterial growth.
Molecular and traditional techniques in the diagnosis of diarrheal disease in Gaza, Palestine

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Objectives: To determine the etiology of acute diarrhea in Palestinian children under 5 years of age and to improve knowledge of the etiology of gastrointestinal pathogens using traditional and molecular diagnostic techniques.

Materials and methods: Various common enteropathogens (viral, bacterial and parasites) associated with diarrhea were investigated by conventional and molecular techniques (PCR) in 150 children less than 5 years of age admitted to the Central Pediatric Hospital, Gaza Strip, Palestine.

Results: The occurrence of enteropathogens identified was as follows: rotavirus 42/150 (28%), Entamoeba histolytica/dispar 23/150 (15%), Shigella spp. 9/150 (6%), Campylobacter coli/jejuni and Escherichia coli O157:H7 7/150 (5%) each, Salmonella spp. 3/150 (2%), Giardia intestinalis 1/150 (1%), and Strongyloides stercoralis 1/150 (1%) of the samples. Shigella and Salmonella isolates were tested for their susceptibility to common antimicrobial agents and most of the isolates were resistant to ampicillin and trimethoprim/sulfamethoxazole.

Conclusion: This study demonstrated that rotavirus, E. coli O157:H7 and Campylobacter, which are not routinely screened for in Gaza Strip, were significant enteropathogens. The results highlight the value of using a combination of traditional and PCR techniques in the diagnosis of enteropathogens related to gastroenteritis.
A primary colon tuberculosis case presenting with hematochezia and mimicking Crohn’s disease: Case report

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Tuberculosis (TB) is a widely prevalent, chronic, granulomatous, multisystem disease. It has been reported that colonic involvement. In intestinal tuberculosis, massive melena is extremely uncommon and hematochezia was described a few case. The differential diagnosis of CD and intestinal Tbc is a dilemma.

A 56-year-old woman was admitted to hospital with massive hematochezia. On admission, physical examination was unremarkable other than a mild tenderness in the abdomen. Laboratory analysis revealed a hemoglobin count of 11.4 g/dl and erythrocyte sedimentation rate of 59 mm/h. Other biochemical analyses were normal. Past medical history revealed a weight loss within the last months and fever. Colonoscopy revealed ulcers around the appendiceal orifice and in the sigmoid colon and terminal ileum was normal. Upper gastrointestinal endoscopy was normal. Histopathologic examination obtained from the margin of the ulcers showed mixed inflammatory infiltrate of the lamina propria, non-caseating granulomas in the mucosa and submucosa. Computed tomography (CT) of the abdomen showed dilated intestinal loops. Barium enema of the small bowel was normal. Chest X ray was normal. With these findings a diagnosis of CD was reached and was placed on Mesalazine treatment. At a follow-up visit two months after the discharge, laboratory analysis revealed an increase in erythrocyte sedimentation rate (73 mm/hr) and alkaline phosphatase level (431 Units/L). A repeat colonoscopy was performed which revealed the same endoscopic findings with the same histopathology. Azathioprine (100 mg/day) was added to mesalazine treatment. Four months later the patient complained of abdominal pain and weight loss. CT of the abdomen revealed multiple nodular collections in the abdominal wall, intramural gastric abscess, and an abscess in the left upper quadrant compressing the stomach. Exploration of the abdomen revealed multiple abscesses and nodular lesions on the peritoneal surfaces, liver, mesenterium and stomach. Histopathologic examination of the biopsy specimens obtained during surgery revealed caseification necrosis. Culture of the biopsy specimens was positive for Mycobacterium tuberculosis. The patient received anti tuberculous treatment for 9 months. Physical examination, laboratory analysis and control colonoscopy at the end of the treatment was normal

Lower gastrointestinal bleeding is an infrequent presentation of both CD and intestinal TB. As prognosis and treatment of CD and TB are different, it is extremely important to make an accurate differential diagnosis for the two diseases.
Cancer antigen 125 levels in inflammatory bowel diseases

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**Background:** Cancer antigen 125 (CA-125) is a tumor marker used for the diagnosis and monitoring of ovarian carcinoma. It can also be elevated in endometriosis, inflammations and in non-gynecological malignancies. Up to date, serum CA-125 levels in inflammatory bowel diseases (IBD) have not been studied before. Aim was to assess the levels of CA-125 in patients with ulcerative colitis (UC) and Crohn’s disease (CD).

**Methods:** Serum levels of CA-125 were investigated in 68 cases with UC (mean age: 42; male/female: 47/21), 32 CD (mean age: 41; male/female: 21/11) and 21 healthy controls (mean age: 42; male/female: 6/15). Levels of CA-125 were also compared among UC patients according to lesion location, severity and activity of CD.

**Results:** Serum CA-125 levels were 17.2 U/ml (2.9–195.6), 15.5 U/ml (4.2–117.6), 8.7 U/ml (3.6–14.1) in patients with UC, CD and healthy controls, respectively. Serum CA-125 levels were significantly higher in UC compared to control group (p: 0.001). Serum CA-125 levels were higher in Crohn’s disease patients compared to control group but there was no significance (p: 0.1). Serum CA-125 levels were higher in pancolitis compared to distal type and left-sided UC.

**Conclusions:** Our data suggest that CA-125 may be a serum marker for the diagnosis of inflammatory bowel disease.
**Inflammatory bowel disease in a Norwegian population-based twin cohort**

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**Introduction:** The relative risk for development of concordant disease among co-twins of twins with inflammatory bowel disease (IBD) was compared to the relative risk of concordant disease among ordinary siblings of patients with IBD. Furthermore, we wanted to explore the risk for development of IBD among twins related to perinatal factors.

**Methods:** Patients with IBD, enrolled in an incidence study 1990 to 1994, and twins with IBD were identified from the Norwegian national birth registry, which was established in 1967. The diagnosis of IBD was confirmed by hospital records.

**Results:** Twenty four twin pairs, 8 monozygotic and 16 dizygotic pairs, in which at least one claimed to have IBD, were recruited and compared to 84 patients of Crohn’s disease (CD) and 87 of ulcerative colitis (UC) from the incidence study. Based on the population prevalence of CD (262/100,000) and UC (505/100,000), the relative risks for concordant disease in MZ pairs were estimated to 95.4 (95% CI: 73.3, 114.6) and 49.5 (95% CI: 35.7, 63.3) in CD and UC, respectively. The corresponding risks in DZ pairs were 42.4 (95% CI: 29.6, 55.2) and 0.0. Among ordinary siblings of CD and UC the risks for concordance were 22.7 (95% CI: 3.3, 41.9) and 4.5 (95% CI: 0.0, 10.9), respectively. The first-born twin in pairs discordant for disease, 12 out of 19 (63.2%), tended to be affected by IBD (p = 0.10).

**Discussion/Conclusion:** Our study confirmed the importance of genetic influence on the development of CD. The risk among DZ twins for concordant disease was twice as high as among ordinary sibling, which might underscore the importance of share environmental factors in uteri and later in life. Perinatal factors like bacterial colonization of the gut seem to influence the development of IBD.
Metabolic alterations and redox homeostasis in IBD

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Introduction: A lot of incorrect pieces of information are spread all over the world by papers, and by other media about the effectiveness of antioxidant consumption and functional foods and their connection to human health prevention.

Methods: Although nobody never examines the redox homeostasis from this point of view, because of expenses, we offer a cost efficient simple methodological triad “DPPH radical scavenging ability, reducing power and induced chemiluminescent intensity” in plasma and erythrocytes as a program to evaluate the individual requirements for correct self control.

Results: 1. So far we could make a difference of inactive, moderate and severe phase during applied therapy in IBD patients vs. healthy controls. 2. We could find a seasonal circadian rhythm in the measured parameters of patients. 3. We also could pick the deviant food consumers among patients. These results were correlated with laboratory parameters and element concentrations of Caucasian IBD patients (n = 194) and healthy volunteers (n = 34) in both genders. The scavenging function of erythrocyte is significantly lower in the severe and moderate phases of Crohn’s disease and slightly lower in the inactive stage. Similar to the control, the patients with inactive ulcerative colitis have a better redox status of erythrocytes. During summer months both defence mechanism and free radical activity differ from those of winter months. The antioxidant defence system is partly related to element status via enzyme activity and uncontrolled free radical reactions. Chemiluminescense examination points to this.

Discussion/Conclusion: With these examinations, routine laboratory parameters can be well extended. Support: ETT-012/2006.
Endothelial dysfunction in inflammatory bowel diseases

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Introduction: Endothelial dysfunction plays an important role in pathogenesis of different chronic diseases.

Aim of the study: To investigate role of endothelial dysfunction in pathogenesis of inflammatory bowel diseases (IBD).

Methods: 34 patients (22 with ulcerative colitis and 12 with Crohn’s disease) were under observation, mean age (43.2 ± 2.13) years, male – 13, female – 21. Ultrasound assessment of endothelium-dependent vasodilatation of brachial artery in test with reactive hyperemia was used. Increase of brachial artery diameter more than 20% was normal, from 10–20% – decrease of endothelium function and less than 10% testified endothelial dysfunction.

Results: Impaired function of vascular endothelium was established in 24 (70.6%) patients, including 11 (45.8%) with decrease of endothelial function and 13 (54.2%) with endothelial dysfunction. In patients with ulcerative colitis deviation of normal range was found in 16 (72.7%) cases, endothelial dysfunction in 9 (40.9%) and decrease of endothelial function – in 7 (31.8%). In Crohn’s disease abnormalities were diagnosed in 8 (66.6%) cases, decrease of endothelial function and endothelial dysfunction both in 33.3%. Impaired function of vascular endothelium in IBD was diagnosed in patients of different age, including young. Mean duration of disease in patients with endothelial dysfunction was (11.9 ± 2.9) years, with decrease of endothelial function – (8.4 ± 2.8) years, with normal endothelial function – (2.9 ± 0.95) years. Connection between severity of disease and degree of endothelial dysfunction was established.

Discussion/Conclusion: Endothelial dysfunction can be considered to be as one of the possible pathogenetic mechanisms in IBD. Further investigation is required.
Anemia in patients with ulcerative colitis (UC)

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Introduction: Anemia is a below-normal level of hemoglobin or hematocrit. Anemia can be a temporary condition, a consequence of other health conditions, or it can be a chronic problem. The etiology of inflammatory bowel disease (IBD) is multifactorial. Chronic blood loss from the colon, along with poor nutrient and iron absorption, can lead to iron deficiency anemia. A number of inflammatory cytokines, such as tumor necrosis factor-α, interferon-β, interleukin-1α, and interleukin-1β, contribute to disease progression.

Aims and methods: The aim of the study was to learn the frequency of anemia and its dependency from activity of the process in patients with UC. All patients with UC (n = 51) were monitored during 2007–2008 by a quality register including hemoglobin (Hb, normal range > 12.0 g/l, anemia < 12.0 g/l, severe anemia < 10.0 g/l).

Results: The frequency of anemia in patients with UC occurred in 39.5%. Anemia depended on clinical disease activity and is associated with significantly higher scores of disease. Treatment of anemia improved Hb concentrations. Anemia treatment with intravenous iron saccharate in patients with severe anemia (Hb < 10.0 g/dL) increases in Hb levels (p < 0.01). Anemia correction in these patients improved scores on the Ulcerative Colitis Activity Index, primarily due to changes in Hct and general well-being levels.

Conclusion: The anemia in patients with UC occurred in 39.5% of patients. The frequency of anemia depends of score activity index of the disease. Intravenous iron medications improve not only Hb level, but the general well-being as well.

References:

The usefulness of serum MMP-3 in degree of activity in inflammatory bowel diseases

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

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

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

Discussion/Conclusion: The serum MMP-3 levels increase in patients with IBD but it is not associated with disease activity and localization.
The utility of serum TGF-beta1 in degree of activity in inflammatory bowel diseases

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

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

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

Discussion/Conclusion: The serum TGF-beta1 levels increase in patients with inflammatory bowel diseases but it is not associated with disease activity and localization.
Typhoid fever presenting with ileal perforation and jaundice

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Introduction: Typhoid fever is a severe febrile systemic infection caused by the gram-negative bacillus Salmonella typhi.

Case report: A 43-year-old man was admitted to our hospital with the complaint of abdominal pain. He had been well until two weeks earlier, when abdominal discomfort, fever, and jaundice developed. His temperature was 39°C. A few days after those complaints, he had been admitted to a physician. Oral ciprofloxacin (500 mg bid) was prescribed and he used it for 5 days empirically. Despite antibiotic therapy, his symptoms did not improve. Thereupon, the patient admitted to emergency department of our hospital. On admission, he appeared ill and malnourished. His abdomen was distended and diffusely tender. His laboratory findings were shown in Table 1. The patient underwent exploratory laparotomy for acute abdomen. At laparotomy, nearly 300 cc hemorrhagic fluid and enteric contents were found within the peritoneal cavity. From 100 cm diameter after trietz to ileoceacal valve, there were multiple perforated areas. The perforated segment of ileum was resected. Surgically removed tissue was sent to pathology department for assessment. The pathology report revealed that ulceration, lymphoid hyperplasia, bowel wall with vascular congestion, inflammation, reactive lymphoid hyperplasia at ileum and caecum (Figure 1). These findings interpreted with changes belonging to Salmonella typhi infection. Serologic tests and blood cultures for typhoid fever were found negative. After surgery, because of elevated liver enzymes the patient was referred to gastroenterology department. His liver tests were shown in Table 1. Other biochemical tests were within normal limits. Serologic tests for viral hepatitis, including hepatitis A, B, and C viruses, cytomegalovirus, Epstein-Barr virus, and herpes simplex virus, were negative. Autoantibodies (ie, antinuclear, antimitochondrial, anti-smooth muscle, anti-liver-kidney microsomal enzymes, anti-soluble liver antigen) were also negative. Abdominal ultrasonography showed hepatomegaly (175 mm) and splenomegaly (145 mm). Elevated liver enzymes attributed to Salmonella typhi infection. During follow-up, his liver enzymes decreased gradually.

