Crossing New Borders in IBD: Thoughts and Demands – From Mechanisms to Treatment

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CROSSING NEW BORDERS IN IBD: THOUGHTS AND DEMANDS – FROM MECHANISMS TO TREATMENT

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Scientific Organization:
F. Magro, Porto (Portugal)
A. Dignass, Frankfurt (Germany)
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100. Evaluation of CD40 and CD80 receptors in the colonic mucous membrane of children with Crohn’s disease
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105. Diagnostic accuracy of tissue transglutaminase antibodies for detecting persistent villous atrophy among adult patients on a gluten-free diet
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107. Association between inflammatory bowel disease and celiac disease: About 4 cases
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108. Active disease prevention in inflammatory bowel disease through exercise
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110. Are lower levels of fecal calprotectin reassuring in Crohn’s disease patients?
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111. C-reactive protein/albumin ratio is a good predictor of response to intravenous corticosteroids in acute severe ulcerative colitis
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112. Surgical aspects of Crohn’s disease
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113. Appendiceal Crohn’s disease presenting as acute appendicitis
    S. Mrabet, I. Akkari, R. Letaief, F. Hemila, E. Ben Jazia (Sousse, TN)

114. Surgical treatment in Crohn’s disease
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115. Appendectomy in Crohn’s disease: Is it a risk factor or a mis-diagnosis?
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116. Is transabdominal ultrasonography as effective as CDAI and MR enterography in Crohn’s disease?
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117. First experiences with vedolizumab therapy in a Croatian tertiary center
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118. Can we predict the adverse reactions in patients with inflammatory bowel disease treated with azathioprine?
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119. Clinical aspects of microscopic colitis
    O. Petrascu, A. Solomon (Sibiu, RO)

120. Challenges in patients with ulcerative colitis and primary sclerosing cholangitis
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121. What factors affect the processes of fibrosis in pediatric inflammatory bowel diseases?
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122. Sleep impairment and inflammatory bowel disease activity
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123. The role of Helicobacter pylori eradication on disease activity measures in patients with Crohn’s disease
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124. TH1 transcription factor T-bet as a new target for Crohn’s disease therapy
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125. Simultaneous presentation of Crohn’s disease in siblings: Genes or environment?
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126. The results of the newfound Department of Gastroenterology with Endoscopy Unit of Prijedor Hospital
G. Predojevic, E. Iglic (Prijedor, BA)

127. Correlation of fecal calprotectin with endoscopically defined activity index and localization in IBD patients
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128. The selectivity of the neutrophils infiltration in ulcerative colitis may be dependent on the claudin-4 expression
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129. Irritable bowel syndrome may be associated with elevated hepatic enzyme and metabolic syndrome
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130. Can the inflammatory bowel disease biologics registry lead to improved quality of care?
I. Rikaby, L. Alrubaiy, H.A. Hutchings, J.G. Williams (Cardiff, Swansea, GB)

131. Systematic review of the clinical disease severity indices for inflammatory bowel disease
I. Rikaby, L. Alrubaiy, M. Sageer, H.A. Hutchings, J.G. Williams (Swansea, Cardiff, GB; Massachusetts, USA)

132. Paradoxical reaction to anti-tuberculosis therapy in a patient with disseminated tuberculosis under infliximab
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133. A non-treated Crohn’s disease flare during pregnancy: The impact of perianal disease

134. Sustained deep remission with intermittent low-dose rifaximin schema for antibiotic-dependent pouchitis – A 2-year open-label study data
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135. Extraintestinal manifestations of Crohn’s disease and its clinical features among patients in Split-Dalmatia County, Croatia
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136. The severity of endoscopic lesions in ulcerative colitis: Between the assessment of endoscopist and the Ulcerative Colitis Endoscopic Index of Severity score
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137. Correlation between Crohn’s Disease Activity Index and the severity of disease flare-up
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138. Azathioprine and Crohn’s disease: Efficacy and tolerance
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139. Predictive factors for a severe clinical course in ulcerative colitis
L. Safer, M. Zakhama, W. Ben Mansour, W. Bouhlel, A. Guediche, M.H. Loghmari (Monastir, TN)

140. Predictive factors of recurrence of Crohn’s disease after ileocecal resection
L. Safer, A. Guediche, R. Baklouti, F. Aissaoui, M. Zakhama, W. Ben Mansour, W. Bouhlel, M.H. Loghmari (Monastir, TN)

141. Which ulcerative colitis patients are at risk of having proximally extending disease?
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142. The prevalence of Clostridium difficile infection in patients with inflammatory bowel disease – A study in a tertiary care center in Romania
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143. The correlation between fecal calprotectin and disease location in patients with Crohn’s disease
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144. Patient perception and approval of fecal microbiota transplantation (FMT) as an alternative treatment option for ulcerative colitis
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145. The efficacy of 5-ASA and infliximab therapy in patients with Crohn’s disease

146. Role of laboratory markers in pediatric inflammatory bowel disease
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147. A rare cause of retroperitoneal fibrosis
S. Shwana, A. Ur Rahman, E. Slowinska (Merthyr Tydfil, GB)

148. Violations of the intestinal microbiocenosis on the background of non-specific ulcerative colitis exacerbation
I.M. Skrypnyk, G.S. Maslova, R.I. Skrypnyk (Poltava, UA)

149. Clinical and psychological features of patients with different variants of non-specific ulcerative colitis
I.M. Skrypnyk, G.S. Maslova, R.I. Skrypnyk (Poltava, UA)

150. Correlation between endoscopic and histological activity in IBD with level of the FCP
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151. Treatment of patients with ulcerative colitis and arthritis
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152. Ulcerative colitis and adenocarcinoma – Case report at 24-year-old pregnant with long-lasting IBD
R. Tamburic, J. Petkovic-Dabic, M. Kostic, L. Jovandic, S. Dabic (Banja Luka, BA)

153. Eosinophilic esophagitis, clinical practice: Case report and literature review
R. Tamburic, J. Petkovic-Dabic, M. Kostic, S. Trbojevic (Banja Luka, BA)

154. Gene expression profile of endoscopically active and inactive ulcerative colitis: Preliminary data
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155. The importance of an early proactive anti-TNF therapy monitoring in patients with ulcerative colitis
A. Tudora (Timisoara, RO)
156. Elements influencing health-related quality of life in patients with collagenous colitis
A. Tudora (Timisoara, RO)

157. Is postoperative course of rescue colectomy in severe acute ulcerative colitis affected by preoperative biologic treatment?
B. Unsal, Z. Akpinar, E. Saritas Yuksel, F. Topal, B. Oğut Aydin, C. Cekic (İzmir, TR)

158. The expression of MMP-7 dependent of CD45-positive cells in lamina propria of inflammatory bowel disease
W. Ustymowicz, A. Pryczynicz, M. Maciorkowska, L. Zakrzewski, J. Zinczuk, K. Zareba, E. Maciorkowska (Białystok, PL)

159. Epidemiology, complication, extraintestinal manifestation and treatment of inflammatory bowel disease in Sanliurfa region of Turkey
A. Uyanikoglu, A. Ciftci (Sanliurfa, TR)

160. Hyperbaric oxygen therapy in the treatment of ulcerative colitis
A. Uzunova, Z. Kirvikov (Sofia, BG)

161. Efficacy of vedolizumab in inflammatory bowel disease refractory to anti-TNF-α

162. The diagnostic yield of small bowel capsule endoscopy in postsurgical Crohn’s disease

163. Switching from subcutaneous anti-TNF to intravenous anti-TNF in ulcerative colitis: A multicenter study

164. TrueColours Ulcerative Colitis (TCUC): Will patients with UC complete digital questionnaires in real-time?

165.* Transcription factor GATA-3 in ulcerative colitis: Use of specific DNAzymes to inhibit experimental colitis
B. Weigmann, V. Popp, K. Gerlach, A. Turowska, H. Garn, R. Atreya, I.-C. Ho, H. Renz, M.F. Neurath (Erlangen, Marburg, DE; Boston, US)
166. Clinical and translational outcomes in patients with primary sclerosing cholangitis and inflammatory bowel disease receiving vedolizumab  

167.*Perianal Crohn’s disease – Association with significant inflammatory activity in proximal small bowel segments  
S. Xavier, T. Curdia Goncalves, F. Dias de Castro, J. Magalhaes, B. Rosa, M.J. Moreira, J. Cotter (Guimaraes, Braga, PT)

168. Stricturing Crohn’s disease – Can we predict need for surgery at first hospitalization?  
S. Xavier, T. Curdia Goncalves, F. Dias de Castro, J. Magalhaes, M.J. Moreira, J. Cotter (Guimaraes, Braga, PT)

169. A case of pyoderma gangraenosum associated with ulcerative colitis  
P. Yaneva, R. Shentova, M. Baycheva, P. Hadjiiski, D. Konfinova, C. Zhelev (Sofia, BG)

170. Fecal calprotectin for detection of postoperative endoscopic recurrence in Crohn’s disease: Systematic review and meta-analysis  
D.E. Yung, Y.S. Tham, S. Fay, T. Yamamoto, S. Ben-Horin, R. Eliakim, A. Koulaouzidis, U. Kopylov (Edinburgh, GB; Tel-Aviv, IL; Mie, JP)

171. Entero-MRI in Crohn’s disease: Predictive value of the inflammatory angiogenesis  
H. Zaghouani, S. Majdoub, N. Mallat, F. Bouzaiene, E. Ben Jazia, D. Bakir (Sousse, TN)

172. Role of DWI and ADC maps in Crohn’s disease  
H. Zaghouani, S. Majdoub, N. Mallat, F. Bouzaiene, E. Ben Jazia, D. Bakir (Sousse, TN)

173. The evaluation of CD40 and CD80 receptors in the colonic mucosal membrane of children with ulcerative colitis  
M. Zakrzewski, M. Maciorkowska, W. Ustymowicz, I. Roszko-Kirpsza, B. Kaminska, A. Szlagatys-Sidorkiewicz, E. Maciorkowska, K. Guzinska-Ustymowicz (Bialystok, Gdansk, PL)

174. Spleen abscess: Rare complication of Crohn’s disease  
P. Zalizko, V. Mokricka, M. Pavars, J. Pokrotnieks, A. Pukitis (Riga, LV)

175. Toxic myocarditis as a consequence of change in mesalamine therapy  

176. Extraintestinal manifestations of pediatric inflammatory bowel disease – Experience from a tertiary center  
C. Zhelev, P. Yaneva, R. Shentova, M. Baycheva, P. Hadjiiski, D. Kofinova (Sofia, BG)
Session I

“OMICS” science in IBD
Host-microbiome interactions – Reality or myth?

Harry Sokol
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The pathogenesis of the inflammatory bowel disease (IBD) is linked to an activation of the gastrointestinal immune system toward the gut microbiota in genetically susceptible hosts and under the influence of environment. The microbial community in the human gastrointestinal tract is fundamental to the health and is under the influence of both environmental and genetic factors. Loss of the fragile equilibrium within this complex ecosystem, termed dysbiosis, is involved in numerous pathologies, including IBD. Patients with IBD exhibit an altered gut microbiota composition with notably a decreased abundance of anti-inflammatory bacteria such as Faecalibacterium prausnitzii. We also observed alteration in the fungal microbiota composition in these patients. The association of several polymorphisms of innate immunity genes involved in microbial sensing with IBD is another argument for the involvement of the gut microbiota in the IBD pathogenesis. Some genetic factors involved in IBD might indeed act through a microbiota effect. We notably demonstrated that this is the case for the IBD susceptibility gene CARD9. Gut microbiota alterations are thus not only a consequence of intestinal inflammation but a key actor in the disease pathogenesis. Fecal microbiota transplantation studies, by showing some efficacy in IBD confirm that the gut microbiota can now be considered as a potential therapeutic target.
Microbiota-derived metabolites – Homeostasis and bacterial activities

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The microbiome differs significantly between ileal Crohn's disease, colonic Crohn's disease, ulcerative colitis, subjects with and without primary sclerosing cholangitis and healthy subjects. Dysbiotic features are observed both in faeces and in mucosal biopsies. Some of them are shared in various situations of IBD and others are so specific that the term “signature” is proposed (usually defined as combinations of presence and absence of microbial species).

Dysbiotic characteristics can serve as disease markers (living microorganisms being considered as bio-indicators reflecting ecological conditions which shape their profile) or therapeutic targets. Whatever their use, these markers can be either taxonomic descriptors of the microorganisms or metabolic markers, the later resulting from the global metabolism of the host and microbiota.

There is a greater knowledge on how to modify metabolisms and thus a theoretical advantage of deciphering metabolic abnormalities and evaluating metabolites rather than microorganisms contributing to their production.