Discussion: The diagnosis of typhoid fever was established on the basis of history, clinical examination, isolation of Salmonella typhi, and a positive Widal test. Laboratory confirmation of clinical diagnosis in patients with perforation is difficult because of blood or bone marrow cultures commonly show no growth. As in our case, failure to grow Salmonella typhi may be due to treatment with antibiotics before blood samples obtained for culture. Diagnosis was confirmed by intraoperative and pathological findings.
Immunohistochemical evaluation expression of IGFRI in children and adult patients with ulcerative colitis

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Introduction: The insulin-like growth factors regulate proliferation and differentiation many types of cells, as well as the mucosa of the gastrointestinal tract.

Methods: The investigated group considers of 55 patients with ulcerative colitis (30 children and 25 adults). An immunohistochemical analysis was perform in formalin-fixed, paraffin-embedded tissue specimens with monoclonal antibody IGFRI (mouse anti-insulin receptor; Chemicon, Canada).

Results: The reaction was observed in membrane of cells epithelium in bowel. In both group patients with ulcerative colitis, adults and children, we observed reduction expression of IGFRI in the epithelium cells. Increased expression of IGFRI was observed in control group compared to UC patients.
In control group the expression of IGFRI was stronger than in the group with UC. There was no difference in expression of IGFRI between children and adults.

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The recurrence of inflammatory bowel diseases: The role of interaction between the main regulatory mechanisms

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Introduction: The purpose of this study was to determine the immune regulatory mechanisms that can influence the recurrence of inflammatory bowel diseases (ulcerative colitis and Crohn’s disease).

Methods: Mononuclear cells were isolated by standard immune techniques. Immune indices, such as CD3, CD4, CD8, CD19 and circulated immune complex in patients’ blood, were estimated. Moreover, sensitivity of T-cells to stress-realized (cortisol, adrenalin) and stress-limited (histamine, serotonin) factors was studied. The analysis of interaction between immune and neurohumoral mechanisms in patients with ulcerative colitis and Crohn’s disease was done.

Results: 34 patients were investigated: 20 patients with ulcerative colitis (1 group) and 14 patients with Crohn’s disease (2nd group) were included in this study. Taking into consideration revealed immune changes we established main four types of immune status in patients with IBD. First type was characterized with normal account and ratio of T- and B-cells. This type was observed in 42.9% patients with Crohn’s disease and 20.0% patients with ulcerative colitis. Decrease of the T lymphocytes, incorrect subset of T-cells (because of principally CD4 decrease) and normal content of CD19 were described for the second type. It was revealed mainly in patients with UC (30.0%) and rarely in patients with Crohn’s disease (14.3%).

The third type includes such immune changes: significant decrease of CD19 and minor one of CD3: 35.0% patients with ulcerative colitis and 28.6% patients with Crohn’s disease have this type of immune disorder. The fourth type, which includes significant decrease of CD3, CD19 and imbalance of CD4, CD8, was observed in 15.0% patients of 1 group and 14.3% patients of 2 group. Furthermore, the most significant immune changes were revealed in patients with patients with recurrence of ulcerative colitis.

The personal sensitivity of receptor of T-lymphocytes to modulators was changed in most patients of both groups. The mobilization of patients’ functional potential of CD3-receptors concerning histamine and serotonin was established in most patients of both groups. Most patients of 1 group has mobilization of functional potential concerning such factors as cortisol and adrenalin, at the same time patients of 2 group often has the exhaustion of receptor potential linked with these factors.

Conclusion: These findings support hypothesis that immunoregulatory abnormalities may have importance in course of IBD. It seems that there are different types of immune disorders that influence recurrence IBD.
First experience with OMOM capsule endoscope system in Baltic States

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Introduction: Video capsule endoscopy (VCE) has become a very important tool for diagnosing of many small bowel disorders. One of the latest capsule endoscopy technologies is OMOM capsule endoscope system. Aim of study was to evaluate OMOM capsule endoscope system in small bowel pathology diagnostic: image quality, safety, convenience in use.

Methods: All the patients that undergo OMOM capsule endoscopy procedure had strict indications for VCE, such as obscure gastrointestinal bleeding/anemia and Crohn’s disease. OMOM Image Workstation ver. 5.31 was used to analyze all the cases.

Results: Total 10 capsule endoscopies were performed (5 females and 5 males). Diagnoses were Crohn’s disease, arteriovenous malformation (angiodysplasia), hemorrhagical erosive small bowel damage. Capsule worked ~8 hours. Capsule was possible to control in the body (possible to measure real time viewer, image format, sampling frequency, flash intensity). In all cases capsule reached ileocecal area. All the patients tolerate the procedure very good and didn’t record any side effects or pain. In total in every case we received ~50,000 images. OMOM Image Workstation has a possibility to locate physiological valves along the recorded video and simulation diagram of Gastro-Intestine. Images quality was acceptable, though a bit dark. This system provide additional programme which allows to edit images (marking, size measuring, zoom, image enhancing). Using all these tools doctor could analyze any suspicious or unclear images very precisely and put the right diagnosis. Analyzing process was simple and took ~2 hours per case depends from indications.

Discussion/Conclusion: Preliminary data shows that OMOM endoscope capsule system is safe and well tolerated capsule endoscopy equipment. Image Workstation provided tools allow analyzing received small bowel images very carefully.
The comparison of three capsule endoscopy systems’ software

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²Dr. Falk Pharma Russia, St. Petersburg, Russia

Introduction: There are several types of video endocapsules commercially available for small bowel investigations. This study was designed to compare three systems’ software (EndoCapsule Software ver. 1.0.7., Given Diagnostic System Rapid Reader ver. 4.1.8. and OMOM Endoscope Capsule System Image Workstation ver. 5.31.): tools, features and convenience in use.

Methods: From our date basis we selected 30 VCE: 10 patients examined using Olympus Endocapsule, 10 – Given PillCam and 10 – OMOM.

Results: The capsule worked ~8 hours.

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Discussion/Conclusion: All three systems are similar in functionality. For beginners it seems be better to start with Given Imaging and after receiving some experience use the Olympus and OMOM, which is more powerful.
Ulcerative colitis associated with myelofibrosis in childhood

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Introduction: Myelofibrosis (MF) is a rare disorder in childhood which is characterized by splenomegaly, extramedullary hematopoiesis, teardrop erythrocytes and myelofibrosis. It may be primary or idiopathic as a chronic myeloproliferative disease or secondary to large number of events associated with some other disorders. It has a variable clinical spectrum and the etiology is not well understood. A possible autoimmune basis has been suspected according to reported association of myelofibrosis and autoimmune disorder. Systemic lupus erythematosus, scleroderma, primary biliary cirrhosis, Sjogren’s syndrome and rheumatoid arthritis have been uncommonly reported associate with secondary myelofibrosis.

Case report: Here we describe a 6-year-old girl who was admitted to our hospital with a 5-month history of abdominal pain, fatigue and diarrhea. She was initially diagnosed with ulcerative colitis (UC) on the basis of clinical and pathological signs and later also found to be suffering from MF.

Discussion/Conclusion: Up to date, MF is not recognized as an extraintestinal manifestation. In 2002, an adult case with MF and UC was first reported. The estimated co-incidence of MF and UC are exceedingly small and it was accepted as a new association. Best of our knowledge, our patient is the first pediatric case of UC association with MF. Therefore, we conclude that this new association needs to be reminded in cases with either UC or MF in pediatric practice.
Active human cytomegalovirus infection in newly diagnosed patients with ulcerative colitis

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Background/Aim: Early studies suggested that CMV infection initiates some cases of ulcerative colitis (UC), plays a role in UC exacerbation, causes self-limited colitis, and increases the incidence of complications, emergency surgery or death in patients with UC.

Patients and methods: Thirty-seven patients with first-time diagnosed ulcerative colitis were selected retrospectively and included in this study. Patients were classified into two groups, group I ulcerative colitis patients infected with CMV; group II ulcerative colitis patients not infected with CMV. Severity of UC was assessed clinically using Montreal classification of severity of ulcerative colitis, colonoscopically using Montreal classification of extent of ulcerative colitis. Histologically, diagnosis & severity was graded using microscopic scores for the assessment of disease activity in UC.

Results: Patients were comparable with controls according to age, and sex. Clinical and laboratory parameters showed no statistically significant differences, except for reduced serum albumin and hemoglobin in group I (p < 0.05). The highest sensitivity for detection of infection with CMV in patients with UC was achieved in immunohistochemistry, while the lowest one was achieved in detection of inclusion bodies in H & E-stained biopsy.

As regards assessment of severity in patients with UC with or without CMV infection, no significant differences between both groups were detected.

Conclusions: CMV infection in patients with UC may be common and is often underestimated. This has definite clinical significance and therefore should not be ignored.
Pediatric Crohn’s disease and ulcerative colitis: Pathogenesis and treatment

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Inflammatory bowel disease (IBD) is an enduring disease involving mostly young people and children, with symptoms of bloody diarrhea and abdominal cramps. The phases of the endointoxication were discovered for children with IBD. There were observed five phases. It should enhance our understanding of the pathophysiology of IBD.

Introduction: Inflammatory bowel disease (IBD) embodies a spectrum of disorders that affect the gastrointestinal tract, the 2 major entities being Crohn’s disease (CD) and ulcerative colitis (UC). IBD is a lifelong disease, often in a severe way. They cause life impairing symptoms, necessitate long-term dependence on powerful drugs, and often result in debilitating surgery and even death. Enhanced injured surface in IBD contributes to auspicious conditions for bacterium and toxin penetration in blood flow. Developed endotoxicosis accordingly contributes to maintain and to progress of metabolic and immunological changes. The endointoxication contributes to maintain and to progress of metabolic and immunological changes. It is accompanied by disturbance of regulating homeostasis system with the following disturbances of organs and systems of detoxication.

Methods: We estimated quantitative and qualitative changes of metabolic status in accordance with LMMWP (low and medium molecular weight peptides – universal markers of intoxications) and OP (oligopeptides), defined in erythrocytes, plasma and urine. Correlation between the extent of affection, expression of symptoms with the degree and the stage of endointoxication.

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

Discussion/Conclusion: This will lead to the introduction of new and accurate tools for diagnosis, stratification, and follow-up of patients with IBD. The most prominent endointoxication was observed in children with extraintestinal manifestations. On the base of these findings we calculated the adequate dose of enterosorbents, used in a complex therapy of IBD.
Hormones or the operation while treating for ulcerative colitis among children?

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Aim: To reveal the additional criteria of indications for hormone and surgical children’s treatment for ulcerative colitis.

Introduction: We have tried to answer the question whether to choose hormones or the operation when 5 aminosalicylic acid medications are not effective.

Methods: 45 children with ulcerative colitis at the age of 3 till 16 with an unfavorable clinical course. There are 20 children among them who underwent the hormone therapy, 25 children were subjected to the surgical treatment. Retrospectively by Culback’s method the forecasting criteria for the prescription of hormones or operation were determined.

Results: It was revealed that the character of rearing on the 1st year of life is highly informative for therapy prognosis. The artificial feeding had a high forecasting factor regarding surgical treatment. The longer is the period from the first symptoms till the beginning of the appropriate therapy, the more likely that the conservative treatment will be ineffective. The beginning similar to dysentery was often discovered in the group with surgical treatment, while the atypical beginning required the hormones prescription. If there are the dyspepsive, asthenovegetative and colitic syndromes the conservative therapy will be most likely ineffective. A great stab shift in leukogram was observed more often among patients in the surgical group. While a low level of albumins of blood and an increase of transaminases are typical for children with the therapeutic effect on hormones.

Discussion/Conclusion: Thus, we have tried to answer the question whether to choose hormones or the operation when 5 aminosalicylic acid medications are not effective.
Assessment of ulcerative colitis related dysplasia – Comparative study between ultrastructural changes and the expression of p53 immunohistochemical marker

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Introduction: Evaluation of dysplasia in longstanding ulcerative colitis (UC) is a difficult and subjective task.

Aim: To detect UC associated dysplasia at an earlier stage and distinguish regenerative from premalignant changes.

Methods: During surveillance colonoscopy, multiple random biopsies from 25 patients with longstanding UC were taken at 10 cm intervals throughout the colorectum for ultrastructural assessment. The biopsies were contrasted with acetate-uranyl and lead-citrate and studied with a JEM-1010 electron microscope. Seventy-five sections were stained immunohistochemically to detect nuclei positive for the proliferation marker p53 (positive p53 immunoreaction – > 5% stained nuclei, negative p53 immunoreaction – < 5% stained nuclei).

Results: Ultrastructural parameters for mucosal remodeling correlate well with UC duration, indicating accumulation of structural alterations. We observed that the main ultrastructural changes that seem to indicate a degeneration process which leads to premalignant lesions were the enlarged, irregularly shaped nuclei and changes in the relationship of adjacent cells. In these specimens the immunohistochemical stain for p53 showed strong intensity of p53 staining in cases of low and high grade dysplasia (L-HGD). Irrespective of the intensity of the inflammatory process all regenerative atypia were p53 negative.

Discussion/Conclusion: Positivity of p53 immunoreaction in LGD (20%) and HGD (40%) demonstrated that p53 gene mutation is an early event in the colorectal carcinogenesis. In our study we observed that p53 expression correlates well with ultrastructural changes of dysplasia suggesting that this technique could be trusted for the evaluation of colorectal mucosa in order to improve diagnostic accuracy and to appreciate the risk of malignant transformation.
Prognosis of course of inflammatory bowel disease

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Introduction: To study the dynamics of course of inflammatory bowel disease (IBD) and develop criteria of prognosis of puss-inflammatory complications.

Methods: Peculiarities of the course of IBD (ulcerative colitis and Crohn’s disease) in 57 patients for 5 years have been studied. The age of patients was 20–67 years. For diagnostics endoscopic, morphological, X-ray, biochemical and general clinical methods were used. Indices of cell tests of reactivity and intoxication (leukocyte and lymphocyte indices, index of leukocyte shift) were studied. Computer program for analysis of data has been developed.

Results: Mild degree of IBD was in 8 (14.04%) patients, moderate – in 30 (52.63%), severe – in 19 (33.33%). Puss-inflammatory complications were revealed in 14 patients. Treatment of severe degree of IBD included: Salofalk®, prednisolone, antibiotics, amino acid, protein, saline solutions. Maximal changes in cell tests of reactivity and toxicity were observed in patients with a severe degree of IBD and puss-inflammatory complications. Major shift of leukocyte intoxication index was discovered. After operative treatment of 11 patients (colectomy) normalization of reactivity and intoxication indices was observed.

Discussion/Conclusion: Indices of cell tests of reactivity and intoxication characterize endogenic intoxication and development of puss-inflammatory complications in patients with IBD. Changes of indices of cell tests of reactivity and intoxication allow us to control dynamics of IBD course, prognosis and to correct treatment.
The prevalence of primary sclerosing cholangitis in patients with inflammatory bowel disease

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Introduction: The aim of this study was to determine the prevalence of primary sclerosing cholangitis (PSC) in patients with IBD and to investigate the effect of UCDA therapy in these patients. Also, we monitored antibodies to neutrophil cytoplasmic antigens (ANCA) in patients with IBD.

Methods: We studied 122 patients with IBD: 79 with UC and 43 with CD. In this group, 12 patients had PSC. The diagnosis of IBD is done according to clinical, endoscopic, radiologic, histochemical and microbiological criteria. PSC was diagnosed in all patients with the use of endoscopic retrograde cholangiopancreatography (ERCP).

Results: PSC was diagnosed in 8 patients with UC (6 female, 2 male) and 4 with CD (2 female, 2 male). The mean ages at the onset of the UC was 39.81 ± 6.53 years and 36.5 ± 7.22 years in Crohn’s disease. In two patients diagnosis of PSC preceded the diagnosis of IBD, six had simultaneous diagnosis and in four patients PSC was diagnosed after the onset of IBD. Patients with PSC had elevated alkaline phosphatase activity and gamma-glutamyl transpeptidase levels at the time of diagnosis. All patients were treated with UCDA alone or in combination with immunosuppressive medications. Positive clinical and/or biochemical response occurred under therapy in 10 patients. One of the two non-responder patients underwent liver transplantation, while the other died in cholangiocellular carcinoma. ANCA were found by indirect immunofluorescence in 8 of 12 patients with IBD and PSC, (6 patients with UC and 2 patients with Chron’s disease). p-ANCA have been found consistently in patients with UC (5 of 8 patients) and in a much smaller percentage in patients with CD (1 of 4 patients).

Discussion/Conclusion: PSC commonly associated with IBD, especially UC. ANCA seem to be associated with a severe activity of UC. In the forms with hepatic determination, especially PSC, ANCA is more increased.
Sclerosing cholangiopancreatitis – A manifestation of primary sclerosing cholangitis or autoimmune pancreatitis?

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Introduction: Literature data confirms incidence of combined sclerosing changes of biliary and pancreatic ducts. Despite rare clinical manifestations of chronic pancreatitis as a result of primary sclerosing cholangitis (PSC), on ERCP there are present changes of pancreatic ducts in a one third of cases. Steatorrhea due to primary or biliogenic pancreatic insufficiency is determined even more frequently. And vice versa regions of biliary duct narrowing and cholestasis are revealed almost always in autoimmune pancreatitis.

Methods: We studied 5 patients with combination of stenosis of common bile duct and Wirsung’s duct (by ERCP results).

Results: 1 patient had AIDS and the possible cause of duct affection was CMV. 2 patients had non-specific ulcerative colitis and cholestasis which was predominant in the clinical picture. This fact helped us to produce diagnosis of PSC. Both patients had steatorrhea. Corticosteroids were of no effect.
2 patients had predominant pseudotumorous pancreatitis in clinical picture. Corticosteroids (prednisolone 40–60 mg/day) had a rapid and significant effect. These patients also needed Creon, but after 3–4 weeks of the corticosteroids therapy the dose of Creon was significantly decreased. These patients had diagnosed to have autoimmune pancreatitis.

Discussion/Conclusion: Sclerosing cholangiopancreatitis may develop in PSC, autoimmune pancreatitis and AIDS. In case of pseudotumorous pancreatitis in association with stenosis of bile and pancreatic ducts and without non-specific ulcerative colitis the most probable diagnosis is autoimmune pancreatitis in which corticosteroids are of high effectiveness.
Expression of Bcl-xL in pediatric and adult patients with ulcerative colitis

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Introduction: Bcl-xL is a transmembrane molecule in the mitochondria. It is one of several anti-apoptotic proteins which are members of the Bcl-2 family of proteins. This protein is also involved in the neoplastic process. According to numerous studies, Bcl-xL overexpression contributes to carcinogenesis by protecting tumor cells from death. Patients with ulcerative colitis after 10 years if involvement is beyond the splenic flexure carries a significantly increased risk of developing colorectal cancer. The study objective was the immunohistochemical assessment of the expressions of the apoptosis-regulating proteins Bcl-xL in ulcerative colitis.

Methods: The study group included 30 pediatric patients and 25 adult patients. Tissue samples were obtained by endoscopy and in each cases affirmed active ulcerative colitis. The protein expression was evaluated by immunohistochemical reaction using antibodies for Bcl-xL (Bcl-xL, N-19, sc-492-G, Santa Cruz Biotechnology).

Results: Expression of Bcl-xL protein was observed in cytoplasm of epithelium cells. Increased expression of Bcl-xL were found in dysplastic crypts both in pediatric and adult patients.

Conclusion: These investigations didn’t show any difference in expression of Bcl-xL protein in pediatric and adult patients with ulcerative colitis.

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PCR and electron microscopy in Whipple’s disease – Case report

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In Whipple’s disease the bacteria Tropheryma whippelii accumulate within macrophages and appear as a granulomatous infectious disease. A 61 year old man developed weight loss and diarrhea. Biopsy of the gastric mucosa and colorectal mucosa was negative, whereas duodenal biopsy revealed distorting the villi and PAS-positive foamy macrophages within the lamina propria. In electron microscopy we found Tropheryma whippelii (Whipple bacillus). The polymerase chain reaction (PCR) assay was used to detect a gene sequence corresponding to the Whipple bacillus in gastric and duodenal biopsies before and after therapy. An antibiotic treatment of Biseptol 2 x 960 mg was used for 3 months. After antibiotic treatment we observed histological changes but in electron microscopy and PCR Whipple bacilli was eliminated.

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Collagenous colitis: A retrospective survey of chronic diarrhea

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**Introduction**: The aim of this retrospective survey is to determine the frequency of collagenous colitis among patients who presented with chronic diarrhea to our gastroenterology outpatient clinic and to evaluate the demographic, clinical and laboratory findings of these patients and the treatment modalities.

**Methods**: We reviewed the charts of the patients who were registered to our outpatient clinic to identify those who had presented with chronic diarrhea. We identified all patients who were diagnosed to have collagenous colitis on histopathological examination.

**Results**: Collagenous colitis was diagnosed in seven of 93 (7.5\%) patients who had colonoscopy and histopathological examination. Six of these patients were female, the mean age was 64 ± 11.5 years. The mean duration of chronic diarrhea was 5 ± 4.9 years. Celiac disease was diagnosed before the diagnosis of collagenous colitis in 2 patients. Stool examination showed leukocytes in 5 patients but no erythrocytes. Laboratory examination showed anemia in 2 patients, hypoalbuminemia in 4 patients and high CRP levels in 3 patients. Five patients were treated with mesalazine, 1 patient with salazopyrine and 1 with prednisolone.

**Discussion/Conclusion**: Collagenous colitis was detected in 7.5\% of the patients who presented with chronic diarrhea to our gastroenterology outpatient clinic. The cases with collagenous colitis were usually aged female patients, the mean duration of diarrhea before the diagnosis of collagenous colitis was long.
Total colonoscopy or rectosigmoidoscopy during activation of ulcerative colitis in adolescent?

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Case report: A 13-year-old female patient was admitted to the pediatric gastroenterology department for control visit. She was diagnosed as ulcerative colitis 6 months before. Her daily stool count was three in average and with no blood in stool. She was using mesalamine treatment at 25 mg/kg/day and mesalamine enema (60 ml) at alternative days. Her physical examination was normal. There was an increase in erythrocyte sedimentation rate (120 mm/h) in her laboratory. In order to decide the disease activity total colonoscopy was planned but due to inappropriate cleaning only rectum and sigmoid colon able to visualised. The disease activity was 2 over 10 in that region. Serology for rheumatological, hematological and infectious diseases was all negative. Total colonoscopy was performed after optimal cleansing. The disease activity was 10 over 10. Steroid treatment was started and her daily stool number decreased to 1 per day and her sedimentation rate decreased to 16 mm/h in three weeks time.

Discussion/Conclusion: Ulcerative colitis (UC) is a chronic inflammatory bowel disorder characterized by exacerbations and remissions. Endoscopic evaluation of mucosal appearance is the cornerstone for diagnosis and clinical management of ulcerative colitis patients, as it offers valuable prognostic tools and information on mucosal damage, useful to decide about treatment strategies. If the clinical response to medical therapy is not enough, change of treatment modality to steroids or other immunosuppression drugs must be started according to the degree of disease activity in colonoscopy. This case reminds the importance of making total colonoscopy instead of rectosigmoidoscopy during an attack of ulcerative colitis since the different parts of colon may reflect different activity findings especially in cases which use rectal flushing or foams of salicylic acid derivatives.
Duodenal plasmacytoma presenting with jaundice

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Case report: A 59-year-old male admitted with complaint of decreased urination and emesis. Physical examination was unremarkable. Laboratory findings were as follows; serum creatinine: 11.0 mg/dl, BUN: 232 mg/dl, ESR: 78 mm/h, hemoglobin: 7.2 g/dl. Proteinuria (1340 mg/day) was detected. Ultrasonography revealed small-sized kidneys with increased parenchymal echogenicity.

A Tenckhoff catheter was inserted for peritoneal dialysis and per-cutaneous renal biopsy was performed. ANA, rheumatic factor, and ANCA were negative. In serum protein electrophoresis, monoclonal gammopathy was found (gamma 29% [normal, 11.6–20.4%]). Serum immune fixation was compatible with monoclonal gammopathy (IgG, kappa light chain). Bone marrow examination showed diffuse mono-morphic plasma cell infiltration. Amyloid fibrils were inspected in renal biopsy specimens. With the diagnosis of multiple myeloma, the patient was placed on combination chemotherapy with high dose melphalan and prednisolone regimen.

Four months later, the patient returned with onset of jaundice, abdominal pain and progressive weight loss. In laboratory examination; serum creatinine was 5.7 mg/dl, blood urea nitrogen 73 mg/dl, total bilirubin, 6.2 mg/dl; direct bilirubin, 4.8 mg/dl; AST, 119 IU/L; ALP, 556 IU/L; LDH 755 IU/L and GGT 308 IU/L. Abdominal ultrasonography and MRCP revealed biliary dilatation. ERCP could not be performed, since severe edema in duodenum did not permit us to visualize ampulla Vateri. At endoscopy there were multiple nodular and polypoid masses in the stomach and in second part of duodenum (Figure 1). Biopsies were taken from those lesions showing plasma cell myeloma. Biliary drainage was provided by percutaneous transhepatic route. The clinics of patient got worse progressively and two weeks later he died because of sepsis.

Discussion/Conclusion: Gastrointestinal tract is rarely involved by multiple myeloma diffusely or as a focal mass. Duodenum is rarely involved during the course of multiple myeloma. This case is the first report of duodenal plasmacytoma presenting with biliary obstruction.
Surveillance of ulcerative colitis related dysplasia through Ki-67 and p53 immunohistochemical markers

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Introduction: In longstanding ulcerative colitis (UC) it is difficult to detect dysplasia endoscopically and to discriminate these changes from inflammatory regenerative epithelium pathologically.