In this talk, I will summarize the present knowledge on bacterial metabolites or components of interest in subjects with IBD. These include short chain fatty acids (especially butyrate), volatile compounds, bile salts (especially isomers with beta epimerization), sulphides, methane, immunomodulating molecules (especially those involved in the microbial quorum sensing and the MAM protein from Faecalibacterium prauznitsii). All of them have the potential to become clinically relevant markers or treatment targets.
Tandem State-of-the-Art Lecture

Translation of “omics” science into clinical relevance for IBD

Claudio Fiocchi
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Progress in practically all fields of human endeavor is becoming increasingly dependent on technological advances, as this is also true for biological sciences and medicine. Two main factors are responsible for this situation: the first is the realization that most chronic diseases affecting humanity, such as IBD, fall in the category of complex diseases, where environmental, behavioral, genetic, microbial and immune factors interact to initiate, promote and mediate intertwined biological events that underlie disease pathogenesis; the second is the increasingly obvious reality that every patient is becoming a “big data” source due the continuously expanding amount of clinical information derived from numerous sophisticated tests. These changes require new approaches that allow integrating large amount of data, yielding more integrated mechanisms of disease, and identifying new therapeutic targets. Integration of biological and medical knowledge can be achieved by assessing each individual pathogenic component – an “ome” – in its totality. Therefore, “omics” becomes the study and in-depth evaluation of all omes relevant to the disease process under investigation.

Considering its overall nature, IBD is the perfect entity that can benefit from an “omics” approach. Its pathogenesis is still undefined and its treatment is far from ideal in spite of significant progress achieved in the last few decades. If so, how will an “omics” perspective change our overall approach to IBD and deliver clinically relevant information that can benefit patients with Crohn’s disease and ulcerative colitis? This can be done by adopting a “network medicine” approach where, rather than trying to force disease pathogenesis into a one cause-one effect model, different networks are identified that translate the complexity of multiple influences on IBD. By developing technologies that comprehensively assess genetic variation, environmental influences, molecular alterations, cellular metabolism, and protein function, network medicine is opening up new paths for uncovering causes and identifying cures. These concepts are at the core of the “IBD interactome”, defined as a disease network where dysregulation of individual omes causes intestinal inflammation mediated by dysfunctional molecular modules that control pathogenic events. To characterize the IBD interactome new concepts and new tools are needed based on a systems biology approach, an unbiased data-driven integration strategy that reveals the key players of the system, pinpoints the central drivers of inflammation, and allows developing targeted therapies.
Session II

Targeting inflammation
Cytokines play a crucial role in the pathogenesis of inflammatory bowel diseases (IBD: Crohn’s disease, ulcerative colitis) by controlling multifaceted immune mechanisms of inflammation. In particular, the imbalance between pro- and anti-inflammatory cytokines controls the critical crossroad between resolution of inflammation and disease perpetuation with tissue destruction. However, recent studies suggest the existence of a hierarchical network of regulatory cytokines with important implications for therapy. Here, the role of cytokines produced by innate and adaptive immune cells is discussed as well as their relevance for future therapy of IBD. In particular, the role of cytokine controlling innate and adaptive immune systems such as IL-12/IL-23, IL-9, IL-6 and IL-22 will be discussed. Moreover, newly discovered cytokines of the IL-12 family such as IL-27 and IL-35 will be discussed. Finally, new cytokines of the IL-1 family such as IL-36 and IL-38 and their function in the mucosal immune system in IBD will be presented. While some of these cytokines are currently used as targets for therapy, others have shown limited efficacy when targeted by neutralizing antibodies and some are currently tested as IBD targets in early phase 2 studies. It is expected that targeting of cytokines will be a cornerstone of our future therapeutic strategies, although concept for personalized medicine in this context are urgently needed.
T-cell trafficking in IBD: Mechanisms and therapeutic targets

Stefan Schreiber  
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Targeting immune cell trafficking into the inflamed mucosa appears to be a relevant therapeutic development given the large number of activated immune cells leaving circulation and entering areas of intestinal inflammation in IBD.

Several attempts have been made to interrupt the entry of lymphocytes into the lamina propria. While blockade of ICAM1 (alicaforsen) had only limited efficacy and inhibition of CCR9 (CCX282/Trafficet-EN) had no appreciable clinical impact, blockade of α4 integrins conveyed strong anti-inflammatory effects accompanied by a clinical benefit. The first compound, natalizumab, a monoclonal antibody blocking both α4β1 and α4β7 integrins is clearly effective in both multiple sclerosis and Crohn’s disease. However, it became clear that blockade of immune cell trafficking to the brain (via α4β1 integrin blockade) gives rise to reactivation of dormant JC-Virus infection leading to devastating progressive multifocal leucencelopathy which rendered the use of natalizumab as a therapy for IBD obsolete.

With vedolizumab more focused inhibition of α4β7 integrin is carried out. Although there is appreciable anti-inflammatory clinical activity in induction and maintenance of remission and mucosal healing in both ulcerative colitis and Crohn’s disease no severe side effects (in particular no immunosuppressive side effects) are seen by the use of this drug. Presently the therapeutic target is further broadened by follow up developments investigating oral topical agents that specifically inhibit α4β7 integrin at the site of the mucosa and by agents that systematically inhibit lymphocyte trafficking through stimulation of the S1P1 receptor (ozanimod, etrasimod) leading to retention of lymphocytes in lymph nodes and other lymphatic structures.

However, the exact mechanisms of α4β7 blockade, that delivers a strong clinical benefit, remains not fully understood. Not only that relevant concentrations of the blocking monoclonal antibody need to be achieved that are well beyond saturation of the integrin target in peripheral blood it also appears that early changes in mucosal morphology that can be detected by ultrasound already a few days after initiation of treatment do not correlate with inhibition of T cell trafficking. It rather appears as if innate immunity and potentially non-T cells represent therapy relevant target mechanisms, too.
Fibrogenesis in IBD – Mechanisms and targets

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The inflammatory bowel disease (IBD) course is highly heterogenous. Intestinal fibrosis causing clinically apparent stricture formation is a common feature of both entities of IBD, Crohn’s disease and ulcerative colitis. In its most pronounced form it can cause intestinal obstruction as well as need for surgical intervention. This constitutes a major treatment challenge. Despite the emergence of stronger immunosuppressive medications, we can only minimally reduce the incidence and prevalence of fibrostenosing IBD. No specific antifibrotic therapy is available. Fibrosis results from the response of gut tissue to the insult inflicted by chronic inflammation. The underlying fibrogenic mechanisms are complex and dynamic, involving multiple cell types, interrelated cellular events, and a large number of soluble factors. Luminal bacterial products leak into the interstitium and induce an innate immune response mediated by activation of both immune and non-immune cells. Damage-associated molecular patterns, intracellular components released by necrotic cells, can also induce mesenchymal cell activation and contribute to stricture formation. Fat wrapping around the bowel wall, the so-called 'creeping fat', typical of Crohn’s disease, can drive fibrogenesis through the release of free fatty acids that induce intestinal muscle cell proliferation. Clinical and experimental evidence indicates that once fibrosis is established it can progress independently of inflammation. The composition of the intestinal extracellular matrix, its mechanoproperties and matrix bound factors are dramatically altered in chronic gut inflammation and can actively promote fibrosis. The conventional view that intestinal fibrosis is an inevitable and irreversible process in patients with IBD is gradually changing in light of an improved understanding of the cellular and molecular mechanisms that underlie the pathogenesis of fibrosis. If so, identification of the unique mechanisms of intestinal fibrogenesis should create a practical framework to target and blockade specific fibrogenic pathways. Novel animal models assist in the discovery and testing of novel anti-fibrotics. We provide a roadmap for the translation of novel anti-fibrotic compounds in patients with IBD.
Translation of basic observations into clinical relevance in IBD

Subrata Ghosh
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The incidence of inflammatory bowel disease (IBD) is increasing in newly industrialized countries, though it has stabilized in the Western countries. The incidence is still increasing in pediatric population in several countries. Environment dominates over host genetics in shaping human intestinal microbiota. The strong circumstantial evidence that environment, particularly diet, and its change with industrialization may play a significant role predisposing intestinal inflammation in a genetically susceptible host has been supported by epidemiology data as well as significant advances in the basic science of metagenomic sequencing and functional analysis. Understanding the pathways affected by loss of function mutations in cytosolic pattern recognition receptor NOD2 that is activated by peptidoglycan fragment muramyl dipeptide after the discovery of NOD2 polymorphisms as the first identified susceptibility gene for ileal Crohn’s disease firmly associated the microbiota with IBD. This is now driving translational opportunities such as fecal microbial transplant, synthetic biology and nutrient derived microbiome manipulation.

Targeted therapies of intestinal inflammation in IBD has been driven by major advances in understanding of immunological pathways in IBD and in other immune mediated inflammatory diseases. The number of targeted therapies, monoclonal antibodies or oral molecules is increasing, involving targets such as TNF, integrins, IL12/23 and IL23 and JAK family. The evolution of anti-integrin therapy for IBD was a tremendous example of translation of basic science understanding of gut immune cell trafficking into a specific therapy thus avoiding the devastating complication of progressive multifocal leukoencephalopathy.

We currently have major opportunities for translational medicine in IBD. The explosion of genomic data, molecular profiling, pathway analysis, evolution of cell based therapies provide us with the platform for stratification and precision medicine to predict better the disease course and increase the efficacy of drugs. The sophistication of analysis of molecular networks and pathways, the exponential increase in ability to synthesize big data and develop predictive models and the ability to design and synthesize small molecules with target specificity as well as new types of monoclonal antibodies such as bifunctional antibodies and Chimeric Antigen Receptor T cells are able to use the specificity of mAb to retarget the cellular immune system, concepts which have become reality in cancer. It is important that biomarker discovery translates to precision medicine type clinical trials in IBD with appropriate positive and negative controls. Many hurdles remain for accelerating the pace of translation of basic science discoveries to clinical benefit including the regulatory environment, the ethical boundaries, the route to rapid validation of novel biomarkers, encouragement of biomarker discovery platforms, designing accelerated trials and novel trial designs such as
‘bucket’ and ‘umbrella’ type trials as well strengthening applied health research for adoption and implementation. Very large data set collections and informatics will play a major role in this as happening worldwide despite considerable hurdles.
Session III

Different sides of colitis
Microscopic colitis – Diagnosis and treatment

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Microscopic colitis (MC) is an idiopathic, chronic inflammatory bowel disease and a common cause for recurrent watery, non-bloody diarrhea, especially in elderly females. Additional symptoms may include abdominal pain, nocturnal diarrhea, urgency and fecal incontinence. There is an association with other autoimmune diseases and a significant symptom overlap to diarrhea-type irritable bowel syndrome. Smoking and specific drugs (NSAIDs, PPI, SSRI) have been identified as potential risk factor for MC. The endoscopic appearance of MC is usually normal, but in few cases unspecific alterations such as edema, erythema, mucosal nodularity or abnormal vascularity may be found. The diagnosis of MC relies on the histological examination of multiple colonic mucosal biopsies. The two major histological subtypes of MC are collagenous colitis (CC) and lymphocytic colitis which usually can be differentiated by conventional stainings. CC is defined by a thickened collagen band underneath the surface epithelium, and LC by an increased number of surface intraepithelial lymphocytes. In both types, there is increased inflammation in the lamina propria, but only little or no crypt architectural distortion. More recently, the term “incomplete microscopic colitis” (MCi) has been established which describes incomplete or variant forms of MC showing less characteristic histological features. Up to now, there are no established serum or fecal biomarkers in MC. There is also a lack of widely accepted measures for disease activity. Due the overall symptom burden, health-related quality of life is significantly reduced in MC patients.

Current guidelines (EMCG, AGA, SMCG) recommend oral budesonide 9 mg/day for 6 to 8 weeks as treatment of choice to induce clinical remission in patients with MC. Randomized placebo-controlled trials in CC (n = 4) and LC (n = 3) have reported remission rates with oral budesonide between 73% and 100%. After cessation of treatment clinical relapse may occur in up to 80% of cases. In these cases, oral budesonide should be reintroduced and continued as maintenance therapy with a lower dose. Three randomized placebo-controlled trials in CC have shown maintenance remission rates around 80% with budesonide 6 mg/day after 6 months or 4.5 mg/day after 12 months. At present no other drugs are established in MC. In patients with mild disease activity, cholestyramine, loperamide or bismuth subsalicylate may be considered for symptom control. Mesalazine was not better than placebo in 2 randomized controlled trials. In case series, MC patients with severe steroid-refractory disease responded to immunosuppressives or anti-TNF-α drugs (infliximab, adalimumab). Therefore, these drugs may be considered as alternative to surgical therapy.
Microscopic colitis or only drugs?

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In this session, we will discuss the role that drugs play in causing microscopic colitis and the similarities and differences in the pathology, pathophysiology, and treatment of drug-induced microscopic colitis (DIMC) and other forms of drug induced colitis.

The diagnosis of microscopic colitis (MC) is based on characteristic histologic abnormalities in the colonic mucosa. The pathophysiology of MC is likely related to an abnormal immune reaction to various luminal antigens in predisposed hosts. There have been several case reports of patients with apparent DIMC, and more recently several large series that have furthered our understanding of this entity.

In 2005, a systematic review of the existing literature identified several medications with a high likelihood of inducing MC, including non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs) and serotonin reuptake inhibitors (SSRIs). Subsequently, several studies have affirmed that a subset of MC appears to be caused by these and other drugs. A recent large case control study from the UK confirmed these earlier observations and demonstrated that concomitant use of NSAIDs and PPIs had a particularly high risk of DIMC, indicating a synergistic effect. The pathology of DIMC is not different than that of cases that are not caused by drugs. The treatment of DIMC is to stop the offending drug if at all possible, after which the symptoms typically resolve. If diarrhea persists for more than three months after stopping the potentially offending agent, the UK study showed that the drug was not likely the cause of the MC, in which case standard treatment for MC is recommended.