Aim: To detect UC associated dysplasia at an earlier stage and to distinguish regenerative changes from premalignant ones.

Methods: In 78 UC cases showing features of high-grade dysplasia (n = 16), low-grade dysplasia (n = 24), ‘indefinite for dysplasia’ (n = 14), or regenerative atypia (n = 24) we studied location and intensity of Ki-67 and p53 to detect differences in the frequency and pattern of nuclei positive for the proliferation markers. Regarding to Ki-67 staining, the results were divided into 4 categories: 'basal zone' (staining restricted to the basal third of the crypt); 'mid-zone' (extension into the middle third); 'top zone' (extension into the upper third); and 'surface' (extension into the surface epithelium). Related to p53 immunostaining we assessed: location and intensity (weak, moderate, strong).

Results: In high grade dysplasia the distribution of Ki-67 positive cells was diffuse throughout the full length of the crypt, whereas low grade dysplasia and epithelium indefinite for dysplasia, as well as regenerative epithelium, showed an expanded basal zone. The rate of p53 overexpression was significantly higher in UC associated colorectal cancer than in non-neoplastic mucosa. None of the regenerative atypia cases showed strong intensity p53 staining compared to dysplasia cases.

Discussion/Conclusion: Assessment of Ki-67 and p53 immunostaining could be combined with routine histological evaluation in longstanding UC to improve the diagnostic accuracy and to appreciate the risk of malignant transformation.
Increased serum vascular endothelial growth factor and endostatin levels in adults with ulcerative colitis

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Introduction: Angiogenesis is an important part of ulcer healing through it obtains oxygen and nutrients to the regenerating mucosa. Increased serum levels of vascular endothelial growth factor (VEGF), a potent angiogenic factor, in patients with active ulcerative colitis (UC) was demonstrated in previous studies. Although expression of angiogenesis inhibitors such as endostatin in experimental colitis mucosa have been determined recently there is a few study why the healing of UC related mucosal injury is impaired despite the increased serum levels and expression of VEGF. In this study we purpose to determine the serum levels of VEGF and endostatin.

Methods: Blood samples were collected from 39 patients with ulcerative colitis and 28 irritable bowel syndrome (IBS) patients as controls. VEGF and endostatin were assayed by enzyme-linked immunosorbent assay. VEGF and endostatin levels were assessed in terms of disease activity, localization and treatment.

Results: Mean serum VEGF levels 512 ± 377 pg/mL in UC patients, 305 ± 121 pg/mL in IBS patients and mean serum endostatin levels 155 ± 60 ng/mL in UC patients, 117 ± 24 ng/mL in IBS patients. A statistically significant difference among the mean levels of VEGF and endostatin in the two groups was found (p = 0.032, p = 0.009). There was a positive significant correlation between serum VEGF and endostatin levels in ulcerative colitis patients (r = 0.422, p = 0.008). Mean serum VEGF and endostatin levels also correlated significantly in patients between mild and severe UC patients (p = 0.004, p = 0.008). No significant association between disease localization and treatment was found.

Discussion/Conclusion: In comparision with UC patients to IBS were found to have an active angiogenic and antiangiogenic profile as detected by serum VEGF and endostatin levels. Also there was a significant positive correlation between endostatin and VEGF levels in UC patients. This study showed us elevation of angiogenesis inhibitors instead of angiogenic factors.
Colonoscopic findings in patients with Behçet’s disease

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Background: Gastrointestinal tract may be involved during the course of Behçet’s disease. There are very few literature data regarding colonoscopic findings in those patients.

Aim: To document endoscopic findings of colon and terminal ileum in patients with Behçet’s disease

Methods: This prospective study evaluated patients who were diagnosed with Behçet’s disease in Ankara Education and Research Hospital. Cases where total colonoscopy could be performed and ileum could be visualized were included in the study (46 cases). Biopsies from terminal ileum were taken in all cases. Other organ involvement and inflammatory markers were also noted.

Results: All of the cases (25 female, 21 male) had normal colon at endoscopy. Macroscopically 9 of 46 patients had lesions (aphthous ulcers and erosions) in the terminal ileum. Biopsies of those lesions revealed vasculitis (5 cases), eosinophilic (1 case) and non-specific (2 cases) ileitis, and amebiasis (1 case). Ileum biopsies of remaining 37 patients were normal but one showing microscopic vasculitis. Cases with and without macroscopic and/or microscopic ileal lesions were comparable in respect to inflammatory markers and other organ involvement.

Discussion/Conclusion: About one fifth of patients with Behçet’s disease have macroscopic lesions in the terminal ileum. Terminal ileum should be visualized at colonoscopy in those patients and biopsies should be taken even if there are no macroscopic lesions.
Pro- and anti-inflammatory colonic mucosal cytokines and pANCA, ASCA in benign and not benign course of inflammatory bowel disease (IBD) in children

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Aim: To assess a level of pro- and anti-inflammatory cytokines in colonic mucosa and serum autoantibody pANCA and ASCA in children with Crohn’s disease (CD) and ulcerative colitis (UC) according the course of disease.

Material and methods: The level of pro-inflammatory (IL-6, IL-8, INF-γ, TNF-α) and anti-inflammatory (RaIL-1) cytokines in biopsies of colonic mucosa was studied by IFA in 60 8–17 year old children: 20 with CD, 20 with UC and 20 with IBS (control group – CG). pANCA and ASCA were assessed in serum of the CD and UC patients. 13 CD and 11 UC patients were in an active phase, 7 CD and 9 UC patients had an inactive phase of disease. 10 UC and 11 CD patients had unfavorable course of disease according following criteria: no remission more than 6 months or relapse of disease during 1 year despite correct treatment.

Results: The level of all studied cytokines in colonic mucosa, except IL-8 and TNF-α in CD, was increased in several times in all IBD patients compared to CG (p < 0.05). In the active phase of CD and UC the level of pro-inflammatory cytokines was higher, than in the remission. INF-γ was especially high in active CD (530.0 ± 117.9 pg/ml), in the remission it decreased to 113.2 ± 72.6 pg/ml. An unfavorable course of CD had a tendency to keep the high level of INF-γ. TNF-α was lower, than other pro-inflammatory cytokines. The level of RaIL-1 was much higher, than pro-inflammatory cytokines in all IBD patients, especially in active UC (1188.6 ± 347.8 pg/ml). In CD RaIL-1 was lower than in UC, but had a tendency to increase in the remission. RaIL-1 was higher in the patients with unfavorable course of CD and UC (925.2 ± 76.3 and 1692 ± 217.4 pg/ml respectively).

13 (65%) UC patients and nobody with CD had increased level of pANCA. ASCA was increased only in 8 (40%) patients of CD and none of UC. As in CD, as in UC, unfavorable course of disease was accompanied by increase of ASCA or pANCA in 80%, favorable course – only in 0–10%. In case of high autoantibody level disease had extraintestinal signs and complications.

Conclusion: ASCA or pANCA have strong specificity for CD and UC respectively. High level of anti-inflammatory cytokines (RaIL-1), ASCA or pANCA can predict an unfavorable course of IBD.
The effectiveness of blood treating with ultraviolet light in ulcerative colitis

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The aim of the investigation was to study the effectiveness of intravenous blood treating with ultra-violet (UV) light in Medical management of ulcerative colitis (UC).

Methods: A group of 58 UC patients (37 with mild and 21 with severe forms) was surveyed. All the patients were divided in 2 groups: 28 patients treated with "basic therapy" i.e. prednisone and Salofalk® (G1) and 20 patients were administered "basic therapy" and intravenous UV (G2). UV blood treating procedure was performed with the use of quartz optical fiber linked with UV generator. UV session started from the 2nd–3rd day of hospitalization, in general 5 procedures by duration of 50–60 minutes, each 1–2 days.

Results: 70% of G2 UC patients treated with UV light performed lower stool frequency after 2–3 days, 28% of the patients after 4–5 days. Contrastly only 65% of G1 patients exhibited the same results up the 5th day. 55% of G2 and 45% of G1 patients showed the lower frequency of haemorrhage. After UV blood treating G2 patients improved their peripheral blood index (haemoglobin concentration and red blood cells count increased, leukocytosis and ESR decreased). In G1 only leukocytosis and ESR decreased. Moreover, G2 patients showed the decrease of their Intoxication Index, estimated according to blood rate indices compared to G1 patients. The endoscopic activity indices in G2 improved in shorter time too.

Conclusions: The combination of blood treatment with UV light and "basic" preparations resulted in better effectiveness of UC treatment.
The antirotavirus cow dry oral lactoimmunoglobulin (ACDOL) application for treatment and prevention of rotavirus gastroenteritis (RGE)

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The rotavirus infection (RVI) morbidity among children in Minsk (Belarus) in 2007 was 922.1 cases on 100,000 of population.

The aim of our research was to study efficiency of ACDOL application, developed by the State Research Institute of Epidemiology and Microbiology (Minsk) for prevention and treatment of patients with the RVI.

Materials and methods: ACDOL consist from the basic lactoimmunoglobulin fraction (secretory IgG [94%]). The main mechanism of action is creation of passive immunity in the gastrointestinal tract. The clinical research was performed at the Pediatric Minsk Hospital of Infectious Diseases at 2007–8. The diagnosis RVI was confirmed by detection of a rotavirus antigen (RA) in stools by EIA.

Results: We observed 84 children with RGE at the age of 6–60 months Me (R25–R75) 22 (13.0–34.0) (p > 0.05). All of them had basic therapy (rehydration, diet). ACDOL was prescribed at 1 dose (500 mg) 3 times a day till 5 days. This treatment was started at 1–11 day from the beginning of disease Me (R25–R75) 2.0 (1.0–3.0) (p > 0.05). The control group was 53 patients with RGE Me (P25–P75) 20 (14.0–29.0) (p > 0.05). They had basic therapy only. After the ACDOL treatment the improvement of the condition was observed (restoration of appetite Me (R25–R75) 2.0 (1.0–3.0; n = 77) vs. 4.0 (3.0–5.0 n = 53) (p < 0.05), normalization of diarrhea 3.0 (2.0–4.0; n = 82) – 5.0 (4.0–5.0; n = 53) (p < 0.05), discontinuance of vomiting 1.0 (1.0–2.0; n = 33) – 2.0 (1.0–2.0; n = 33) (p < 0.05); normalization of temperature 1.0 (0.0–2.5; n = 46) – 2.0 (1.0–3.0; n = 26) (p < 0.05). The efficacy of ACDOL for treatment of patients with the RVI was estimated. The disappearance of RA from stools was observed in 35 from 84 cases (41.7%) of patients with ACDOL and 18 (33.9%) patients with RVI (p < 0.5) from controls. 14 patients from close contacts with other patients with RVI had preventive treatment with ACDOL. At 13 of these children for all time of supervision the RA in stools was not found. Conclusion: Thus, the certain efficacy of ACDOL for treatment is prescribed and emergency preventive maintenance RVI at children. ACDOL may be useful in RVI prevention in close contacts.
Infliximab monotherapy more effective in treating Crohn’s disease than azathioprine alone

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Introduction: We want to determine which of the therapies (infliximab monotherapy or azathioprine monotherapy) is most efficacious in reducing CDAI score at 26 weeks in patients with moderate to severe Crohn’s disease.

Methods: All study patients were randomized into two groups, first group of 17 patients diagnosed with Crohn’s disease was treated with 5 mg/kg intravenous infusions and second group of 15 patients was administered azathioprine 2.5 mg/kg capsules a day. The infusions were administered at week 0, 2, 6, and every 8 weeks after and azathioprine 2.5 mg/kg daily capsules through week 30. Final efficacy assessments were collected at week 26 including endoscopy for all patients.

Results: Results showed that 46% of the patients in the infliximab monotherapy group remission (CDAI < 150) at week 26 compared with 30.6% of the azathioprine monotherapy group. The difference between the azathioprine and infliximab therapies was apparent as early as week 6.

Discussion/Conclusion: Therapy with infliximab or azathioprine alone improving CDAI score in patients with Crohn’s disease but the infliximab monotherapy is superior to azathioprine monotherapy. Infliximab monotherapy is superior to azathioprine monotherapy in mucosal healing associated with Crohn’s disease after 26 weeks of treatment.
A comparison of subjective and objective measures of adherence to 5-aminosalicylic acid medication (5-ASA) amongst patients with ulcerative colitis (UC)

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Introduction: Determining why UC patient are non-adherent to 5-ASA therapy is an important means to increasing adherence. However, it is not clear which measures of adherence should be used measuring it accurately. This study examined the agreement among measures of adherence to oral 5-ASA medication.

Methods: 5-ASA medication adherence was assessed by using two subjective measures (patient self-report with a limited response scale and calibrated patient self-report with a five-point Likert scale) and objective measure of urinary drag excretion. Participants completed the Beliefs about Medication Questionnaire and a study-specific questionnaire. Urinary 5-ASA and N-acetyl-5-ASA were measured by high-performance liquid chromatography. Relationship between different measures was examined by using Chi-square analysis.

Results: 170 patients from three UK sites were studied. Urine data were available for a sub-cohort of 151 cases. The self-report measure with a limited response scale classified 58 participants (34%) as low adherers. Calibrated self-report identified 75 participants (44%) as low adherers and 61 patients (40%) were classified as low adherers by urinary analysis.

Chi-square analysis revealed significant correlation between both subjective (self-report) measures ($X = 64.5, p < 0.001$) in identifying the same non-adherent patients. Neither the self-report measure with a limited response scale nor the calibrated self-report measure correlated closely with levels of adherence detected by urine testing. This was true for complete non-adherence where 5-ASA or N-acetyl-5-ASA was not detected in 20 patients ($X = 3.17, p < 0.07$) and more so for partial non-adherence which was seen in 41 patients ($X = 0.12, p < 0.73$).

Discussion/Conclusion: Different measures applied to the same patient determine different level of adherence. Adherence is likely to be overestimated by self-report with limited response scale. Urinalysis for 5-ASA and its metabolites confirms only pre-measurement adherence, long-term adherence remaining unknown. The calibrated self-reported measure appears more sensitive for detecting non-adherence although a wider study is needed.
Is urinary drug excretion in spot samples from patients with ulcerative colitis (UC) an objective measure of 5-ASA medication adherence?

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Introduction: The determination of 5-aminosalicylic acid (5-ASA) and its major metabolite N-acetyl-5-ASA by high performance liquid chromatography (HPLC) in biological fluids is an objective measure of medication adherence. However, the level above which adherence can be determined was previously undefined.

Methods: Urinary concentrations of 5-ASA and N-acetyl-5-ASA were measured by HPLC. We aimed to study the range of urinary drug excretion over a 24 hour period in 15 UC patients and to investigate whether urinary drug excretion in a spot sample can be used as an objective measure of adherence.

Results: We found a larger inter-subject variability in the concentration of 5-ASA and N-acetyl-5-ASA following administration in the mesalazine compared the olsalazine and balsalazide groups. The urinary excretion for 5-ASA and N-acetyl-5-ASA did not increase with a slight increase in oral dose from 1.5 g to 2.0 g (Pentasa) and from 1.6 g to 2.4 g (Asacol).

After administration of olsalazine, 5-ASA was not detectable and only N-acetyl-5-ASA was detected. For patients taking balsalazide 2.25 g three times daily, concentration of 5-ASA was 0 µg/ml and 634.66 µg/ml in the case of N-acetyl-5ASA.

Discussion/Conclusion: The presence of N-acetyl-5-ASA in urine is the most clinically valuable measurement of adherence and the baseline below which non-adherence should be assumed is 60 µg/ml in spot samples from UC patients on maintenance 5-ASA therapy.

We conclude that whilst urinary drug excretion in spot samples can be used as an indicator of a degree of adherence to 5-ASA therapy, its effectiveness as a definitive test, is should be questioned.
Constipated celiac disease patients: An interesting complaint in the treated patients that may cause refusal of the diet

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Introduction: Celiac disease is being increasingly diagnosed worldwide. The treatment is mainly based on gluten-free diet. With diet, diarrhea, abdominal bloating and disease related symptoms are mostly relieved. However patients on diet sometimes are faced with constipation that may cause refusal of the diet which may have dangerous consequences.

Case 1: 24 year old lady was admitted with diarrhea 2–3 days a month, constipation 4–5 times a month, together with abdominal distention and malaise. Blood serology, histological examination of the duodenal endoscopic biopsy, small bowel barium graphy were all compatible with the celiac disease. She was put on appropriate diet and one month later she started to experience constipation (difficulty in defecation, hard stools, defecation once in 4–5 days). She did not like the laxatives and she preferred to eat gluten for softer stools. Explanation about the importance of the diet with relation to the risk of small bowel cancer could not change her idea.

Case 2: 72 year old lady was admitted with diarrhea 3–4 days a month, constipation 1–2 times a month, together with abdominal distention. Blood serology, histological examination of the endoscopic duodenal biopsy and small bowel barium graphy were all compatible with the celiac disease. She was put on gluten-free diet and one month later she started to experience constipation (difficulty in defecation, hard stools, defecation once in two days). She was treated with osmotic laxatives and she is still on gluten free diet now rich in fibre. She could understand the importance of the gluten-free diet.

Result, discussion: With gluten free diet constipation may be an unexpected new problem in the celiac disease patients. To cope up with this problem some are unwilling to take laxatives but prefer gluten rich food to have easy defecation, which is surely dangerous for the disease outcome.
Pyogenic granuloma of the sigmoid colon: Report of two cases and a review of the literature

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Introduction: Pyogenic granuloma (lobular capillary hemangioma) usually a small, benign, red polypoid lesion, is relatively common in skin and oral mucosa. However, it is extremely rare in the intestinal tract. Microscopical study reveals a lobular arrangement of proliferation of varying sizes of capillaries within an edematous stroma. Cases of pyogenic granuloma in the small intestine, esophagus and left colon were described in the English literature. It may cause rectal bleeding or intussusception in the small intestine. Differential diagnosis includes inflammatory polyp and other vascular tumors such as bacillary angiomatosis and the angiomatous variant of Kaposi's sarcoma.

Case 1: 64-year-old constipated, diabetic male was admitted with abdominal distention and pain. In colonoscopy diverticulosis of the descending and sigmoid colon with a 1 cm polyp near a diverticular orifice in the sigmoid was spotted and removed. Histological examination revealed pyogenic granuloma. He did not have rectal bleeding. Two years later colonoscopy showed no recurrence.

Case 2: 77-year-old constipated, diabetic female was admitted with vomiting, abdominal pain, distention and diarrhea. Stool analysis showed white blood cells, red blood cells. Microbiological studies revealed no pathogen. CT revealed obstruction at the level of sigmoid colon. Digital subtraction mesenteric angiography showed spasm in the inferior mesenteric artery that was absent weeks later. Acute renal failure and anemia developed. She was treated with IV hydration, nutrition, blood transfusion and antibiotics. First colonoscopy showed 7–11 mm white yellow slightly elevated lesions in the mucosa of the descending colon and sigmoid with normal looking mucosa in between. Histological examination of the biopsies was compatible with pyogenic granuloma. Mesalamine enema, tablets and budesonide enema were used in the treatment as well. In the follow up colonoscopies the lesions coalesced and stayed in a segment of sigmoid colon that decreased in size gradually. 20 months later there was no lesion at all.

Conclusion: Pyogenic granuloma may affect the sigmoid colon most commonly. There may be a relation of pyogenic granuloma with DM and constipation. Mesalamine and budesonide may be effective in the treatment.
Intestinal diffuse large B cell lymphoma presenting as multiple lymphomatous polyposis

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Case report: A 53-year-old man presented with a one-month history of abdominal pain, weight loss and fever. His past medical history and physical examination were unremarkable. Laboratory findings were normal other than hemoglobin (7.1 g/dl), ESR (87/hr) and positive stool blood. Upper endoscopy revealed diffuse nodules and polyps (2–8 mm) in whole duodenum. Colonoscopy showed similar lesions in ileocecal valve and ileum (Figure 1). Abdominal tomography revealed multiple abdominal lymphadenopathies. Duodenum and ileum biopsies were compatible with diffuse large B cell lymphoma. They were positive for CD-20, Bcl-6, CD45 and negative for CD3, Bcl-2 and CD10. Ki67 staining showed 90% reactivity. Although chemotherapy was planned, the patient died two days after diagnosis.

Discussion/Conclusion: Multiple lymphomatous polyposis (MLP) is a term applied to a specific lymphoma characterized by a distinctive pattern of gastrointestinal involvement in which gut is superficially infiltrated by multiple white nodular or polypoid tumors. Extensive small bowel infiltration by either B or T lymphocytes have been reported rarely. Although most of MLP cases have mantle cell lymphoma, MALT lymphoma, follicular lymphoma and peripheral T-cell or T/NK lymphoma may also present with MLP. To our knowledge there are very few reports defining diffuse large B-cell gastrointestinal lymphoma presenting with excessive intestinal MLP.

Differential diagnosis for intestinal MLP includes benign polyposis syndromes, enteropathy associated T-cell lymphoma, nodular lymphoid hyperplasia and variants of immunoproliferative small intestinal diseases. Bcl-2, Bcl-6 and CD-10 protein expression has been found to be independent prognostic factors. As in our case a proliferation fraction of > 80% Ki67 is generally considered to be an adverse prognostic factor. Prognosis of MLP is poor due to its accelerated proliferation.
Delayed diagnosis of celiac disease increases the risk of associated cancer: A case report

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Introduction: Celiac disease is a chronic autoimmune enteropathy with an incidence of 1/100 in Europe and United States. The association between celiac disease and cancers, especially gastrointestinal cancer has been long time ago established. Recent studies postulate that the delayed diagnosis of celiac disease increases the risk of associated malignancies.

Methods: We report the case of a 33-year-old woman presenting with progressive dysphagia. Esophageal cancer was easily diagnosed by endoscopy, CT-scan and ultrasonography of cervical region and confirmed by biopsy. Pathological examination revealed an undifferentiated squamous cell esophageal carcinoma. Endoscopical examination also revealed a typical inflammatory pattern of duodenal mucosa, suggestive for celiac disease.

Results: Pathology report confirmed the appearance of chronic inflammatory enteropathy with total villous atrophy corresponding to MARSH IV histological staging. Immunohistochemical techniques identified the predominance of T cell lymphocytes CD3⁺. The anti-endomysium and anti-transglutaminase antibodies were also positive.
The patient entered the cisplatin-fluorouracil chemotherapy protocol.

Discussion/Conclusion: Our case has the particularity of a delayed diagnosis of a latent celiac disease which has been asymptomatic for many years and was revealed by an associated malignant condition. The lack of a gluten free diet in undiagnosed celiac disease maintains a chronic inflammatory condition of the intestinal mucosa, thus increasing the risk of gastrointestinal associated cancers.
Another particularity of this case was the appearance of the esophageal tumor on ultrasonographic examination of the cervical region and the presence of a multilevel squamous esophageal cancer.
The role of capsule endoscopy in small bowel Crohn’s disease

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Introduction: 20–30% of the Crohn’s disease (CD) localizes only in the small bowel. In many cases, well-developed CD remains concealed when traditional radiological and endoscopic methods are applied. The “wireless” capsule endoscopy (CE) allows the non-invasive and painless examination of the entire small intestine.

Patients and method: At our department, we carried out a total of 100 CE examinations on 95 patients through a period of 48 months. The indication of the examinations was obscure gastrointestinal bleeding in 66 patients. CE was carried out due to suspected CD in 13 cases and due to recurrence after surgery in 4 cases of known CD. Familial polyposis syndromes (FAP, Peutz-Jeghers syndrome) were followed up in 3 cases. In 4 cases we carried out CE examinations in order to search for tumours. In 6 cases, the indication of CE was diarrhoea and abdominal pain. Our retrospective examination aimed at judging the efficiency of CE in groups of patients with various indications.

Results: A definitive small bowel bleeding sources was detected in 68.4% of the cases studied by CE in bleeding patients. Second to angiodysplasias, the most frequent bleeding source was CD (8 cases). The diagnostic yield of the method in relation to examinations carried out due to suspected CD was 84%. In case of familial polyposis syndromes, we found lesions requiring further observation in two patients. Both in tumour research and patients examined with the indication of diarrhoea only 1 – 1 case proved to be positive, respectively. Each of the Crohn’s patients received medicine therapy based on the findings of CE.

Conclusion: As opposed to all other examination methods, the use of CE has diagnostic advantages in patients with both known and suspected CD. CE makes it possible to judge the extent, severity and activity of the disease. As a result, CD of the small bowel can be diagnosed at an earlier and more treatable phase. Furthermore, CE is also suitable to measure the efficiency of the therapy.
Parasites and inflammation in the intestinal tract

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Amongst the parasites enabling to cause inflammation in intestinal tracts mention should be made of *Trichuris trichiura*, *Ascaris lumbricoides*, *Strongyloides stercoralis*, *Trichinella spiralis*, *Fasciolaris buski*, *Heterophyes heterophyes*, *Metagonymus yokogawai*, *Schistosoma spp.*, *Entamoeba histolytica*, *Giardia lamblia*, and *Cyclospora*. Many of these parasites are among the most prevalent parasites infected millions of people worldwide.

_Trichocephal_ in heavy infections with more than 1000 worms can cause an insidious chronic colitis similar to Crohn’s disease, along with a rectum with inflammation. Strongyloidosis can embrace a pronounced inflammatory response to secondary bacterial invasion. Its larvae in the lymphatics cause a granulomatous lymphangitis which in conjunction with the inflammation, atrophic mucosa and fibrosis causes a marked congestion and loss in elasticity of the gut. In intestinal schistosomiasis, papilloma and inflammatory polyps may be such that lead to obstruction of the lumen of the gut. The mechanism of producing intestinal inflammation in parasitic disease more or less is identical and the etiology mostly includes mechanical effects followed by toxin release.

In terms of treatment, praziquantel can be effective in treatment of all trematodes and cestodes except *Fasciola* spp. Treatment of nematodes with albendazol in many cases is possible followed by mebendazol.

Diagnosis of these parasites mostly includes stool exam three days consecutively because many parasites intend to release their eggs every other day. Abundantly clear some of them, e.g. *Trichinella* release nothing in faeces and their diagnosis mostly rooted in serology tests being of most important is ELISA test.