There are other forms of drug-induced colitis that are different than DIMC. For example, mycophenolate mofetil can cause a colitis that grossly can resemble inflammatory bowel disease, although some cases are only identified on microscopy. Histologic findings range from acute colitis to a chronic colitis resembling IBD to a graft-versus-host like appearance, but an MC-like appearance is not expected. A more recent observation is the occurrence of colitis due to check point inhibitors, which also may mimic IBD grossly and to some extent histologically, although crypt architectural distortion is usually not seen.

In summary, a proportion of MC is drug induced, although the symptoms, histology, and treatment of this subset are the same as MC not due to drugs. There are other forms of drug induced colitis that may or may not have gross endoscopic abnormalities, but even those cases with only microscopic findings should not be confused with MC based on histologic findings. The first line treatment of DIMC and other forms of drug-induced colitis is stopping the offending drug whenever possible, although some cases will require specific treatment, often consisting of corticosteroids or immune suppressing medications.
Pathology perspective – Are all cases idiopathic?

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The histologic examination of biopsies or resection specimens remains a key step in the work-up of patients with suspected of IBD, particularly in the differentiation of UC from CD and other non-IBD related colititides. However, from a pathologic perspective, ulcerative colitis (UC) and Crohn’s disease (CD) are diagnosis of exclusion. Many entities can mimic the histologic features of both conditions and the correct diagnosis of IBD depends on the combination of medical history, clinical evaluation, laboratory data and typical endoscopic, histologic and radiologic findings.

Many inflammatory conditions of the gut have symptoms but also histologic features that can imitate UC and CD. Although both UC and CD show characteristic histological features, none of the morphological changes seen in either condition is entirely specific. Infectious agents (Salmonella, Shigella, Campylobacter jejuni, Yersinia spp., Tuberculosis, Amoeba, CMV, Clostridium difficile, Strongyloides stercoralis, Schistosoma spp.), other inflammatory diseases (diverticulitis, microscopic colitis, diversion colitis), vascular lesions, radiation, iatrogenic factors (NSAIDs, endoscopic cleaning solutions, immunotherapies).

It may be difficult to differentiate infectious colitis, particularly in a resolving phase, from CD in colonic biopsy specimens. Poorly circumscribed microgranulomas are a feature of some infective colititides, particularly Salmonella and Campylobacter. Occasionally, UC-like changes may be seen in more chronic forms of infectious colitis, particularly chronic Shigellosis and Amoebiasis. Acute chlamydial proctitis may resemble active UC. Well-formed granulomas are a feature of some infective colititides with Chlamydial infection, Yersiniosis, and Tuberculosis being the most characteristic. CMV, HSV, and Cryptosporidiosis may produce a florid active enterocolitis, masquerading as active UC, particularly in patients immunosuppressed.

Chronic strictures in ischemic enterocolitis may suggest a diagnosis of CD. Histologically, the reparative and chronic phases of ischemia disclose microscopic fissures, crypt epithelial regeneration and distortion, and chronic inflammation, features suggestive of chronic inflammatory bowel disease.

Now accepted as one of the commonest causes of clinically important ileal ulceration are non-steroidal anti-inflammatory drugs (NSAIDs). Cancer immune-based therapies, including the widely used class of agents known as immune checkpoint inhibitors, can also be associated with mucosal damage mimicking IBD and intestinal manifestations, with diarrhea being one of the most frequently reported adverse effect.

In conclusion, some of the pathological mimics are iatrogenic, but common diseases, such as bacterial infection, ischemia, and diverticulosis may produce confusing histological appearances.
Histopathologists must be aware and be able to recognize the “non-idiopathic” cases to ensure appropriate management for patients with inflammatory pathology of the intestines.
Pathology perspective – Drugs can not be ruled out

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Drug-associated injury of the gastrointestinal tract can mimic many gastrointestinal disorders clinically, endoscopically and histologically. Histology in drug-induced colonic injury is often nonspecific and may resemble many types of colitides, including inflammatory bowel disease (IBD), microscopic colitis, ischemic colitis, or GVHD. The wide spectrum of histopathologic changes seen in IBD can be caused by a variety of therapeutic agents, including non-steroidal anti-inflammatory drugs, antibiotics, and antineoplastic agents, and lead to erroneous diagnosis. Drug-induced gastrointestinal pathology can present with ulceration, stricture formation, variable inflammatory processes and ischemia while histological features favoring a drug etiology include raised numbers of eosinophils, epithelial damage in the form of apoptosis, cytoplasmic vacuolation, increased intraepithelial lymphocytes, and melanosis coli, though none of these findings are specific. Pathologist should bear in mind that, a single type of medication may cause multiple patterns of injury, which can involve the entire GI tract or just some parts of it. In the colon, drugs can cause erosions and ulcerations, various types of colitis including pseudomembranous colitis, microscopic colitis, neutropenic enterocolitis, malakoplakia, ischemic colitis, focal active colitis, and apoptotic colopathy. In addition to the direct effect of the drug, secondary effects such as microbial colonization due to immunosuppression caused by the drug may occur as in antibiotics or immunosuppressive agents where C. difficile and CMV could colonize the mucosa, respectively. Drugs presenting with IBD-like pathology include mycophenolate mofetil, diclofenac, clofazimine and antineoplastic agents such as aminoglutethimide. Mucosal pathology could resemble ulcerative colitis or Crohn’s disease with or without granuloma formation. Novel drugs used in advanced stage neoplastic conditions, the “immune checkpoint inhibitors” comprising CTLA-4, PD-1 and PDL-1 inhibitors can also cause colitis with IBD-like features. Moreover, some drugs have been linked to cause or worsen IBD like conditions which include isotretinoin, antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), oral contraceptives, mycophenolate mofetil, etanercept, ipilimumab, rituximab and sodium phosphate. Differential diagnoses can be very difficult without appropriate clinical information. Diseases in the differential diagnoses need to be excluded, and in some cases, withdrawal and re-exposure may be necessary to confirm the diagnosis.
Session IV

Evaluation of IBD
Evaluating damage in Crohn’s disease

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Crohn’s disease (CD) is a chronic progressive destructive disease. The chronic process of inflammation and resolution can result in complications such as strictures, fistulas and abscesses with consequent intestinal resection and irreversible structural bowel damage.

Cross-sectional imaging, such as magnetic resonance imaging and computed tomography are accurate in assessing the presence and the progression of bowel damage over time. Recent studies suggest that also bowel ultrasound might be able to assess and quantify bowel damage.

In the last decade, a cross-sectional imaging-based index, the Lémann Index, has been proposed and developed by an international panel of experts, and emerging data are confirming that the Lémann Index can also measure bowel damage with good sensitivity to change. Although limited evidence is currently available, current effective therapies, especially anti-TNFs, can stop or even reduce bowel damage in CD patients. Moreover, quantifying bowel damage in CD since diagnosis may predict long-term disease progression and may be helpful in treating earlier in order to avoid bowel damage or to stop existing bowel damage progression.
Assessing disease severity in Crohn’s disease

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Current therapeutic strategies in Crohn’s disease are aimed towards achievement of long-term durable clinical remission along with prevention of long-term structural complications and alleviation of the need for surgery, hospitalizations and requirement for corticosteroids. Our available therapeutic armamentarium is still only partially successful in achievement of these goals.

There is still an ongoing debate regarding both the outcomes of interest and the optimal strategies of assessment of these outcomes. Patient-related outcomes such as achievement of symptomatic remission, improvement in the quality of life, absenteeism etc are of ultimate and increasing importance as the patients are increasingly more and more involved in therapeutic decisions and selection of treatment strategies. However, there is a clear lack of association between clinical symptoms and the burden of underlying inflammation in Crohn’s disease, and a growing need for selection of more objective severity measures. Mucosal healing is the most widely explored therapeutic goal in CD, and is associated with improved short-and long-term outcomes. However, in most cases evaluation for mucosal healing requires invasive monitoring, which is not always feasible or acceptable by the patient. Moreover, involvement of proximal small bowel, inaccessible to conventional ileocolonoscopy, is very common in CD, leading to possible underestimation of the inflammatory burden. Surrogates of direct endoscopic assessment may include fecal biomarkers and imaging modalities (intestinal ultrasound, magnetic resonance enterography and more). Moreover, in the small bowel capsule endoscopy may provide a more comprehensive overview of mucosal inflammation. In addition to mucosal healing, imaging modalities allow for assessment of transmural inflammation and healing that may prove to be of a significant clinical merit, as well as assessment of comprehensive panenteric structural damage. Each of the aforementioned clinical goals can be monitored using distinct quantitative scores, with only some of them undergoing extensive clinical validation.

The current talk will provide an overview of different aspects of disease severity (patient-related outcomes, mucosal healing, biomarkers, transmural healing and structural damage), their long-and short-term clinical value and the available tools for assessment of these outcomes.
Assessing disease severity in ulcerative colitis

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The European Crohn’s and Colitis Organization (ECCO) recommends the use of indices, such as the Mayo score for ulcerative colitis, for measuring clinical disease activity. Most of these instruments categorize active disease as mild, moderate or severe, although the thresholds for categorizing disease activity as well as the definition of remission are poorly validated. Objective markers of inflammation such as laboratory (primarily C-reactive protein and faecal-Calprotectin), imaging and endoscopic parameters, including histopathology, represent supportive tools that can be used to predict outcomes. More recently, the concept of patient reported outcomes (PROs) has been introduced, and these clinical parameters (normalization of stool frequency and absence of blood in stool) can be used in combination with absence of mucosal lesions at endoscopy to define remission. Consistently, the labels for drugs, approved for the treatment of ulcerative colitis, have been based on the use of indices that categorize disease activity as mild, moderate or severe.

However, in a real-world setting, decisions on disease management are not based on a cross-sectional assessment of inflammatory activity only, but also takes parameters of overall disease severity, such as past disease course, response to previous medication, quality of life, impact on daily life (disability), structural damage and co-morbidity, into account. Thus, disease severity represent an important dimension of ulcerative colitis, especially to guide disease management at long-term. A disease severity index has recently been created based on specialists’ opinion. Mucosal lesions, impact on daily activities, CRP and previous response to biologics were identified as the top four attributes that contribute to overall disease severity in patients with ulcerative colitis.

In summary, overall disease severity is a holistic dimension of ulcerative colitis that takes both present disease status and previous disease history into account. The recently developed disease severity index may become an important tool for consistent evaluation of disease severity and for guidance of long-term management of patients with ulcerative colitis.
Advances in the development of therapeutic agents for inflammatory bowel disease have enabled improvement of end-points and innovations in trial design. Nevertheless, outcome definitions have not yet been standardized nor has the community agreed on a core set of endpoints to be used in clinical trials as well as daily practice. Having clear treatment goals is important, not only for clinical trials but even more for clinical practice. Conventional end points for trials in ulcerative colitis and Crohn's disease were based on composite indices, such as the Mayo Clinic Score and the Crohn’s Disease Activity Index (CDAI). These scoring systems include symptoms, signs, laboratory markers, global physician’s assessments and sometimes endoscopic assessments. In daily practice, these indices are only rarely used. This has caused a disconnect between clinical trials and practice. Because of these concerns, the use of composite endpoints in trials has been re-evaluated and alternative measures of outcome and definitions of response are being developed. So have we observed in recent years, a shift to composite outcomes including patient-derived outcomes and endoscopic assessments. Histologic assessment, fecal and serum biomarkers are also increasingly used as secondary endpoints. A greater proportion of trials published after 2007 reported objective outcomes (96.5% endoscopic, 26.3% histologic, and 36.8% biomarker outcomes), but standardized definitions of histologic or biomarker endpoints are still lacking. Patient-reported outcome measurements (PROMs) are instruments created and defined by patients themselves and have been pushed also by regulatory agents as endpoints in clinical trials. A combination of these PROMs and an objective evaluation of inflammation by endoscopy, offers a clinically meaningful and better alternative to existing composite indices. Also are these endpoints more accepted by physicians for use in daily practice. Until true PROMs are developed and validated, currently Mayo score-derived PRO2 for UC (number of diarrhea and blood) and CDAI-derived PRO2 for CD (abdominal pain and stool frequency) are accepted as clinical endpoint in trials. As endoscopic endpoint, both SES-CD and CDEIS are used and – while a 50% decrease is generally accepted as the definition of endoscopic response, there is no universally accepted definition of endoscopic remission or mucosal healing.
How can we transfer evidence from clinical trials to the management of individual IBD patients: Are we asking the right questions and studying the correct patients?

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Clinical trials provided crucial evidence in support of the efficacy of novel agents and approaches in the treatment of patients with ulcerative colitis and Crohn’s disease. However, in order to limit a variety of confounders and to investigate novel agents safely, clinical trials often study a relatively homogeneous population of patients that may not reflect populations treated in the real world setting. Populations most often enrolled in clinical trials include patients with active symptoms and evidence of active inflammation. Additionally, patients enrolled include adult patients, most often ages 18 to 70 years, who have ileal and/or colonic inflammation in Crohn’s disease, and who do not have isolated proctitis in ulcerative colitis. Such studies tend to exclude children and the elderly, those with disease isolated to the proximal small bowel or upper tract in Crohn’s disease. Also often excluded are Crohn’s patients with strictures or stomas. Dedicated studies of postoperative prevention of recurrence or fistulas are uncommon in Crohn’s disease, as are studies of pouchitis in the ulcerative colitis patient who has undergone colectomy. Furthermore, non-Caucasian populations are under-represented in clinical trials in IBD. Therefore, study findings in the usual clinical trials that lead to drug approval may not reflect efficacy or safety issues among patients treated in the real world. Additional limitations include the fact that outcomes longer than 2 to 3 years are difficult to study; relative paucity of data among patients with early disease, due to the difficulty of identifying and enrolling such patients; and relatively few studies that have focused on mild disease. Studies that compare new treatments head-to-head with best available therapy are also uncommon, due to the large sample sizes needed to demonstrate superiority. Studies of treatment strategy and of combinations of therapy are also uncommon. Future work needs to focus on collecting real world evidence in large observational studies to supplement data obtained from clinical trials, and to validate evidence obtained from more homogeneous and narrow populations. Precision medicine approaches that employ predictive biomarkers to select patients will improve study efficiency as well as real world application of novel therapies. Comparative effectiveness studies will be critical, as will strategies to enroll early and mild patient groups. Studies that enroll patients according to accurate prognostic indicators will also advance the field. Finally, regulatory reform and harmonization will allow novel populations to be studied, and novel outcomes to be employed.
Session V

Shaping old drugs
Mesalazine has been successfully used for the treatment of mild to moderate inflammatory bowel diseases (IBD) for several decades and remains a fundamental strategy for the induction and maintenance therapy of mild to moderate ulcerative colitis (UC). Rectal application of mesalazine as suppositories, enemas or foam preparations is the most efficacious treatment in distal UC. Oral mesalazine formulations have been shown to be highly effective in inducing and maintaining remission in mild to moderate UC with extensive and also left-sided involvement. Interestingly, combined treatment with oral and rectal application of 5-ASA improves the therapeutic responses in both distal and extended UC.

Recent interest focuses on the optimization of 5-ASA use in both UC and CD. Recent studies assess new dosing schedules, new formulations with different release kinetics and combination of oral and rectal 5-ASAs. New 5-ASA dosing schedules with once daily dosing have demonstrated that patients’ adherence to 5-ASA therapy was improved significantly. Furthermore, patient empowerment has supported patient-adapted dose modifications of 5-ASA therapy in UC patients, which have demonstrated a further improvement of efficacy of 5-ASA. In addition, 5-ASAs have demonstrated to exert chemopreventive effects in patients with longstanding UC.

The role of 5-ASAs in Crohn’s disease is less clear. There seems to be a slight benefit in a subgroup of patients with mild CD and also in the postoperative setting in order to prevent recurrence of disease following surgical therapy of CD. A number of unsolved questions remain to be addressed in the future regarding optimal use of 5-ASA’s in IBD.
Do biosimilars provide the basis of a new paradigm in IBD management?

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Anti-TNF agents have changed the course of IBD, with higher rates of steroid-free remission and of mucosal healing. These outcomes are in turn associated with decreased rates of hospitalizations and surgeries. Furthermore, patient-reported outcomes are also improved, as well as their work productivity. The success of these biological therapies has been responsible for a profound switch of the major direct healthcare costs drivers in IBD. From the situation prior to anti-TNFs in which > 75% of the costs were linked with hospitalization, the costs are nowadays mostly driven by medication, mainly biologicals. However, access to anti-TNF agents remains limited in many countries, even in Europe, pointing towards inequities in access to pharmacological treatment for these conditions.

Biosimilars of infliximab have been the first approved monoclonal antibodies biosimilars approved in Europe. They are now present in most European markets since 1–2 years for the treatment of Crohn’s disease and ulcerative colitis, in addition to their rheumatological and dermatological indications. The most studied, CT-P13 (Inflectra®, Remsima®) has been extensively studied in real-world practice. Its efficacy and safety appear to be comparable to those of its originator, although some heterogeneity of efficacy in switch studies, especially the NOR-switch secondary endpoint results point to a possible inferiority of this compound as compared to Remicade® specifically in Crohn’s disease, which is supported by the known variations in glycosylation patterns of CT-P13, which decreases its affinity to macrophage FcRIII receptors. Interestingly the next infliximab biosimilar, SB2 (Flixabi®) carries a glycosylation modification that inversely affects the same binding. Comparison between the 2 biosimilars may lead to a more precise use of these biosimilars on specific diseases, integrating their modifications in a personalized medicine approach.

The reduced cost burden of biosimilars should allow for a more widespread use of biological therapies in IBD. In particular early access to anti-TNF should be favored, as thousands of additional patients could be treated with the same budget per country. A wider real-world demonstration of a top-down approach may thus become feasible. In addition, as biological therapies targeting other immune-mediators and homing receptors are now available against IBD, combination of biological therapies in refractory cases may become possible. Some cases reports are already available in this direction, which should be further studied.
Therapeutic drug monitoring: Is it essential or superfluous?

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Therapeutic drug monitoring (TDM) is a personalized approach that involves measuring drug concentrations with a subsequent change in therapy in order to maintain drug concentration within the therapeutic range. In the old days empiric dose adjustments were performed based on clinical symptoms. However, nowadays a more proactive TDM based personalized approach is frequently used in daily practice. Most evidence regarding the usefulness of TDM in IBD patients has been obtained with thiopurines and anti-tumor necrosis factor (TNF) agents. Timely assessment of drug levels and anti-drug antibodies may provide valuable insight into the possible etiology of unfavorable outcomes and allow for appropriate management strategies, resulting in improved clinical outcomes. In case of loss of response, TDM can guide the clinical decision making process by selecting appropriate management strategies, combined with clinical, laboratory, endoscopic and imaging results. Besides improved clinical outcomes, TDM might also reduce healthcare costs by using these expensive agents in their most effective way. There is evidence to support the idea that TDM is more cost effective than clinically based dosing in IBD patients with loss of response to anti-TNF agents. However, there is still debate about the optimal therapeutic window of various biologicals. Here, an update will be given on the optimal serum concentrations of various biologicals, including anti-TNF agents (infliximab, adalimumab and golimumab), the integrin inhibitor vedolizumab and ustekinumab (a therapeutic antibody directed against IL-12 and IL-23) in IBD. Pharmacokinetic and pharmacodynamic data as well as concentration-response associations for these different biological agents will be shown. Factors that affect serum concentrations of biologicals will also be discussed. Last but not least, the main outcomes will be presented of the first two controlled trials that investigated the clinical use of TDM based dosing compared to symptom based dosing of IFX in Crohn’s disease patients, the so-called TAXIT and TAILORIX trial.

Keywords: Inflammatory bowel disease (IBD), Crohn’s disease, ulcerative colitis, therapeutic drug monitoring (TDM), biologicals, infliximab, adalimumab, golimumab, ustekinumab, vedolizumab
Session VI

Challenging problems in IBD management I
Intra-abdominal abscess – Medical treatment or surgery?
Pro medical treatment

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Intra-abdominal abscesses are common in Crohn’s disease (CD). The first step of management is percutaneous drainage and antibiotics. It is successful in approximately 75% of patients. Patients in whom it is unsuccessful should be operated upon. Surgery can be avoided after successful percutaneous drainage in a significant proportion of patients, provided immunosuppressants and biologics (mostly anti TNF) are prescribed, to prevent recurrence. Good candidates for medical treatment are those with early, non-refractory disease, no intestinal stenosis and patients with extensive small bowel or colonic disease in whom surgery would lead to extensive resection.
Intra-abdominal abscess – Medical treatment or surgery?

Pro surgery

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**Background:** Around 10–20% of patients with Crohn’s disease will develop an intra-abdominal abscess. A substantial amount of these abscesses arise on the basis of enteric fistulas [1]. There is virtually no high evidence data on how to best treat patients with such an abscess in Crohn’s disease.

**Treatment options:** Two settings need to be distinguished:

*Acute abscess:* There is broad consensus that patients with a large abscess should primarily be drained and this should preferably be done interventionaly. Smaller abscesses (≤ 3 cm) should be primarily treated by antibiotics alone. If a large abscess can not be drained interventionaly, surgery is generally advised [2]. This strategy seems to result in less morbidity and less stoma formation. A recent meta-analysis indeed showed that around 30% of patients undergoing interventional drainage do not have to undergo surgery later [3]. But the same meta-analysis could not find any of the above suggested advantages. Moreover, most available papers do not specify on how exactly surgery was done when interventional drainage was not possible: only drainage of the abscess and then delayed surgery or primary resection of the affected bowel with or without stoma formation. Finally, there is a high risk of selection bias in the available studies as probably more patients in a worse clinical condition and with more risk factors underwent surgery. Therefore the data is difficult to interpret and the postulated advantages of interventional versus surgical treatment in the acute setting need to be viewed with caution. Especially in patients with short segment disease and concurring fistulas and in acceptable general condition (especially adequate nutritional status), primary surgery should remain an option. Such patients can be operated with low morbidity and the recurrence rate is significantly less than after simple drainage or antibiotic treatment. Finally, the high enterocutaneous fistula rate of 13% and more occurring after interventional drainage has to be considered [4].

*After resolution of the abscess under antibiotics with or without drainage:* Guidelines are conflicting in regard to whether patients after successful non-surgical treatment in the acute setting need to be operated electively later in order to prevent recurrent abscesses or other complications in the future. The German guidelines recommend early evaluation of elective surgery after successful drainage whereas the current french guidelines recommend anti-TNF-treatment [5, 6]. The rationale for recommending surgery is that around 50–70% of patients after initial non-surgical treatment will require surgery anyway in the future in comparison to only 18% after initial surgical drainage [7]. Negative predictors for recurrence after interventional drainage or antibiotics alone are concomitant fistulas and stenosis, these patients should undergo elective surgery. No adequate RCTs are available on whether medical treatment in this setting is equivalent or better than surgery. Intra-abominal abscesses often occur on the basis of blind ending fistulas and if such patients then undergo immunosuppression severe sepsis can occur [5]. Moreover, quality of life in these patients need to be considered, "surgery should not be viewed as a ‘failure’ when it can be the swiftest, safest and most effective route to physical and psychosocial rehabilitation" [7].
Conclusion: In summary, based on the low level evidence available, an intra-abdominal abscess can be treated by antibiotics and, if possible, drained interventionally, but surgery is also an option for patients with large abscesses not drainable interventionally and for patients deteriorating under antibiotics. The only larger available meta-analysis, however, could not demonstrate any disadvantage for a primarily surgical strategy. After successful initial non-surgical treatment, surgery should be considered in the elective setting, especially in patients with risk factors.

References:

Stenosis of small and large bowel in CD – Medical treatment or surgery?

Pro medical treatment

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More than half of Crohn’s disease (CD) patients develop symptoms of stricturing disease, mainly in the small intestine or areas of anastomosis. Colonic strictures harbor the risk for malignancy and accordingly, cause other clinical and therapeutic problems.

Strictures are best defined by luminal narrowing, wall thickening, pre-stenotic dilation and the presence of obstructive symptoms. Magnetic resonance imaging is considered the optimal technique to define and characterize strictures but there is no appropriate technique to confidently quantify the fibrotic component of a small bowel stricture.

The management of stricturing inflammatory bowel diseases has long been based on surgery and steroid therapy. The CREOLE study, a large prospective interventional cohort study conducted by the GETAID, enrolled 97 patients with a diagnosis of CD and small bowel strictures accompanied by obstructive symptoms. All patients underwent magnetic resonance enterography (MRE) before study entry and a treatment with adalimumab was administered. 62 (64%) patients reached success at week 24. At a median follow-up of 3.8 years, 45.7% of patients were still receiving adalimumab and had required neither dilation nor surgery at the end of follow-up, indicating that 29% of the original cohort responded successfully to adalimumab.

In this study, the investigators also arrived at a prognostic score to better predict response to medical treatment. Factors that contributed to a patient’s prognostic score included both clinical (recent and severe obstructive symptoms, previous treatment with azathioprine) and radiological (length of stricture below 12 cm, severe delayed enhancement intensity, dilation below 30 mm diameter and no fistula) features of the disease. With these results, clinicians are getting closer to being able to predict which patients with CD and strictures should go to surgery without delay and which may well respond to treatment and deserve a chance at medical therapy first, leading to a risk-stratify strategy without needing to treat every stricture the same.
Stenosis of small and large bowel in CD – Medical treatment or surgery?
Pro surgery

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Although new biologic agents and immunomodulators have revolutionized treatment of Crohn’s disease (CD), almost 60% of patients would require surgery after 20 years of disease and the indication for surgery is bowel obstruction caused by intestinal stricture in nearly 50% of cases. According to the Montreal classification, stricturing CD has been defined as “occurrence of constant luminal narrowing with prestenotic dilatation or obstructive signs/symptoms without presence of penetrating disease”, but the definition of stricture is not uniform across studies. Some CD patients have no clinical obstruction symptoms with endoscopically identifiable strictures, whereas others have severe symptoms and need urgent surgery. Endoscopic balloon dilatation (EBD) has been proposed as safe and efficacious alternative to surgery in selected patients with symptomatic short-length strictures: immediate technical success is high in most of studies, although only a selected group of patients (short accessible stricture, no other complicating features) can be selected for this procedure and the rate of recurrence is high. Strictureplasty or surgical resection and anastomosis can provide dramatic relief of obstruction symptoms. Furthermore, the rate of endoscopic recurrence after surgical resection has been decreased by the aggressive postsurgical prophylaxis strategy implemented in the last decade. The superior long-term results after surgery reduce the need for repetitive dilations in many of the patients undergoing EBD. Moreover, laparoscopic techniques and the spread of enhanced recovery after surgery protocols give several advantages to CD patients, as earlier recovery normal bowel function, shorter hospital stay, lower postoperative morbidity and rate of incisional hernia or adhesions, better cosmesis scores and body image. This is particularly important in patients who could be require repeated surgery during the history of the disease.
Anal disease – Medical treatment or surgery?
Pro medical treatment

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In population-based studies the occurrence of perianal fistula varies between 21 and 23%, with a cumulative frequency of 12% at 1 year, 15% at 5 years, 21% at 10 years and 26% at 20 years. The prevalence varies according to disease location. Perianal fistulae were noted in 12% with isolated ileal disease, 15% with ileocolonic disease, 41% with colonic disease and rectal sparing, and 92% with colonic disease involving the rectum.