Keywords: parasites, intestinal inflammation, helminths, protozoa
Serum ANCA versus endoscopic histopathological findings in diagnosis of patients with ulcerative colitis

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Introduction: Ulcerative colitis (UC) is defined as continuous idiopathic inflammation of colonic mucosa that begins in the rectal area and may extend through the entire large bowel. The diagnosis of UC depends on clinical picture, stool analysis, endoscopic appearance and histopathological assessment of endoscopic biopsy. The aim of this work was to assess the value of pANCA in the diagnosis of UC as a non-invasive diagnostic tool versus the endoscopic and histopathological examinations.

Methods: This study included seventy patients which were grouped into three groups: Group (I) included 20 patients with UC, Group (II) included 20 patients with non-specific colitis and Group (III) included 30 subjects with normal lower endoscopy as control group.
All patients were subjected to thorough history taking, full clinical examination, urine analysis, stool examination and culture, ESR, CRP, complete blood picture, serum iron, liver function tests, renal function tests, abdominal plain X-ray, abdominal ultrasound, lower endoscopic and histopathological examinations, pANCA detection by ELISA and confirmed by IF technique.

Results: Perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) detected by ELISA were positive in 75% of UC patients and in 10% of non-specific colitis patients while all control group subjects were negative. pANCA detected by ELISA had 75% sensitivity, 95% specificity, 88.2% positive predictive value and 90.5% negative predictive value for ulcerative colitis patients.

pANCA detected by IF technique were positive in 85% of UC patients and 25% of non-specific colitis patients while none of control group was positive. pANCA by IF had 85% sensitivity, 90% specificity, 77.3% positive predictive value and 93.7% negative predictive value for ulcerative colitis patients.

Discussion/Conclusion: pANCA is a beneficial seromarker detected in 75–85% of patients with ulcerative colitis. pANCA detected by ELISA technique has high specificity and relatively low sensitivity for ulcerative colitis. Combined ELISA and IF technique for detection of pANCA may add higher sensitivity for pANCA as a seromarker for diagnosis of ulcerative colitis and can be used as a non invasive tool for diagnosis of ulcerative colitis especially when lower endoscopy is contraindicated.
Assessment of anticardiolipin antibodies (ACA) in patients with ulcerative colitis

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Introduction: Ulcerative colitis (UC) is a chronic recurrent disease characterized by diffuse mucosal inflammation involving only the colon. Patients with UC are susceptible to thrombosis in the active phase of the disease. Thrombotic events represent a significant cause of morbidity and mortality in patients with UC. Phospholipids represent a major component of the cell membrane; and there is a variety of phospholipids contained within the membrane of cells including cardiolipin.

The aim of this study was to detect presence of anticardiolipin antibodies (ACA) in UC and their relation to the activity of the disease.

Methods: The study was carried out on 40 persons of both sexes referred to the department of Tropical Medicine, Tanta University Hospital. The studied cases included 15 cases of UC in the active phase, 15 cases of UC during remission and 10 control healthy persons. Cases were subjected to history taking, complete clinical examination, laboratory investigations including ACA and anti Ds-DNA and colonoscopy with biopsy taken for histopathological examination.

Results: In this study ACA were found positive in all cases of UC, with thrombotic manifestations in six cases (20%). Thrombotic cases had higher ACA level than other cases of UC. No correlation was found between ACA and activity of the disease.

Discussion/Conclusion: ACA is increased in UC, but was not a useful diagnostic tool for the disease, and it cannot be added to the battery of investigations available. ACA was high in cases of UC with thrombotic manifestations, and was a good tool to anticipate complications in UC patients. ACA was a poor prognostic tool for follow-up of UC activity. The mechanisms of thrombotic manifestations in UC are rather complex, and should not be explained by ACA alone. So, further studies are needed to underline the mechanisms of such thrombosis.
Increased thrombin generation in inflammatory bowel diseases

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Introduction: Inflammatory bowel diseases (IBD) are characterized by an increased thrombotic risk. Endogenous thrombin potential (ETP), a parameter of the thrombin generation curve, represents a new tool in the evaluation of thrombotic and bleeding disorders. The aims of the study were to study ETP in IBD patients and to correlate the results with clinical and biochemical features.

Methods: 74 IBD patients (37 ulcerative colitis and 37 Crohn’s disease) and 74 sex- and age-matched healthy controls. ETP values, measured with or without thrombomodulin, are expressed as nM thrombin times minutes.

Results: In the presence of thrombomodulin, IBD patients with increased C-reactive protein (CRP) had significantly higher mean (± SD) ETP values (1.721.3 ± 458.0 nM x min) than either patients with normal CRP (1.356.6 ± 394.5 nM x min) and controls (1.261.2 ± 384.8 nM x min) (p < 0.001). A slight significant correlation was observed between ETP and CRP (r = 0.28, 95% CI: 0.06–0.48, p = 0.015) and erythrocyte sedimentation rate (ESR) (r = 0.26, 95% CI: 0.04–0.47, p = 0.022). ETP evaluated as ratio (with/without thrombomodulin) was significantly higher in IBD patients than in healthy individuals (0.69 ± 0.14 vs. 0.62 ± 0.18; p < 0.006).

Discussion/Conclusion: ETP is increased in IBD patients, mainly in those with increased acute-phase reactants. It may be considered as a candidate test to be used in prospective studies aimed at assessing the risk of thrombosis in IBD patients.
Amebiasis and ulcerative colitis – Causal connection or coincidence

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Introduction: Clear etiology of inflammatory bowel diseases is still unknown, although different environmental reasons including infections are taken under consideration.

The aim of this work is to present case of 11 years old girl, which was consulted because of diarrhea with blood and mucus, abdominal pain, weight loss and weakness. There is gastroenterocolitis underwent in Egypt two months ago in the case history. The girl was hospitalized, iron deficiency and hypoalbuminaemia were stated, most infectious causes were excluded. Next, suspecting amebiasis the child was admitted to Clinic of Tropic and Parasitic Diseases, where this diagnosis was confirmed. First routine treatment failed and because of trophozoites and cysts of Entamoeba histolytica still excreted in stool, management was repeated several times. During the second hospitalization fibersigmoidoscopy was carried out and inflammatory changes typical for amebiasis were described. After the third hospitalization with aggressive treatment the stool became free from trophozoites and cysts of Entamoeba histolytica and the girl was informed she’s healthy. Her clinic state was very good. In 2 weeks she discontinued taking of 5-ASA preparations and released the diet. Malaise, abdominal pain, strong diarrhea with blood and mucus appeared in one month. Then the colonoscopy was carried out and changes typical for active ulcerative colitis revealed. The treatment typical for active UC was introduced, steroids were needed to obtain satisfactory improvement. After one month therapy with steroids was finished, now the girl is treated with 5-ASA. She takes drugs regularly, uncompliance is excluded and she’s very well.

Comment: Did the diagnosis of amebiasis delay the diagnosis of inflammatory bowel disease or the ulcerative colitis was the consequence of severe case of amebiasis?
Characteristics of intestinal tuberculosis in ultrasonographic techniques

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Objective: Limited data exists on sonographic criteria for the diagnosis of intestinal tuberculosis.

Design and patients: Prospective evaluation of seven patients with final diagnosis gastrointestinal tuberculosis, a control group of 18 patients suffering from tuberculosis limited to the lungs for sonographic criteria of intestinal tuberculosis and compared the findings to those of 50 healthy controls.

Results: Following signs of intestinal tuberculosis were detectable: asymmetric thickened bowel wall (100%), intramural abscesses (86%), fistula (43%), extramural abscesses (29%), mesenteric thickening (29%), "white bowel" sign (29%), hypoechoic edema of Kercking’s fold with mesenterial thrombosis (14.3%), enlarged mesenteric lymph nodes with inhomogeneous echotexture and circumscribed hypoechoic spots < 3 mm (86%), ascites (29%) and enlarged spleen (14%). These signs were exclusively present in patients with intestinal tuberculosis when compared to patients with tuberculosis limited to the lungs or healthy controls. We could confirm the endoscopically reported right sided prevalence of these wall thickenings. In contrast to the reported literature we found a much higher prevalence of these sonographic signs as they were present in all patients. 6 of 7 patients (86%) showed enlarged mesenteric lymph nodes. This was particularly of interest as those mesenteric lymph nodes have not been described to be enlarged in the majority of other differential diagnosis of the ileocecal region.

Conclusions: The combination of bowel wall thickening of the ileocaecal region with intramural abscesses with or without fistula, abscesses and mesenteric thickening accompanied by enlarged mesenteric lymph nodes was highly predictive for intestinal tuberculosis.

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Bowel bradyarrhythmia as the earliest risk factor of IBD

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Introduction: Bowel coprostasis during functional constipation may increase risk of IBD, because the development of intestinal disorders strongly depends on the luminal content.

Aim: To investigate the effect of 4 main factors of coprostasis (diet, physical activity, regime of sleep and phase of defecation) on the bowel rhythm regularity.

Methods: 145 persons claimed to be healthy (aged 24–60 years) were investigated by questionnaires with special examination of the quality of diet, the level of physical activity, the observance of sleep regime and the phase of defecation.

Results: Bowel bradyarrhythmia was diagnosed in 26 from 91 persons (29%) with unsatisfactory diet, but in 13 from 54 persons (24%) with optimal one. Thus, diet satisfaction can decrease bowel coprostasis in 1.2 times.
Bowel bradyarrhythmia was exposed in 31% persons with unsatisfactory physical activity, but in 22% persons with optimal physical activity. So, satisfactory level of physical activity is connected with lesser (in 1.4 times) risk bowel bradyarrhythmia than unsatisfactory one.
Bowel bradyarrhythmia was diagnosed in 31% of persons with unsatisfactory sleep regime, but in 21% of persons with optimal regime. Optimal sleep regime can diminish risk of bowel bradyarrhythmia in 1.5 times.
Bowel bradyarrhythmia was exposed in 56% of persons with the worst phase of defecation, but only in 15% of persons with optimal one. So, optimal phase of defecation can decrease the risk of bowel bradyarrhythmia in 3.7 times.

Conclusion: Optimal phase of defecation is almost so important for prevention of IBD as regime, diet and physical activity together.
Toxic-septic course of ulcerative colitis and experience of treatment

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Introduction: To study peculiarities of the course of toxic-septic variant of ulcerative colitis (UC) and to improve results of treatment.

Methods: Retrospective analysis of 1884 case histories of patients received with relapse of ulcerative colitis for 20 years (1987–2007) has been carried out. Verification of diagnosis was performed on the basis of complaints, clinical data, results of additional examinations (endoscopy with biopsy, general clinical, biochemical, microbiological investigations).

Results: Toxic-septic variant of ulcerative colitis was diagnosed in 190 patients (10.1%). The disease manifested by increase of temperature over 38°C, changes in hematology results (leukocytosis, increase of neutrophils, ESR). Index of disease activity by Mayo was 10 and more. In biochemical analysis of blood increase of seromucoid levels, histamine, products of degradation of fibrinogen, cathepsin D, peroxide resistance of erythrocytes, decrease of ceruloplasmin, catalase were found. All patients had quantity and quality changes of colon microflora. Basis therapy (Salofalk® 4.0 g per os and 4.0 g in enemas, prednisolone 60–90 mg) was added by metronidazole, combinations of antibiotics (fortum + vancomycin or loksof + dalacin), desintoxicatiion medicines, correction of water-electrolyte disorders. Pre- and probiotics were prescribed in order to improve colon microflora.

Discussion/Conclusion: Severe course of UC with toxic-septic variant can be caused by disorders of barrier function of colon, translocation of colon microflora into the blood flow. In complex treatment of toxic-septic variant of UC it is reasonable to apply antibiotics of wide range, probiotics, desintoxicatiion medicines with the basis therapy.
Risk factors of osteodeficiency in patients with inflammatory bowel diseases (IBD)

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Introduction: Half of all patients with IBD show a significant reduction of their bone mass during the course of their chronic inflammatory bowel disease.

Aim of the study: To determine risk factors of bone destruction in IBD.

Methods: 101 patients with IBD (75 – ulcerative colitis [UC] and 26 – Crohn's disease [CD]) in the age of 17–68 years were under observation, male – 36, female – 65. Estimation of mineral density of bone tissue was performed with ultrasound densitometry of calcaneus with the use of apparatus “Achilles+” (Lunar).

Results: Disturbances of mineral density of bone tissue was found in 73 (72.3%) patients, including osteopenia in 47 (46.6%) and osteoporosis – in 26 (25.7%) cases. Mean age of patients with IBD and osteoporosis was much younger than in population (37.81 ± 2.28) years. The connection between index body mass (IBM) and qualitative and quantitative characteristics of bone tissue were established. In patients with body mass deficiency osteoporosis was in 55.6% of cases and osteopenia was found in the rest. Osteoporosis was diagnosed in 44.1% of patients with severe UC and 50.0% of CD in contrast to 12.2% and 6.2% in moderate form of disease, accordingly (p < 0.005). Normal mineral density of bone tissue occurred 3 times more often in patients with mild diseases. In patients who suffered from UC or CD more than 5 years osteodeficiency has been established in 65.8% and more than 10 years – in 84.0% of cases. It was established dose and time dependent steroid use leaded to loss of bone density: 76.0% in patients who used steroids 1 time per year for short course and 96.5% – in chronic steroid use for the last 5 years.