Fistula determine a considerable morbidity in patients with Crohn’s disease including permanent sphincter and perineal tissue destruction, often causing significant impairment in quality of life with serious clinical and psychological consequences.

The main aspects to be taken into account when planning a strategy for the management of CD fistulae are: Locate origin of the fistula and its anatomy, identify or exclude local sepsis (abscess), determine which organs are affected and the contribution to systemic symptoms or impairment of quality of life, assess nutritional status of the patient, and luminal disease.

The diagnostic approach is crucial in the management of fistulizing perianal CD, since the findings influence the therapeutic strategy. Examination under anesthesia (EUA) is reported to be the most sensitive, with an accuracy of 90%. It has the advantage of allowing concomitant surgery. If an abscess is present or suspected, prompt EUA including drainage is the procedure of choice to prevent the destructive effective of undrained sepsis. It should not be delayed until an MR has been performed, unless the MR scan is immediately available. Nevertheless, MRI has an accuracy of 76–100% compared to EUA for fistulae and may provide additional information. Anorectal ultrasound has an accuracy of 56–100%, especially when performed by experts in conjunction with hydrogen peroxide enhancement. Any of these methods can be combined with endoscopy to assess the presence or absence of inflammation in the rectosigmoid colon. Asymptomatic simple fistula in CD patients do not require specific treatment. In contrast, when a simple perianal fistula is symptomatic, opinion favors a combined medical and surgical strategy.

In complex perianal fistulizing disease infliximab or adalimumab can be used as first line therapy following adequate surgical drainage if indicated. A combination of ciprofloxacin and ant-TNF improves short term outcomes. To enhance the effect of anti-TNF in complex fistulizing disease, combination of anti-TNF treatment with thiopurines may be considered. Locally injected stem cells, both with expanded adipose-derived allogeneic mesenchymal stem cells and autologous bone marrow-derived mesenchymal stromal cells, have shown beneficial effects.
Treatment of extraintestinal manifestations

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Inflammatory bowel disease (IBD) with its two entities Crohn’s disease and ulcerative colitis is not solely restricted to the gastrointestinal tract. Extraintestinal manifestations (EIMs) of IBD are frequent and considerably affect morbidity and mortality. They most frequently affect joints, skin, or eyes, but can also less frequently involve other organs such as liver, lungs, or pancreas. Certain EIM, such as peripheral (type 1) arthritis, oral aphthous ulcers, episcleritis, or erythema nodosum, are frequently associated with active intestinal inflammation and usually improve when the underlying inflamed intestine is treated. Other EIM, such as uveitis or ankylosing spondylitis, usually occur independent of intestinal inflammatory activity. Finally, in some EIM, such as pyoderma gangraenosum and primary sclerosing cholangitis, the association with the activity of the underlying IBD is unclear. The published prevalence of EIMs ranges from 6 to 47%. In 1 of 4 patients, EIMs can present before the first IBD flare. Patients with perianal Crohn’s disease are at higher risk for developing EIMs than other IBD patients. Also the presence of one EIM appears to confer a higher likelihood of developing other manifestations than would be expected by chance alone. The identified pathogenetic autoimmune mechanisms include genetic susceptibility antigenic display of auto-antigen, aberrant self-recognition, and immunopathogenetic autoantibodies against organ-specific cellular antigen(s) shared by colon and extra-colonic organs. Microbes may play an important role, probably by molecular mimicry. EIMs associated with IBD bear a negative impact on patients with UC and CD. Thus, the successful treatment of EIMs is essential for improving the quality of life of IBD patients. Medical treatment modalities are limited with topical and systemic steroids being the most frequently employed agents. TNF antibody therapy is an important treatment option for EIM in IBD patients whereas the role of α4β7 integrin antibodies such as vedolizumab needs to be studied further.
Session VII

Challenging problems in IBD management II
Treating patients with IBD and concomitant or previous cancer

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Patients with IBD and previous cancer are at higher risk of developing new or recurrent cancer than patients with IBD and without a history of cancer, irrespective of the use of immunosuppressants. In patients with chronic immune-mediated disease, including inflammatory bowel diseases, data from individual cohorts and from the first meta-analysis in the field suggest that cancer recurrence is not obviously promoted by the use of thiopurines and/or anti-TNF agents. However, it is likely that prescription of immune-suppressive therapy has been avoided up to now in patients with the most aggressive recent cancers (propensity bias). In addition, there is a rationale for a drug holiday of immune-suppressive therapy after diagnosis and treatment of cancers, as often as possible. This is based both on the concept of immunosurveillance of cancers, and on the transplant specialist experience: in transplant recipients, the use of thiopurines is associated with a high rate of cancer recurrence, particularly within the first two years following transplantation. The immune-suppressive drugs that can be maintained, initiated or resumed, during and after cancer treatment, should be chosen according to the type of the previous cancer, with relative or absolute contraindications to the use of those immunosuppressants that have been shown to promote the type of the index cancer. In this respect, it must be taken into account that, in patients with IBD, thiopurines promote carcinogenesis of Epstein-Barr virus (EBV)-related lymphomas, non-melanoma skin cancers and urinary tract cancers, while anti-TNF agents probably promote carcinogenesis of melanomas and lymphomas. It is likely on a theoretical basis that vedolizumab has no impact on the carcinogenesis of non-digestive cancers, but this is not demonstrated yet. All individual decisions should be made on a case-by-case basis, together with the oncologist, according to characteristics and expected evolution of the index cancer, expected impact of the immunosuppressants on cancer evolution, and intrinsic severity of IBD, with its associated risks. As a general rule, the overall strategy of IBD treatment in a patient with IBD and current or recent cancer should be based on a prudent step-up approach, trying to respect according to the risk of cancer recurrence, as often as possible, a 2 to 5-year interval free of immune-suppressive therapy between completion of cancer therapy and resumption of immune-suppressive therapy (ECCO guidelines). However, major treatments should be used at any time in case of disabling symptoms or life-threatening risks attributable to uncontrolled IBD.
Exploring and treating CMV infection in IBD patients

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The majority of adult patients with inflammatory bowel diseases (IBD) were previously infected with cytomegalovirus (CMV). CMV belongs to the group of herpes virus thus sharing the property to maintain silently in the host until reactivation occurs. Patients with an acute flare of their IBD, and here predominantly colitis, are at increased risk of developing such reactivation. The risk is highest in patients with steroid refractory disease. Why remains CMV a challenge for the gastroenterologist? Two scenarios are possible: i) the virus starts replicating without any impact on the disease course and ii) the virus starts replicating and by this inducing a more severe disease. Several diagnostic measures including immunohistochemistry or CMV-PCR from colonic biopsies or systemic CMV copy number exist. One might argue that the diagnostic proof is if the patient with proven CMV replication improves under anti-viral treatment. However this raises the question whether or not we have to treat all patients? Several studies indicate that the CMV copy number decreases even if only the underlying disease is being treated, suggesting that an improvement of the structural damage itself inhibits replication. Nevertheless the problem remains the diagnosis of disease-relevant CMV replication, and in our view there exists a subgroup that requires anti-viral treatment.

In summary, the talk will provide an algorithm how to diagnose and then treat patients with possible CMV colitis.
Untreated persistent intestinal inflammation results in progressive digestive track damage and poor outcome in both Crohn’s disease and ulcerative colitis. For this reason, therapeutic goals have evolved in both clinical trials and routine practice to include mucosal healing as well as symptomatic improvement. In addition, there is emerging evidence that escalating therapies based upon objective evidence of intestinal inflammation (Treat to Target) delivers enhanced outcomes. Anti-TNF therapies have revolutionised the care of patients with IBD, delivering enhanced mucosal rates of mucosal healing and reducing requirement for surgery in both ulcerative colitis and Crohn’s disease. Anti-integrin agents and antibodies targeting the IL-12/IL-23 pathway are effective in both anti-TNF naïve and experienced patients and licenced have been shown to induce mucosal healing in both clinical trials and real world studies. In addition, the reduced acquisition costs of biosimilar agents have increased access to biologic therapies in many countries. However, the impact of biologics on clinical outcome must be balanced against the risks associated with their use and the concomitant immunosuppression that may be required to reduce the formation of antidrug antibodies that can limit persistence on therapy. The use of biologics has been associated with an increased risk of opportunistic infections, inflammatory skin/joint complications and malignancy as well as infusion reactions. Patient demographics and co-morbidity should be taken into consideration when assessing the risk of biologic therapy and will likely impact on choice of agent as well as the appropriateness of concomitant immune suppression.
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POSTER ABSTRACTS

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Therapeutic drug monitoring of SB2: The accuracy of three different methods

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Background and Aims: Therapeutic drug monitoring is widely used in the adjustment of infliximab (IFX) therapy and is expected to be used in the adjustment of biosimilars. SB2, a biosimilar of the originator IFX, has been recently approved by the European Medicines Agency (EMA) for the treatment of inflammatory bowel disease (IBD). The aim of this study was to evaluate the accuracy of three different methods for the quantification of biosimilar SB2. Moreover, the existence of IFX, CT-P13 and SB2 cross-immunogenicity was also evaluated.

Methods: Three different IFX quantification assays were evaluated: an in-house built method, a commercially-available ELISA assay and a point-of-care device (POC-IFX). Spiking with known concentration of originator IFX, CT-P13 and SB2 were performed in donors’ samples and the percentage of recovery of each assay was evaluated. Reactivity of SB2 to patients-extracted anti-IFX and anti-CT-P13 antibodies was quantified using the in-house built method.

Results: The results show that all tested IFX-optimized assays are equally accurate in measuring SB2 levels: the intraclass correlation coefficient (ICC) between theoretical and measured concentrations varied from 0.945 to 0.983. Quantitative comparison showed an excellent ICC between the three assays when evaluating SB2, originator IFX and CT-P13. Regarding SB2, ICC was 0.986, 0.979 and 0.974 for POC IFX/in-house ELISA/in-house and ELISA/POC IFX, respectively. Finally, the anti-IFX and anti-CT-P13 sera reacted almost to the same extent to SB2, originator IFX and CT-P13, with ICCs ranging from 0.986 to 0.993.

Conclusion: Our results suggest that either ELISA commercial assay, POC IFX or the in-house method can be used to measure IFX biosimilar SB2 in an accurate fashion. Moreover, these drugs were shown to have a high cross-immunogenicity: This means that switching between them in a patient that has measurable levels of anti-drug antibodies will likely yield no clinical benefit.
Predictive factors of surgery in the course of Crohn’s disease

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Introduction: Surgical treatment in Crohn’s disease (CD) is unavoidable in about 70% of patients during the course of the disease. Early intensive therapy is necessary in these patients to reduce the risk of bowel damage leading to surgery like strictures or fistulae.

The aim of our study is to assess risk factors for surgery during the course of CD.

Methods: Retrospective analytic study, collecting all patients diagnosed with Crohn’s disease in our department from January 2007 to June 2017. Surgical intervention for perianal disease was excluded from the study. Independent risk factors of surgery were evaluated by univariate and multivariate analysis.

Results: One hundred and twelve CD patients were enrolled with a mean age of 42 years old and a sex ratio (W/M) of 0.96. In total, 41 patients (36.6%) underwent surgery after a mean follow-up of 14.6 months. Thirty patients (73%) had ileal disease, 6 (15%) had colonic disease and five (12%) had ileocolonic disease. Indications for surgical treatment were: bowel obstruction in 26 patients, intraabdominal abscess with ileal disease in 9 patients, and acute severe colitis in 6 cases.

Presence of obstructed bowel symptoms (p = 0.03), complicated disease at diagnosis (intestinal stenosis, fistula) (p = 0.001), ileal CD affecting > 35 cm in extent at diagnosis (p = 0.04), young age (< 30 years) at diagnosis (p = 0.012) and Crohn’s disease activity index (CDAI) > 250 (p = 0.03) were independent predictive risk factors for subsequent surgery in CD.

Discussion/Conclusion: Surgical treatment is a common outcome in luminal CD. Independent risk factors for surgery during the course of the disease were: History of obstructed bowel signs, complicated behavior at diagnosis, CD involving more than 35 cm of the ileum at diagnosis, young age at diagnosis (< 30 years), and CDAI > 250.
Value of neutrophil-to-lymphocyte ratio in predicting loss of response to anti-TNF treatment in Crohn’s disease patients: A single-center study

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Introduction: The advent of TNF (tumor necrosis factor) inhibitors in therapeutic arsenal of Crohn's disease (CD) has immensely changed their prognosis, and made mucosal healing the main target in the treatment strategy. Despite these advances, loss of response (LOR) to treatment remains a major issue. The aim of this study is to assess the importance of neutrophil-to-lymphocyte ratio (NLR) in predicting LOR in CD patients receiving TNF inhibitors.

Methods: Retrospective, analytic study including all Crohn's disease patients in our Department of Gastroenterology from January 2007 to June 2017. Patients treated with infliximab or adalimumab were evaluated for risk factors of loss of response. Baseline inflammatory markers were measured within 2 weeks before anti-TNF treatment.

Results: A total of 112 CD patients with a mean age of 42 years old (17–52) were enrolled. 26 patients (23%) were into biotherapies: 18 (70%) received infliximab and 8 (30%) were into adalimumab. Twenty patients (65%) showed clinical and biological response after induction therapy among whom 8 (36%) patients presented with LOR to treatment after a mean duration of 22 weeks. Baseline C-reactive protein levels (CRP) were not significantly higher in LOR group (44 mg/l versus 35 mg/l; p = 0.2). Baseline NLR was significantly higher in LOR group (p = 0.012). In univariate analysis, baseline NLR was significantly correlated to relapse-free survival (p = 0.04). Multivariate analysis showed that NLR was an independent risk factor for LOR (p = 0.03).

Discussion/Conclusion: In our study, baseline NLR was an independent risk factor for loss of response in patients receiving TNF inhibitors. CRP baseline level did not predict LOR.
Predictive factors of postoperative septic complications in Crohn’s disease: A single-center study

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Introduction: Surgical treatment is unavoidable in most Crohn’s disease (CD) patients despite the efficacy of medical treatment especially biotherapies. The aim of our study was to evaluate the effects of immunosuppressive and immunomodulatory drugs on post-surgical outcomes in CD and assess the predictive factors of septic complications (SC) of surgery.

Methods: Retrospective study including all CD patients who underwent surgery in our institution from January 2007 to June 2017. We considered early SC those taking place within 30 days of surgery. Patients were considered under the effect of immunosuppressive or immunomodulatory treatment if they were into treatment in the 4 weeks before surgery. Patients who had surgery for perianal lesions were excluded.

Results: A total of 72 patients with a mean age of 38.4 years old were enrolled (18–42). Ileal disease (55%) was more common than colonic or ileocolonic disease. Treatment was indicated for stricturing disease in 61% of patients and for penetrating disease in 39% of cases. Early SC developed in 19 patients (26%): 10 patients (52%) had wound infection, 2 had anastomotic leak, 2 developed intraabdominal abscess, 3 had enterocutaneous fistula and 2 presented bronchopulmonary infection. SC were significantly more frequent in patients operated for fistulizing disease (p = 0.02). Wound infection and anastomotic leak were significantly more common in patients who were into steroids or biotherapies in the four weeks before surgery (p = 0.015). Serum Albumin levels were significantly lower in SC group (p = 0.04). In univariate and multivariate analysis, independent risk factors for postoperative SC were: fistulizing disease (p = 0.02) and steroids intake within four weeks before surgery (0.012).

Discussion/Conclusion: Penetrating disease, steroids before surgery and low Serum Albumin levels are risk factors for SC after surgery for CD.
Predictive factors of penetrating complications in Crohn’s disease: A single-center study

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Introduction: Crohn’s disease (CD) is an evolving entity which can be complicated by strictures or fistula. The aim of this study is to assess the incidence of fistulizing disease during the course of CD and to evaluate the predictive factors of penetrating complications.

Methods: Retrospective analytic study including all patients diagnosed with CD in our department of Gastroenterology between January 2007 and June 2017. We defined 2 groups of patients:
G1: Patients with penetrating disease (n = 20)
G2: Patients without penetrating disease (n = 92)
Incidence of fistulizing luminal disease as well as independent risk factors for penetrating complications were assessed by univariate and multivariate analysis

Results: One hundred and twelve CD patients were studied with a mean age of 42 years old (17–52) and a sex ratio (W/M) of 0.96. Fifty-one patients (45%) had non-stricturing non-penetrating disease, 31 (28%) had stricturing disease, 20 (18%) patients had fistulizing disease and 10 (9%) had stricturing and penetrating disease. Twenty-nine patients had perianal disease (PAD). Perianal lesions were significantly more frequent in G1 than in G2 (75% vs. 15%; p = 0.012). In G1, 7 patients (35%) had no fistulizing complications at diagnosis and have developed penetrating disease after a mean follow-up of 26 months. Young age at diagnosis (< 40 years) (p = 0.02), PAD at diagnosis (p = 0.015), ileocaecal localization (0.04) and active smoking (0.04) were independent risk factors for penetrating complications. Crohn’s disease activity index was not significantly associated with penetrating behavior (p = 0.12).

Discussion/Conclusion: In our study, independent predictive risk factors for penetrating behavior of CD were: Young age at diagnosis, ileocaecal localization, active smoking, and perianal lesions at diagnosis.
Can the first presentation of ulcerative colitis predict the course?

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Introduction: The first presentation of a patient with ulcerative colitis may differ from mild to severe, but the course of the disease may not necessarily be the same during the follow-up. Mild ulcerative colitis (UC) patients may be treated with only mesalazin but more severe patients will usually need steroids, immunomodulators, biologic agents and sometimes surgery. We aimed to investigate whether the first clinical presentation of UC patients predict their disease course in the follow-up.

Methods: Hundred UC patients who were followed for at least 5 years were included into the study, and records were analysed retrospectively. Need for steroids, immunomodulators, biologic agents, colectomy or hospitalization were searched. Mild UC patients were defined as no need for immunomodulators, biologic agents or colectomy. Records were taken from the first and fifth year of the disease.

Results: During the follow up 7% of UC patients had needed colectomy, 20% had used immunomodulators and 10% had needed anti-TNF agents. When there was no need for the use of corticosteroids or need for hospitalization during the first year of presentation, this would predict that the disease course will be mild during the first five years (p = 0.03 and p = 0.009, respectively).

Discussion/Conclusion: Considering that the first year course of UC will predict the severity of the disease in the following years and may be colectomy eventually, patients who are thought to be under risk should be followed closely and those who are predicted to have a severe course may be started ‘top down’ treatment early.

Keywords: colectomy, first year, steroid treatment, ulcerative colitis
**Inflammatory bowel disease in the UK: Is care improving?**

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**Introduction:** The aim of this study is to examine the quality of care provided for inpatients with inflammatory bowel disease (IBD) in the UK.

**Methods:** We did a comparison of the results of three national clinical audits from 2006 to 2010. The audits included all UK hospitals routinely admitting patients with IBD. Data were collected on adult patients with IBD admitted to hospital between 01/06/2005 to 31/05/2006; 01/09/2007 to 31/08/2008; and 1/9/2010 to 31/08/2011.

**Results:** Participation in these audits by UK hospitals rose from 75% in the first round to 93% and 90% in the second and third rounds respectively. Over six years the mortality has almost halved for both ulcerative colitis and Crohn’s disease, and there have been specific improvements in many areas covered by the National Service Standards for Inflammatory bowel disease. The number of admissions remained almost the same in the last few years, but the number of admissions per patient has reduced. The collection of stool samples; use of prophylactic heparin; prescription of bone protection agents; and use of anti-TNF therapy as a rescue therapy has increased. There has been a reduced frequency of surgery in non-elective admissions with a significant increase in the percentage of operations performed laparoscopically. A significant increase in the percentage of inpatients reviewed by the IBD specialist nurses during their admission. High proportion of patients was not reviewed by dietetic services.

**Discussion/Conclusion:** The results show clear evidence of improvement in most aspects of the quality of care for IBD inpatients over the last five years.
Clinicians’ knowledge about the ionizing radiation of the common investigations used in inflammatory bowel disease

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Introduction: Patients with inflammatory bowel disease (IBD) are at risk of high radiation exposure due to repeated radiologic investigations. This study aims to assess the clinicians and IBD nurses’ awareness about ionizing radiation and its consequences.

Methods: This is a prospective questionnaire based study of doctors and IBD nurses’ awareness about ionizing radiation. Participants from Singleton, Morriston, Princess of Wales and Neath Port Talbot hospitals were asked to complete a hard copy multiple choice questionnaire to assess their knowledge of the commonly used investigations in IBD patients: plain abdominal X ray, Barium follow through, CT scan and MRI.

Results: 49 participants (20 consultants, 28 trainees, 1 IBD nurse) completed the questionnaires. The mean score for all the participants was 4.7 out of 10. There was no difference in the mean score between consultants and registrars. 30% of participants achieved a score of 50% or more. 47% of the participants had attended a training course about ionizing radiation; there was no difference in the outcome between those who attended and those who did not attend; 13% of participants knew that abdominal CT is equivalent to 3 years of natural background radiation; 25% of them knew that a cumulative effective dose above 75 mSv is regarded as a high exposure and the patient is at risk of developing cancer.

Discussion/Conclusion: The knowledge about ionizing radiation doses among IBD specialists is poor. Training is needed to improve the awareness about the benefit versus the risk of ionizing radiation.
Crohn’s and ulcerative colitis questionnaire-8 (CUCQ-8), a valid and quick quality of life measure in IBD

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Introduction: Most of the disease-specific quality of life (QoL) measures for inflammatory bowel disease (IBD) are lengthy and time consuming. None has been established for routine use in clinical practice. We designed this study to develop a short QoL measure in IBD.

Methods: A 32-item questionnaire, the Crohn’s and ulcerative colitis questionnaire-32 (CUCQ-32) was developed by reviewing the literature and consultation with patients and experts. Construct validity was carried out using the Short Form 12 (SF-12) and the EuroQol 5 dimensions (EQ5D) questionnaires and two disease severity measures (Simple Clinical Colitis Activity Index (SCCAI) and the Harvey-Bradshaw Index (HBI). Test-retest analysis was done by asking patients to complete the CUCQ questionnaire twice in a period of two weeks.

Results: Data were obtained from 205 patients with IBD who completed the CUCQ-32. Psychometric analysis showed that Cronbach’s $\alpha$ was 0.88, item-total correlations were good and there was no ceiling or floor effects. Stepwise regression identified 8 items that accounted for more than 95% of the variance in the CUCQ-32. The resulting CUCQ-8 demonstrated good internal consistency (Cronbach’s $\alpha = 0.84$); had good reproducibility (intra-class correlation coefficient = 0.94); was well correlated with the EQ5D ($r = 0.58$), the Short Form-12 ($r = 0.65$ for physical component and $r = 0.63$ for mental component); was responsive to change (responsiveness ratio was 0.64, p value < 0.05).

Discussion/Conclusion: CUCQ-8 is a short questionnaire, which has the potential to be an efficient tool for assessing the QoL of all patients with IBD in clinical practice.
Infliximab or ciclosporin for steroid-resistant acute severe ulcerative colitis? Results of a pragmatic randomised trial and economic evaluation (CONSTRUCT)

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Introduction: Infliximab and ciclosporin are of similar efficacy in treating acute severe ulcerative colitis, but there has been no comparative evaluation of their relative clinical and cost effectiveness.

Methods: Between May 2010 and February 2013, 270 patients were recruited to this open-label, parallel-group, pragmatic randomised trial from 52 hospitals in England, Scotland and Wales. Consenting patients admitted with severe colitis who failed to respond to intravenous hydrocortisone within about five days, were randomised in equal proportions to: intravenous infliximab at zero, two and six weeks; or intravenous ciclosporin for seven days followed by oral ciclosporin for 11 weeks. Primary outcome was quality-adjusted survival – the area under the curve (AUC) of scores from the Crohn’s and Ulcerative Colitis Questionnaire (CUCQ) completed by participants at baseline, three and six months, then six monthly over one to three years. Data analysis was blinded. Economic evaluation was nested within the trial. Qualitative interviews were conducted with 23 participating professionals, and twice each with 20 participants.

Results: There was no significant difference in: quality-adjusted survival [analysable data from 121 participants (90%) in each group; mean difference in AUC/day 0.0297 favouring ciclosporin; 95% confidence interval (CI) from -0.0088 to +0.0682; p = 0.129]; EQ-5D scores; SF-6D scores; colectomy rates (55/135 infliximab vs. 65/135 ciclosporin, OR = 0.741, 95% CI: 0.457 to 1.202, p = 0.223); time to colectomy; patients experiencing serious adverse reactions (11.9% vs. 7.4%); serious adverse events; or deaths (infliximab 3 vs. ciclosporin 0, p = 0.247). Total NHS costs were lower for ciclosporin (mean adjusted difference £5.632, 95% CI: -£8.305 to -£2.773, p < 0.001). Interviewed participants spoke more positively about infliximab than ciclosporin. Professionals reported advantages and disadvantages with both drugs, but nurses disliked giving intravenous ciclosporin.