Discussion/Conclusion: Risk factors for osteoporosis development in IBD were established such as duration of disease more than 5 years, severe course of disease, IBM less than 20 kg/m² and chronic steroid use.
Evaluation of QT interval and MPV among inflammatory bowel disease patients

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Objective: Inflammatory bowel disease (IBD) is rarely associated with cardiac findings and also ciprofloxacin, frequently prescribed in IBD patients, is reported to have an influence on QT interval. We looked for the relationship between IBD (ulcerative colitis [UC], Crohn’s disease [CD] and acute coronary syndrome, arrhythmia and sudden death as well as changes in QT interval and mean platelet volume (MPV) with respect to the disease type, duration and activity.

Study design: A total of 96 cases were included in the study. Study group consisted of 62 IBD patients, UC (n = 45) and CD (n = 15). Also there was a control group consisted of 34 healthy people. There were 51 women and 45 men and mean age was 40.77 ± 13.58 years ranging between 18–71 years. The duration of the disease and medication use was inquired among IBD patients. Disease activity was evaluated endoscopically and clinically (Truelove-Witts criteria and CAI). Presence of any cardiac condition, QT prolonging medication use, systemic disease, anemia and electrolyte imbalance were excluded from the study. The QTc, QTd and MPV values were compared between the two groups.

Results: The mean age, QTd (p = 0.613), QTc (0.790), MPV (p = 0.847), WBC count, Htc and Plt counts were similar between the groups (p > 0.05). In the same way, QTd (p = 0.806), QTc (p = 0.851) and MPV (p = 0.521) values were similar among the UC and CD groups. Duration of the disease was not associated with QTd (p = 0.954), QTc (p = 0.585) ve MPV (p = 0.132) levels. QTd, QTc, MPV and Plt levels were similar between the active and in remission UC patients. QTd (p = 0.619) and QTc (p = 0.889) levels were similar between IBD patients on antibiotic treatment for at least one-week (metronidazole 3 x 500 mg/d and ciprofloxacin 2 x 500 mg/d (n = 11)) and the others.

Conclusion: Type, activity and duration of the disease were not associated with QT interval and MPV. Several reports of deaths considered to be associated with ciprofloxacin use should be reconsidered for electrolyte imbalance during the active phase of the disease rather than changes in the QT interval and further studies should be planned.
**Effect of infliximab infusion on the activation of the coagulation cascade in patients with inflammatory bowel diseases (IBD)**

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**Introduction:** Inflammatory bowel diseases (IBD) show a prothrombotic state and a condition of hypercoagulability. It is known that molecules involved in the coagulation cascade play a significant role as pro or anti-inflammatory factors. Conversely, TNFα, as well as other pro-inflammatory cytokines, promote the activation of coagulation and reduce the production of anticoagulant molecules. Aim of our study was to evaluate whether anti-TNFα infusion induces changes in the levels of markers of coagulation activation in IBD patients.

**Methods:** 152 plasma samples obtained before and 1 hour after 76 infliximab infusions (5 mg/kg) performed in 18 IBD patients (10 men; mean age: 40.8 ± 16.58 years; 11 Crohn's disease, 6 ulcerative colitis, 1 indeterminate colitis). 10 IBD patients (6 Crohn's disease, 4 ulcerative colitis) were naïve for infliximab therapy. F1+2 and D-dymer levels were measured by means of ELISA methods.

**Results:** Median F1+2 levels were markedly reduced 1 hour after anti-TNFα infusion: median pre-and post-infusion levels were 192.64 pmol/L and 162.9 pmol/L respectively (p < 0.0001). Median D-dymer levels were also significantly reduced, from 253.06 ng/mL to 248.52 ng/mL (p = 0.0001). For D-dymer these modifications were more evident in patients naïve for infliximab therapy (p = 0.003). At a separate analysis of infliximab-naïve patients, baseline F1+2 and D-dimer levels were significantly higher than in matched controls (p = 0.028 and p = 0.005 respectively). After 14 weeks of infliximab treatment, median D-dymer levels were markedly reduced (p = 0.018). Median F1+2 levels were also reduced, from 237.35 pmol/L to 167.62 pmol/L, but this difference did not reach a statistical difference (p = 0.063).

**Discussion/Conclusion:** Infusion of infliximab significantly reduces the activation of coagulation cascade in IBD patients. This effect is early enough to suggest a direct effect of infliximab on the coagulation cascade and a possible new anti-inflammatory mechanism of action of this therapy.
Audit on Barrett’s oesophagus surveillance

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Introduction: Barrett’s oesophagus is a precursor lesion for oesophageal adenocarcinoma, incidence of which has increased tenfold in last three decades. Surveillance endoscopy has shown to detect tumours earlier and improve survival. Aim of this audit is to assess our current practice against British Society of Gastroenterology (BSG) guidelines on Barrett’s oesophagus surveillance.

Methods: 100 consecutive cases of patients undergoing surveillance endoscopy for Barrett’s oesophagus in a District General Hospital based in North West England between February to September 2008 were audited retrospectively. Data was analysed to identify patient characteristics, Barrett’s segment length and biopsy sites documentation, whether adequate biopsies were taken and histological outcome of biopsies.

Results: Median age was 61 years (male 72, female 28). Barrett’s segment length was documented in 95 cases with > 50% being < 4 cm. Biopsy sites were documented in 42 cases. Quadrantic biopsies for every 2 cm Barrett’s segment were taken in 39 cases (45%). No biopsies were taken in 2 cases. Histology revealed low grade dysplasia in 2, high grade dysplasia in 1 and oesophageal ulcers in 2 cases.

Discussion/Conclusion: 39 cases (45%) were compliant with BSG guidelines for quadrantic biopsies in Barrett’s segment. Patient with low grade dysplasia was followed up after 6 months instead of recommended 3 months. Likely factors responsible for lower number of biopsies were thought to be:
1) Time consuming
2) Unsedated patients may not tolerate serial biopsies (37% did not have sedation)
3) Endoscopist being unaware of BSG guidelines.

Recommendations: A dedicated Barrett’s oesophagus screening endoscopy list preferably performed by a selected few endoscopists is likely to improve the quality of screening and also following the robust screening methods as per BSG guidelines.
The effect of glycosinolate rich food supplementation and seasonal variation of element homeostasis in moderately active ulcerative colitis

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Introduction: In IBD, redox homeostasis and signal transduction pathways are altered. Proteins participating in these processes are mainly metal containing/activated. Therefore the examination of metal homeostasis in supplementation with or without antioxidants (glycosinolate derivates (GL) which are Nrf2 activators) may be important in respect to seasons.

Methods: The Al, Ca, Cu, Fe, Mg, Mn, P, S, Zn contents were measured by ICP-OES in erythrocyte of 15 volunteers, 15 UC patients with therapy recommended by WHO and 12 patients treated with recommended therapy and GL (0.2 g/day). Routine laboratory parameters and scavenger capacity in erythrocyte were also determined.

Results: Decreased Ca (0.975 ± 0.440 microg/g), Mg (1.02 ± 0.24 microg/g) and Zn (0.776 ± 0.482 microg/g) levels were observed in UC compared to control (2.90 ± 2.25 microg/g, 18.28 ± 9.66 microg/g, 1.05 ± 0.48 microg/g). Element status continuously varies according to seasons in three groups. The element levels and their variation tendencies differ in patients suffering from UC compared to healthy subjects. GL supplementation changes the element concentrations and in some cases the variation tendencies. The tendencies were unchanged for Fe, Mg, Mn, S, although element levels increased in supplemented patients at the end of the experiment.

Conclusion: Considering seasonal changes, long-term GL supplementation affects element/redox homeostasis favourably. The alteration of element homeostasis and the elevated element levels is caused by the local antioxidant effect of bioactive mercapturic acid formed from glycosinolate/isothiocyanate in the intestine, which may contribute to the increased element absorption in UC patients and causes a better element status. These processes may contribute to the normalization of redox homeostasis and signal transduction. Support: ETT-02/2006
Intestinal ischaemia associated with carcinoid tumour: A case report with review of the pathogenesis

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Background: Carcinoid tumours are rare, slow-growing neuroendocrine neoplasms that often are indolent and may not become clinically apparent until there has been metastatic spread or evidence of carcinoid syndrome.

Case report: A 44-year old man presented to our clinic department with a history of previous left colon cancer operation, chronic crampy left lower quadrant pain and mass. A MR scan was obtained which demonstrated a calcified mesenteric mass 12*8*10 cm diameter with surrounding left colon mesenteric infiltration. The liver was normal. A case of ischaemic ileal necrosis is reported. It was associated with elastic vascular sclerosis produced by mesenteric metastases of an ileal carcinoid tumour.

Conclusion: It is postulated that intestinal ischaemia may be of more importance in the production of abdominal pain by carcinoid tumours than has been generally accepted, and that it is the result of functional and structural changes in the around the mesenteric blood vessels, caused by substances secreted by the carcinoid tumour.

Keywords: carcinoid tumor, intestinal ischemia
Is osteoporosis an extraintestinal manifestation of inflammatory bowel disease?

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Objective: It is known that several inflammatory bowel disease (IBD) patients have bone density in osteoporotic or osteopenic range. The aim of this study is to determine the rates of osteoporosis and osteopenia in IBD patients (ulcerative colitis [UC] Crohn’s disease [CD] and in indeterminate colitis [ID]) and to determine the associated risk factors.

Material and methods: Hundred IBD patients underwent dual energy x-ray absorptiometry (DEXA) scanning. For interpreting the DEXA results we used femur T-score (number of standard deviations above/below the average peak young adult bone mineral density), femur Z-score (standard deviation of mineral density in patient age groups) and lomber vertebra T and Z scores. T score between -1 and -1.5 was interpreted as osteopenia, below -2.5 as osteoporosis and above -1 was interpreted as normal.

Results: 64% of patients were female and mean of age was 38.87 ± 12.92 (16–73) years and 62% of patients were UC, 34% were CD and 4% were IC. Osteopenia was detected in 41 of all IBD and osteoporosis was detected in 10 patients. Bone densitometry of 49 patients was normal. When the whole group was evaluated a negative correlation between steroid doses and T lomber (r = -0.37, p = 0.014) and Z lomber (r = -0.463, p = 0.006) values was detected. However, when subgroup analysis was done this correlation was not detected in UC where as it was significant in CD patients (for T lomber r = -0.656, p = 0.006; for Z lomber r = -0.746, p = 0.003). There was not a statistically significant relationship between lomber and femur T and Z scores and gender, menopause, disease, site of involvement in all IBD patients, whereas there was a positive correlation between femur and lomber T scores and body mass index (for femur T score r = 0.408, p = 0.28; for lomber T score r = 0.445, p = 0.029). In CD patients femur T and Z scores were significantly lower than the scores in UC patients (for femur T score p = 0.011, for femur Z score p = 0.007). Steroid dose (UC: 2112 ± 2015 mg, CD: 1431 ± 860 mg) and treatment period (UC: 6 months, CD: 5.8 ± 4.7 months) were higher in UC however this did not constitute a statistically significant difference (p = 0.328). Osteopenia and osteoporosis rates were higher in CD (61.7%) when compared with UC (45.2%).

Conclusion: In half of IBD patients osteoporosis and osteopenia were detected. Whereas steroid doses and treatment periods were higher in UC patients, osteoporosis and osteopenia rates were lower than the rates in CD. These results may indicate that densitometry changes in UC are associated with steroid usage. Whereas higher rates of osteoporosis and osteopenia in CD indicate that osteoporosis and osteopenia may be an extraintestinal manifestation of CD.
Acute upper gastrointestinal bleeding: Retrospective evaluation of endoscopic records

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Background/Aim: Acute upper gastrointestinal bleeding is a common and potentially life-threatening medical emergency. Endoscopy is very important for diagnosis and therapy of acute upper gastrointestinal bleeding. This study was performed to evaluate etiology and therapeutic outcome of acute upper gastrointestinal bleeding.

Patients and methodes: A total of 570 gastroscopies were performed for upper gastrointestinal bleeding between January 1999 and December 2002 in our hospital.

Results: Five hundred seventy patients (418 men and 152 women, mean age 49 years, range 14–92 years) were evaluated. Etiology of bleeding was detected in 80.3% of the cases. The most frequent cause of bleeding was peptic ulcer (65.2%) and the localization was duodenum (52.6%), variceal bleeding was detected in 31 cases (5.4%). Therapeutic modality for variceal bleeding was banding which was performed in the same or subsequent sessions in 15 cases, for peptic ulcer sclerotherapy was performed in 5 cases. Forty-five patients (7.8%) were evaluated by general surgery department for serious bleeding and hemodynamic instability and 10 of these patients were operated. There was no complication related to the endoscopic diagnostic or therapeutic procedures.

Conclusion: Endoscopy has a crucial role in the diagnosis and treatment of upper gastrointestinal bleeding. Endoscopy is a method which is nearly free of complication and can save the patient from surgery.
Influence of NOD2/CARD15 and TLR-4 polymorphisms on course of disease and treatment in children with inflammatory bowel diseases

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Introduction: Inflammatory bowel diseases (IBD) have strong genetic background and significant influence of the environmental factors. The results of the latest research studies suggested the contribution of the NOD2/CARD15 and TLR-4 polymorphisms to the pathogenesis of IBD. The aim of our study was assessment of NOD2/CARD15 and TLR-4 polymorphisms in children with IBD and their influence on course of disease and treatment.