Discussion/Conclusion: There was no significant difference between ciclosporin and infliximab in clinical effectiveness, but total cost to the NHS was higher for infliximab.
Significance of IL-17/IL-23 axis and TGF-β1 expression in pathogenesis of ulcerative colitis

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Introduction: Interleukin 17 (IL-17) and interleukin 23 (IL-23) are cytokines with important role in development of inflammatory bowel disease (IBD). In our study we investigated and compare distribution of IL-17- and IL-23-positive T-cells in two groups of patients: with ulcerative colitis (UC) and non-specific colitis (NSC).

Methods: We investigated immunohistochemically paraffin specimens from 21 patients with UC and 15 with NSC for CD3, CD68, IL-17, IL-23 and TGF-β1 expression.

Results: We found that IL-17 expression was not found in patients with UC. In patients with UC many CD3- and CD68-positive cells were positive and for IL-17/IL-23. Also, IL-23-positive cells were increased significantly in inflamed mucosa of UC patients compared with NSC ($\chi^2 = 4.24, p = 0.041$). In addition in these patients IL-17-positive cells were significantly higher than IL-23-positive cells ($20.05 \pm 13.0$ cells/mm$^2$ vs. $11.9 \pm 4.3$ cells/mm$^2$, $p = 0.003$). Finally we have established that high expression of TGF-β1 was significantly higher in patients with increased number of IL-17-positive cells ($\chi^2 = 12.1, p = 0.033$).

Discussion/Conclusion: Our results suggest that IL-17-, IL-23- and TGF-β expression in UC patients was increased and may be its associated with altered immune and inflammatory responses.
The peculiarities of intestinal microflora in patients with prolonged use of non-steroidal anti-inflammatory drugs (NSAIDs)

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Introduction: Nowadays there is an indisputable fact about the importance of normo-flora in the functioning and maintenance of homeostasis of the digestive system. Dysbiosis leads to severe functional disorders of the digestive system. The aim of our work was to evaluate the effectiveness of combined treatment by proton pump inhibitors pantoprazole (P) and multiprobiotic “Symbiter® acidophilic” concentrated (M) in patients with NSAIDs-gastropathy in comparison with standard therapy (P).

Methods: We observed 94 patients with osteoarthritis who used NSAIDs for more than 1 month. The mean age was 64.1 ± 0.79. For all of them gastroscopy with further morphological examination, H. pylori detection, laboratory examination were performed. The fecal microflora has been analyzed by bacteriological culture methods. Patients were randomized and placed into two equal groups. The control group was treated with P (20 mg 2 times daily) for 28 days. The main group received combined therapy: P (20 mg 2 times daily) for 4 weeks and M (10 ml per day) for 20 days. Normal distribution of studied parameter for each sampling was checked using Shapiro-Wilka’s criteria.

Results: Changes in colonic microbiota were observed in all patients who used NSAIDs for more than 1 month. The colonization of Escherichia coli was (1.34 ± 0.30) × 10⁶, that in 32 times exceeded the indicator in control group (p < 0.001). The colonization of Enterococcus was increased in 700 times (p < 0.01); the levels of Bifidobacterium and Lactobacillus were decreased in 100 times (p < 0.001) and 1000 times (p < 0.01) accordingly. With age the changes in obligate microflora were observed: the concentration of Bifidobacterium in patients up to 60 years was (11.0 ± 2.3) × 10⁶, in patients 61–70 years – (8.7 ± 2.2) × 10⁵, in patients more than 70 years – (1.8 ± 0.3) × 10⁵. Faecal calprotectin was increased in all patients with prolonged use of NSAIDs.

Discussion/Conclusion: The inclusion of multiprobiotic in the general scheme of treatment of NSAIDs-gastropathies is petrogenetically approved as with age the suppression of motor function of the intestine is observed. NSAIDs lead to significant increase in faecal calprotectin concentration compared with baseline, this difference was much lower in patients who used selective NSAIDs. For those patients who are known to be on NSAID, clinicians have suggested that they should cease taking the drug for 3 weeks before collecting a faecal sample and sending it for analysis.
Evaluation and comparison of serology of viral infection and tuberculosis screening in Central versus Southern Italy: A difference for infectious risk and consequent treatment decisions

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Introduction: ECCO guidelines have recently raised the need for a more accurate screening in inflammatory bowel disease (IBD) patients to investigate former infectious diseases. Epidemiological data of latent infectious disease is variable in different regions, even within the same country. The aim of this study was to investigate the prevalence of hepatitis B and C, latent tuberculosis, and the immunization status for mononucleosis in two cohorts of IBD outpatients, one in Central Italy and the other in Southern Italy.

Methods: We retrospectively revised the patient’s charts in our outpatient clinic in Central Italy (group 1) and Southern Italy (group 2); data on hepatitis B (HBsAg, anti-HBs, anti-HBc) and C (anti-HCV), tuberculosis (TBC; Mantoux skin test or QuantiFERON Gold), mononucleosis (anti-VCA IgG), and cytomegalovirus (anti-CMV IgG) were registered.

Results: The charts from 126 IBD patients in group 1 and 509 patients in group 2 were reviewed (Group 1: ulcerative colitis [UC] 55, Crohn’s disease [CD] 71; median age [range] 49 [14–93] years, males 89; Group 2: ulcerative colitis [UC] 289, Crohn’s disease [CD] 220; median age [range] 42 [17–87] years, males 300). Data on screening positivity and group comparison are given in table 1.

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1 Central Italy</th>
<th>Cohort 2 Southern Italy</th>
<th>OR (95%CI) CD (group 2 vs. group 1)</th>
<th>OR (95%CI) UC (group 2 vs. group 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tot (%+ve)</td>
<td>CD (%+ve)</td>
<td>UC (%+ve)</td>
<td>Tot (%+ve)</td>
<td>CD (%+ve)</td>
</tr>
<tr>
<td>HBsAb*</td>
<td>33.3%</td>
<td>35.9%</td>
<td>28.6%</td>
<td>30.2%</td>
</tr>
<tr>
<td>HBsAb (&gt; 38 years)</td>
<td>22%</td>
<td>21.95%</td>
<td>22.2%</td>
<td>13.1%</td>
</tr>
<tr>
<td></td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>1.8%</td>
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<td>--------</td>
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</tr>
<tr>
<td>HbsAg</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>1.8%</td>
</tr>
<tr>
<td>HBcAb</td>
<td>8.3%</td>
<td>6.1%</td>
<td>13%</td>
<td>6.5%</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>0.9%</td>
<td>1.6%</td>
<td>0%</td>
<td>2.5%</td>
</tr>
<tr>
<td>IgG VCA EBV</td>
<td>81%</td>
<td>87%</td>
<td>73.7%</td>
<td>90.5%</td>
</tr>
<tr>
<td>IgG CMV</td>
<td>75.4%</td>
<td>70.3%</td>
<td>82.1%</td>
<td>66.5%</td>
</tr>
<tr>
<td>TBC</td>
<td>8.1%</td>
<td>6.8%</td>
<td>11.1%</td>
<td>6.7%</td>
</tr>
</tbody>
</table>

**Tab. 1:** *data including vaccinated patients; **p < 0.01 vs. corresponding group of cohort 1; CD: Crohn’s disease; UC: ulcerative colitis*

A 3-fold risk for HBV infection in patients with CD in Southern Italy, whereas 5-fold risk was present in UC patients from Southern-Italy to test positive for HCV and for VCA IgG showing a higher herd immunization for the latter. No differences were found for TBC and for CMV IgG.

**Discussion/Conclusion:** Southern Italy patients are at increased risk for HBV and HCV infection compared with patients in Central Italy. Moreover, the same patients showed a higher herd immunization for EBV. The first data may be important for the need of HBV and HCV screening and infection treatment, while the latter may have implication on the choice of IBD therapy.
Correlation between inflammatory biomarkers and endoscopic scores in ulcerative colitis: Thus extension makes the difference?

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Introduction: Several endoscopic scores have been used to assess the severity of inflammatory activity in ulcerative colitis (UC), however, few consider the extension of the disease. Scores such as the Dublin Score (DS) and the Modified Mayo Endoscopic Score (MMES) combine the severity of inflammation with the extent of the disease.

Aim: To calculate the correlation between the endoscopic scores – Mayo Endoscopic Score (MES), DUBLIN, MMES and the biomarkers of inflammation – erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and calprotectin – and to compare the ability of these scores to predict calprotectin > 100 µg/g.

Methods: Retrospective study, including patients with diagnosis of left or extensive UC who underwent colonoscopy between 2015 and 2016. The biomarkers were obtained with a maximum interval of one week in relation to colonoscopy and without introduction of new therapy. The Spearman test calculated the correlation between scores and biomarkers. ROC curves (AUC) were obtained for each score to predict calprotectin > 100 µg/g.

Results: 60 patients were included, 46.7% female patients with mean age 45.3 ± 12.8 years with mean values of ESR 4.4 ± 12.8 mm, CRP 5.12 ± 6.00 mg/l and calprotectin 354 ± 430 µg/g.

The correlation between calprotectin and MES was rs = 0.623 p < 0.001, for DS rs = 0.548 p <0.001 and for MMES rs = 0.588 p <0.001.

Regarding CRP, a correlation with the MES was rs = 0.415 p = 0.001 and with the MMES was rs = 0.404 p = 0.001, but no correlation was found with the DS.

There was no significant correlation between ESR and endoscopic scores.

To predict values of calprotectin > 100 µg/g the AUC for the MES was 0.848, for the DS 0.801 and for the MMES 0.815, and there was no statistically difference between the curves.

Discussion/Conclusion: Although there is a good correlation between endoscopic scores and calprotectin, the correlation between scores that take into account the extension were not superior to Mayo Endoscopic Score.
IBD – Is it a risk factor for the diagnosis of hepatic steatosis?

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Introduction: Although is not yet established, recent studies suggest an increase prevalence of hepatic steatosis (HS) in patients with inflammatory bowel disease (IBD). Factors such as chronic inflammation, previous surgeries, drug-induced hepatotoxicity, malnutrition and intestinal dysbiosis seem to be involved in the pathogenesis of this disease.

Aim: To assess the frequency of HS in IBD patients quantified by CAP (controlled attenuation parameter) and by clinical-analytical methods: Hepatic Steatosis Index (HSI) and Fatty Liver Index (FLI). A secondary aim is to investigate risk factors associated with HS in IBD patients.

Methods: Cross-sectional study that included consecutive outpatients that were observed in our department between January and March 2017. Patients with known liver disease or alcohol habits were excluded. HS was defined as HSI ≥ 36 or FLI ≥ 60 or CAP > 248.

Results: 149 patients included with mean age 40.7 ± 13 years, 83 female (55.7%), 59.7% with Crohn’s disease (CD). 62 patients (41.7%) had CAP > 248, 20 (13.4%) FLI > 60 and 40 (26.8%) HSI > 36. There were no differences in the mean CAP value (244 ± 54.2), HSI (33.3 ± 5.18), and FLI (31.5 ± 25.3) among patients with CD and ulcerative colitis.

We found that patients with CAP > 248 were more frequently obese (27.4% vs. 0% p < 0.001), males (54.8% vs. 36.8% p = 0.029) and presented more frequently metabolic syndrome (25% vs. 4.6% p < 0.001). Regarding the IBD factors, patients with HS had a higher frequency of previous surgeries (30.6% vs. 16.1% p = 0.035). There were no differences between hospitalization, duration of the disease, use of corticosteroids or other IBD treatments.

Discussion/Conclusion: In our cohort the frequency of HS varied between 13.4% and 41.7% defined by non-invasive methods. We found that the presence of metabolic syndrome and obesity were more frequent in patients with HS. Regarding factors related to IBD, patients with previous history of surgery were more frequently diagnosed with HS.
Crohn’s disease: What can we expect from the course of the disease?

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Introduction: Crohn’s disease is a chronic and progressive disease that changes its behavior over time. Transmural inflammation in Crohn’s disease (CD) leads to stricturing or penetrating complications.

Aims: To evaluate the frequency of the long-term progression of CD phenotypes and need for surgery and to determine the main factors associated with this evolution

Methods: Retrospective study was conducted with prospective follow-up. Patients included had a minimum follow up of 12 months. Medical records were reviewed. Montreal classification was assessed at the moment of the diagnosis and at the end of the follow-up period.

Results: Included 290 patients, 53.8% female. The mean age at diagnosis was 31.9 (± 11.92) years and the mean follow up was 113 (± 74.7) months. Globally we observed a change in behavior in 46 patients (15.9%); from inflammatory to stricturing in 30 patients, stricturing to penetrating in 7 patients and inflammatory to penetrating in 9 patients.

Cumulative probability of being complication phenotype free in 5, 10, and 20 years: 90.6%; 81.9% and 69%.

Ileocolic localization (60.9% vs. 45.1%; p = 0.049), age at the diagnosis < 16 (8.7% vs. 2%; p = 0.017), and less time exposed to biological therapy (15.9 months vs. 41.32 months; p < 0.001) were the factors associated with changing phenotype.