Methods: Eighty three children (40 girls, 43 boys, mean age 11.4 yrs, range 3–18 yrs) with IBD (47 with Crohn’s disease [CD], 36 with ulcerative colitis [UC] and 40 healthy controls were included in the study. Three main NOD2/CARD15 polymorphisms, R702W, G908R, 1007fs and Asp299Gly polymorphism of TLR-4 gene were assessed using allele-specific PCR, PCR-RLFP and DHPLC.

Results: We found NOD2/CARD15 and TLR-4 polymorphisms in 29.8% of CD children (mutant allele frequency: R702W-9.7%, G908R-4.8%; Asp299Gly-26.6%, p < 0.05) and 30.5% of UC children (R702W-4.8%, G908R-1.2%; Asp299Gly-27.7%, p < 0.05) compared to 2.6% of controls (R702W-0.7%, G908R-0.7%, Asp299Gly-0%, p < 0.05). We have not identified 1007fs polymorphism neither in CD, UC nor control groups. NOD2/CARD15 and TLR-4 polymorphisms were associated with younger age of onset and severe course of disease with early complications. Children with NOD2/CARD15 and/or TLR-4 polymorphisms need more aggressive treatment to induce clinical remission of the disease including infliximab and systemic steroids.

Discussion/Conclusion: NOD2/CARD15 and TLR-4 polymorphisms in children with IBD are associated with severe course of disease and early complications. Top down therapy strategy is more effective in achieving remission in this group of patients.
MEFV gene mutations and its impact on the clinical course in ulcerative colitis patients

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Introduction: Ulcerative colitis (UC) is an inflammatory disease of the colonic mucosa with involvement from distal to proximal. Familial Mediterranean fever (FMF) is the prototype of the periodic inflammatory clinical syndromes. The presence of gene responsible for FMF which frequently causes inflammation may aggravate the clinical course of UC. We aimed to determine the prevalence of FMF gene mutations in UC patients and its impact on the clinical course.

Methods: Four groups were formed as group 1 UC with distal disease, group 2 UC with pancolonic disease, group 3 UC with total colectomy and group 4 Rheumatoid Arthritis (RA) patients. Eleven mutations of FMF gene were investigated.

Results: The mean age of group 1, 2, 3, and 4 were 46.7 ± 13.9, 43.8 ± 12.9, 44.8 ± 14.2, and 45.8 ± 10.9 years, respectively. The mutations were identified in 19 of the 54 UC patients (35.2%). Homozygous E148Q in 2 patients (3.7%) and heterozygous in 17 patients (31.5%) (E148Q 11.1%, M694V 5.6%, V726A 5.6%, K695R 1.8%, M680I 1.8% and compound heterozygous 5.6%) were determined. Frequencies of FMF gene mutations in group 1, 2 and 3 were 30%, 27.3% and 58.3%, respectively. The mutations were identified in 3 of the 20 RA patients (15%). All of them were heterozygous. The rate of FMF gene mutations were higher in group 3 than in group 4 (p = 0.018) and the number of attacks which were treated with steroid in all UC patients with mutation positive were higher than in mutation negative (p = 0.016).
Conclusions: FMF gene mutations may be identified in UC patients up to 58.3%. It may be suggested that the UC patients with severe form should be identified for FMF gene mutations before the judgment of colectomy.

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Peripheral arthritis related inflammatory bowel disease

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Background: Musculoskeletal manifestations of inflammatory bowel disease are well defined and wide range of prevalence has been reported.

Objective: The aim of this study was to determine the prevalence of peripheral arthritis in inflammatory bowel disease, and their relations with the other extra-intestinal manifestations and the clinical spectrum of inflammatory bowel disease.

Methods: The case information of all patients with inflammatory bowel disease, all extra-intestinal manifestations and presence of peripheral arthritis were recorded.

Results: Female patients with peripheral arthritis related inflammatory bowel disease (PAIBD) (40 patients) were more than male patients (26 patients). PAIBD was found in 66 (18.5%) of 357 patients (28.3% Crohn’s disease, 13.5% ulcerative colitis). The PAIBD occurred before the onset of inflammatory bowel disease in 8 patients. Acute self-limiting episodes, recurrences of the attacks, and persistent symptoms of arthritis were present in 40, 26, and 29 patients, respectively. Arthritis was symmetrical in 33 cases. The knees (43 cases) and ankles (41 cases) were the most common affected joints. Erythema nodosum and pyoderma gangrenosum were more common among patients with PAIBD than patients without it.

Conclusion: This study has supported that PAIBD is the most common extra-intestinal complication of inflammatory bowel disease, which is more frequent in Crohn's disease than ulcerative colitis, and is more common in female. It is associated with erythema nodosum and pyoderma gangrenosum, and is frequently coincident with the flares of the bowel disease. In addition, it frequently involves lower limbs and colectomy seems to have protective effects in patients with ulcerative colitis.
A novel and inexpensive indicator of disease activity in ulcerative colitis: Mean platelet volume

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Introduction: Inflammatory bowel disease (IBD) is characterized by chronic inflammation of the intestine with periods of exacerbations and remissions. Many non-invasive tests have been studied for diagnosis and determining the activation degree of IBD. Nevertheless, an ideal test has not been found yet. Mean platelet volume (MPV) is influenced by the inflammation. In a few study, decreased platelet volume have been reported in IBD. The aim of this study is to determine whether platelet volume would be useful in ulcerative colitis activity.

Material and methods: A total of 61 ulcerative colitis patients (male/female: 41/20), and 27 healthy subjects (male/female: 18/9) were enrolled into the study. In patients with UC, clinical activity was defined according to Truelove-Witts criteria. Endoscopic activity index was defined according to Rachmilewitz Index. For all subjects following tests were performed; ESR, CRP, white blood cell count and mean platelet volume.

Results: A statistically significant decrease in MPV was noted in patients with UC (8.29 ± 1.02 fL) compared with healthy controls (8.65 ± 0.79 fL) (p < 0.05). MPV of active UC (8.06 ± 1.19 fL) patients were significantly lower than that of inactive UC (8.45 ± 0.87 fL) (p < 0.05). There was no statistically significant difference in MPV between groups according to lesion location (p > 0.05). However, MPV was lower in pancolitis-expanded UC (7.92 ± 0.81 fL) compared to left sided-distal UC (8.42 ± 1.06 fL). A negative correlation was found between MPV and endoscopic activity index (r:-0.358 p: 0.005). In UC, MPV did not correlate with ESR, CRP and white blood cell.

Conclusion: Our study showed that MPV reduce in UC, particularly in patients with active UC. Decreased MPV may be an indicator for increased disease activity in patients with UC.
The duplex-Doppler sonography of superior mesenteric artery in clinical assessment of intestinal ischemia

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According to literature data, the significant mesenteric arteries stenosis occurs in 17.5% subjects above 65 years old. Females are more often affected than males with ratio 3:1 respectively. Physical examination findings are subtle, so clinical relevance of splanchnic artery stenosis is unclear. The initial segment of superior mesenteric artery (SMA) – the place of atherosclerotic plaque localization, is the convenient area for Doppler examination.

The aim of our study was to analyze of SMA D-D picture in different groups of patients (pts) treated clinically.

Patients and methods: 130 pts were examined by USG method. Patients were fasting and SMA was assessed in the following order: 2D examination (diameter, topography, area abnormalities), the Doppler flow analysis (systolic -PSV and diastolic -PDV velocities, resistance index, type of spectrum shape). The significance of abnormal USG symptoms was analyzed after clinical observation.

Results: Abnormal or atypical results were observed in 40 pts (31%). The following diseases may influence SMA flow: organic intestinal/vessel affection (atherosclerosis, vessel compression), heart and/or respiratory failure, different neuropathies and encephalopathies, SMA anatomical abnormalities, unclear causes.

Comments: The advanced SMA stenosis (above 70%) gives PSV above 300 cm/s and/or PDV above 45 cm/s. It may be diagnosed successfully by D-D method. Others D-D SMA abnormalities – low resistance flow, poststenotical dilatation, turbulent flow, moderate increase PSV and/or PDV flow are difficult for interpretation. Final conclusion should involve actual clinical situation. Due to a collateralization between SMA, celiac axis and inferior mesenteric artery, stenosis and even occlusion of the one vessel may be asymptomatic for a long time. If two of big visceral arteries are occluded or significantly stenosed, abdominal symptoms, become more intensive and may cause acute mesenteric ischemia, which still carries a high morbidity and mortality rate.

Conclusions:
1. The duplex-Doppler examination of superior mesenteric artery is helpful for diagnosis of intestinal ischemia in some patients.
2. Different diseases non compressing superior mesenteric artery may change visceral flow.
3. The duplex-Doppler sonography may be useful to segregate the group of risk for intestinal ischemia.
4. The analysis of duplex-Doppler results is helpful to work out decision for invasive examination of visceral circulation.
Vegetative-immunological continuum in patients with chronic inflammatory bowel disease (IBD)

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Peculiarities of any deregulation with pathology, in particular with colon pathology are decrease of adaptation and dysfunction in main metabolic processes, which are expressed in standardization of basic mechanisms of metabolism and simplification of regulation system.

**Aim of work:** To study criteria of diagnostics of adaptation reactions of organism in patients with ulcerative colitis (UC) for predicting its development.

**Materials and methods:** Object of study – 28 patients with UC. Study of the homeostatic abilities of organism was carried out by analysis of vegetative tonus and vegetative reactivity (VR). Adaptation potential of organism was determined by evaluating vegetative providing of activity (VPA). Indices of non-specific and humoral immunity were studied. Condition of oxidation systems of homeostasis (POL and AOZ) were estimated based on the model of stress-syndrome Selye. Interrelation between indices characterizing homeostatic abilities of organism and indices of immune system revealed insufficient adaptation potential of the studied patients.

Study of the correlations between VR and VPA indices characterizing adaptive abilities of organism and main indices of immune system show tension of compensatory-adaptation reactions of organism i.e. with the increase of hypersymphaticotonic reactions, compensatory reactions of immune system decrease, which is an unfavorable predicting sign of a disease course.

As a result of the carried out correlation analysis between indices of vegetative and immune systems considering indices of oxidation homeostasis four types of reaction of vegetative nervous system have been selected: mobilizing, rigid, compensatory and decompensatory. Mobilizing type is characterized by increased level of AOZ at high level of MDA (alert phase), reactions of tension of VNS, which negatively correlated with T-helpers and T-suppressors, which caused immune deficiency. Rigid type was characterized by a decrease of AOZ indices at intensification of processes of hyper-oxidation (phase of desadaptation) negative correlations between functional activity of B-cells and adaptation reactions of tension in VNS. At compensatory type increase of T-helpers and T-suppressors was observed at irrefutable increase of functional activity of B-cells based on the tension reaction of CNS, while being in the alert condition in state of oxidation homeostasis. Decompensatory type was characterized by immune deficiency, phase of desadaptation of oxidation homeostasis.

Thus, the developed evaluation criteria of adaptation abilities of organism allowed us to optimize diagnostics of IBD.
Diagnostic criteria of disorders in cerebral homeostasis based on the analysis of its biorhythm parameters in patients with chronic inflammatory bowel disease (IBD)

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The most obvious phenomena of desynchronosis are evident in diseases of digestion system, which changes of rhythmic activity, as a rule, are the causes of its functional and structural disorders.

Aim of study: To study biorhythmic structure of indices of haemodynamic parameters of cerebral homeostasis in patients with IBD for optimization of diagnosing.

20 patients with ulcerative colitis (I group) and 14 patients with Crohn’s disease – CD (II group) were examined. On REG reographic index (RI) and coefficient of tonic tension (CTT) were studied. Adaptation abilities of brain vessels were studied using orthostatic probe. Circadian biological rhythms have been analyzed. Parameters of rhythm were estimated by cosinor-analysis method (mesor, amplitude, acrophase and batiphase). Types of curves have been estimated: normal, oscillating, inversional, mixed, monotone, double-inclined. Estimation of functional reserve (FR) was carried out with calculating indices of day adaptation (IDA).

Distinctive peculiarity of oscillating processes of blood filling intensity in vessels was a decrease of amplitude of circadian rhythm, which testifies to disorder of adaptation of cerebral homeostasis in patients with IBD.

For patients with IBD peculiarities of day oscillations of cerebral homeostasis were: change of an average daily level of functioning, amplitude disorders, deformation of a curve, inversion of acrophase and batiphase locations, change of the functional reserve. In orthostatic probe amplitude of oscillation of CTT in patients of both groups on the left and on the right decreased, which determined a monotonic and rigid curve. Significant decrease of IDA index after load showed a decrease of functional reserve of cerebral vessels.

Peculiarities of cerebral haemodynamic in patients with UC are: normal daily rhythm and increased functional reserve.

Peculiarities of cerebral haemodynamics in patients with CD are: inversion of daily rhythm and decreased functional reserve.

It is necessary to note that patients with CD index IDA decreased for 30.0% more than that of patients with UC.

Thus, patients with CD, comparing with patients with UC, have evident insufficient flexibility of adaptation mechanisms.
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