Regarding surgery, 70 (24.1%) were submitted to intestinal resection, of those 34.3% were at diagnosis. For the remaining patients the mean time for surgery after diagnosis was 52.3 ± 55.9 months. Cumulative probability of being surgery free in 5, 10, and 20 years: 78.1%, 74.8%, and 66%, respectively. Smoking status (42.9% vs. 24.8%; p = 0.004), stricturing behavior (47.1% vs. 15.9%; p < 0.001), penetrating behavior (42.9% vs. 2.3%; p < 0.001) and higher number of hospitalizations in the first year of diagnosis (51.5% vs. 8.3%; p < 0.001) were more frequently observed in patients submitted to surgery. Patients submitted to surgery were less treated with biological therapy (5.7% vs. 25.9%; p < 0.001).

Discussion/Conclusion: In our cohort we observed behavior progression in about one-sixth of patients. The most frequent change in behavior was to stricturing pattern. Strictures and penetrating behavior, higher number of hospitalizations in the first year of diagnosis, smoking status, age at diagnosis < 16 and ileocolic localization were factors associated with an unfavorable clinical evolution.
Incidence of preventable diseases in IBD patients candidates for biological treatment

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The ECCO consensus recommends screening patients for preventable infections before initiating the biological therapy.

The aim was to study the incidence of some preventable diseases in IBD patients candidates for biological therapy in one reference centre and during this treatment.

310 IBD patients, 146 of which (47.09%) were screened for biological therapy – 85/CD (58.20%) and 61/UC (41.80%). All patients were serologically tested for hepatitis B, C and D, and for anti-HIV ½ Ag/Ab. A TB skin test (TST) was done, as well as IGRA tests (Quanti FERON®-TB Gold (QFT-GIT) and SPOT®.TB test (T-Spot).

In 14/146 (9.6%) we have a positive TST in a biologic therapy screening. Four (2.7%) are with a positive T-Spot (3/CD and 1/UC) and one UC patient has a positive QFT-GIT. 109/146 (74.7%) were eligible for biological therapy. In the course of the biological therapy and the follow up with clinical data for TB 12 patients had it. Five had a positive IGRA test- 4/CD and 1/UC. During the screening 8 patients (5.6%) had HBsAg(+)/anti-HBcTotal(+). Five receive HBV treatment. Three were not treated due to an undetectable viral replication through PCR for HBV DNA. A total of 16 patients are with anti-HBcTotal(+)/HBsAg(-) – 12/CD and 4/UC, all are with a negative PCR for HBV DNA. Three patients were HCV positive – 1/CD and 2/UC. All 146 of the screened patients are with negative HIV results.

In order to optimize the safety of IBD patients, studies on the early diagnosis of LTB and viral hepatitis should be continued. We need to monitor for preventable infections at the beginning and during the course of the biological therapy.
Why should we monitor glomerular filtration rate in children with ulcerative colitis?

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5-aminosalicylates, including sulfasalazine and mesalazine, are first line therapy in inflammatory bowel diseases (IBD), including ulcerative colitis. Although mesalazine preparations are generally well tolerated, adverse reactions have been described. These include exacerbation of colitis, renal toxicity, such as interstitial nephritis and nephrotic syndrome, pulmonary toxicity (as interstitial lung disease and fibrosis), eosinophilic pleural effusion, pericarditis, pancreatitis, and hair loss.

We present two pediatric patients diagnosed with ulcerative colitis who experienced renal dysfunction in the form of decreased glomerular filtration rate during oral mesalazine treatment. The first patient was treated with an increased dose of mesalazine after an exacerbation (65 mg → 95 mg/kg/d). After 2 months of treatment the creatinine concentration was elevated (133 umol/l) and eGFR was decreased – 40.353 ml/min/1.73 m². These adverse effects resolved after mesalazine was discontinued (creatinine decreased to 107 umol/l and eGFR increased to 50.18 ml/min/1.73 m²). After 3 months the patient’s condition deteriorated and we decided to return to the previous treatment. After 6 months again renal dysfunction was present (decreased eGFR – 63.28 ml/min/1.73 m²). Because of suspected drug-induced interstitial nephritis we resigned from treatment with 5-ASA.

In the second patient after one year of mesalazine treatment (60 mg/kg/d) we noticed an increased creatinine level (74 umol/l) and decreased eGFR (65.16 ml/min). Mesalazine was discontinued. Due to a severe exacerbation 5-ASA treatment was re-introduced, but the patient developed symptoms of kidney dysfunction (decreased eGFR 45.16 ml/min). We suspected drug-induced interstitial nephritis and decided to finally discontinue the treatment.

Decreased eGFR in the course of 5-ASA treatment suggests drug-induced impairment of the renal function, which is a recommendation to terminate the treatment, at least for a short time.

Clinical observation of the patient’s physical condition and monitoring of laboratory parameters in order to diagnose possible renal insufficiency are essential components of the proper treatment of a patient with IBD.
Diagnostic yield of colonoscopic images and biopsy results by tuberculosis culture in patients with distal part of terminal ileum ulcerations

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**Background:** Intestinal tuberculosis (TB) disease can be difficult to diagnose because its symptoms and laboratory results are nonspecific. Moreover, endoscopic lesions resemble those of other diseases such as Crohn’s disease (CD). The aim of this study was to evaluate the diagnostic yield of colonoscopic images and biopsy results by TB culture.

**Methods:** The medical records of 82 consecutive patient with intestinal ulceration (colonic, ileal or both) were analyzed. None had active pulmonary tuberculosis. It was reported that the endoscopic findings most characteristic of intestinal TB that are (1) circular ulcers, (2) small diverticula (3–5 mm), and (3) sessile firm polyps were searched. We defined the patients with all 3 criteria as intestinal TB with 100% certainty according to the published literature, with 2 criteria as probable; and with just one criterion as no TB. More importantly, intestinal tissue PCR, liquid and solid TB cultures were performed in each patient.

**Results:** Of the 82 patients with intestinal ulceration, the endoscopic findings most characteristic for intestinal TB were found in 3 (3.65%); 13 patients had probable intestinal TB; and the rest (66 patients) had no TB according to the endoscopic imaging findings.

Mycobacterium tuberculosis was isolated from the culture of biopsy specimens in 2 patients (2.43%). One patient with solid TB culture positive had all 3 endoscopic futures of intestinal TB (circular ulcers, small diverticula (3–5 mm), and sessile firm polyps). Contrary, one patient without any endoscopic futures for TB had PCR (+) and liquid TB culture (+).

PCR (+) were noted in 3 patients (3.65%). Two of them showed no endoscopic futures for intestinal TB, but PCR (+) and negative TB culture.

Mycobacterium culture established the diagnosis of intestinal TB, CORRECTLY in 2 (2.43%) patients.

Of the 82 patients, 4 had previous pulmonary tuberculosis history. One of them showed positive PCR and TB culture. One had only PCR (+). The rest 2 patients had negative PCR and TB culture.

**Conclusion:** Before getting the result of Mycobacterium culture, the WRONGLY diagnosis could be made by either endoscopic examination or the presence of PCR positivity. Differentiating between intestinal TB and CD is very important since steroid treatment can be life saving in CD and lethal in intestinal TB.
Prevalence of ulcerative colitis and Crohn ileocolitis in patients with celiac disease

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Background It was reported that involvement of lower gastrointestinal (GI) tract is rare in patients with celiac disease. Because of both diseases, inflammatory bowel disease (IBD) and celiac disease, have a similar autoimmune background, the occurrence of IBD was questioned by lower GI endoscopy with biopsy in this study. Our aim was to evaluate IBD in patients with celiac disease.

Methods: We evaluated our celiac disease clinic records, retrospectively. Lower GI tract abnormalities were evaluated by colonoscopy, rectoscopy and/or double balloon enteroscopy (DBE).

Results: Of the 198 patients with celiac disease, 36 had documented lower GI tract endoscopic examination results. Lower GI tract examination was performed by colonoscopy with ileum entubation (IE) and biopsy in 18 patients, rectoscopy in 17 patients and in one patient with DBE. Of the 36 patients with celiac disease, 5 patients had IBD (14%). Of the 4 patients with ulcerative colitis diagnosed, 2 had moderate or severe active pancolitis. The other two patients had left-side ulcerative colitis. One patient had Crohn ileitis which was diagnosed by IE and ileum biopsy. We also found colon polyps in 6 patients (17%). These polyps showed adenomatous, tubulovillous or inflammatory changes with the size from 1 mm to 50 mm. Five of them had multiple polyps.

Conclusion: Our results showed that patients with celiac disease may have IBD, even severely active ulcerative pancolitis or Crohn ileitis. So, we recommend a lower GI tract examination with deep IE and ileal and colonic biopsies in patients with celiac disease to early diagnosis of IBD.
Idiopathic or drug induced acute pancreatitis in patient with Crohn’s disease

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32-year-old smoker patient was hospitalized due to diarrhea, weight loss and iron deficiency anemia in May 2017. Cardiopulmonary status was unremarkable, while abdominal status revealed mild pain in mid and lower right hemi-abdomen. Laboratory showed iron deficiency anemia, other findings were normal. Family and medical history were unremarkable. Esophagogastroduodenoscopy showed multiple aphthous ulceration in duodenal bulb and proximal duodenum. Duodenal biopsies revealed tissue granulation, with acute and chronic inflammatory cells. Colonoscopy showed skip inflammatory areas and ulcerations in colon and ileum. Biopsies revealed chronic inflammation and crypt irregularity. MR enterography was not preformed due to metal object in patient leg. He was diagnosed with extensive Crohn’s disease. According to the guidelines, corticosteroid and azathioprine therapy was introduced with gradual corticosteroid tapering. Shortly after treatment introduction patient was clinically well with no diarrhea and weight loss. In August he was re-hospitalized due to mild acute pancreatitis. With no other causes found, we concluded that pancreatitis was caused with azathioprine therapy. Azathioprine therapy can cause acute pancreatitis in up to 7%, especially in smokers. We continued therapy with budesonide and mesalamine. In late September he was re-hospitalized with new episode of mild acute pancreatitis. Patient linked pancreatitis with mesalamine therapy and stop taking mesalamine. Mesalamine can be rare cause of drug induced acute pancreatitis. Considering two episodes of acute pancreatitis in patient with extensive Crohn’s disease, all previous medical therapy was stopped and biologic therapy was proposed but patient refused any therapy for now. Etiology of acute pancreatitis in this patient remains unclear. It could be caused by azathioprine, mesalazine, duodenal Crohn’s disease with edema of the Papillae Vateri or idiopathic. Endoscopic ultrasound and eventually endoscopic retrograde cholangiopancreatography would be indicated in the further evaluation of pancreatitis in this case.
Crohn’s disease – An unusual first presentation

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28-year-old smoker patient was hospitalized due to iron deficiency anemia in January 2017. Cardiopulmonary and abdominal status was unremarkable. Laboratory showed iron deficiency anemia, while other findings were normal. Family and medical history were negative on colorectal carcinoma. Patient had no symptoms and any clinical signs of illness. Abdominal ultrasound showed no pathology, while abdominal multislice computed tomography showed thickness of rectal wall 5 cm in length. Esophago-gastroduodenoscopy showed mild antral gastritis, Helicobacter pylori was negative. Colonoscopy showed limited, well defined area of edematous, hyperemic, vulnerable elevated mucosa 15 cm from anocutaneous border that comprises one half of colonic lumen. Multiple biopsies were taken that showed increased lamina propria plasma cells and lymphocytes as well as mild neutrophil inflammation. There were not any sign of dysplasia, in spite of macroscopic appearance suspect on neoplasia. During the hospitalisation patient become febrile, control blood laboratory findings, leukocyte and C-reactive protein were increased. We excluded pneumonia or urinary inflammation. Parenteral antibiotic therapy was included (ciprofloxacin 400 mg bid and metronidazole 500 mg tid). After infection was resolved, second short colonoscopy was performed by other gastroenterologist due to negative biopsy on first colonoscopy. During the biopsy, the small part of mucosa was raised with forceps, and the hole in the mucosa was discovered. Afterwards, carefully inspection of the anal region revealed small scar. Fistulography was preformed that showed anorectal fistula 10 cm long. MR enterography, performed after, showed terminal ileum wall thickening with luminal stenosis. Diagnosis of Crohn’s disease of terminal ileum with anorectal fistula was made. This is unusual presentation of Crohn’s disease without typical clinical presentation and changes in the rectum with the anorectal fistula, which imitated and aroused suspicion on neoplasm.
Early diagnosis in inflammatory bowel disease (IBD) – A pilot study

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Introduction: The diagnostic delay in IBD still represents a major problem and at diagnosis frequently irreversible damage has already occurred. The aim of the present territory-based study was to adopt diagnostic criteria and to integrate them with fecal calprotectin (fCAL) before the referral to an IBD specialist.

Methods: Participating General Practitioners (GP) enrolled prospectively patients with symptoms suspicious for IBD (symptom characteristics: 2 major criteria: diarrhea lasting at least 3 weeks or presence of blood in feces; 5 minor criteria: recurrent abdominal pain, weight loss (at least 10% of body weight), (former) presence of perianal fistula, recurrent fever of unknown origin, anemia, or family history for IBD. Fulfilment of 1 major or at least 2 minor criteria was followed by free fCAL testing (Calfast, Eurospital, Trieste; Italy). With positive testing, fCAL > 70 mg/kg, the patient was referred to an IBD specialist for further work-up.

Results: Eighty-six GPs participated at the study and 55 patients were tested for fCAL between May and October 2017. Among major criteria for clinical suspect, chronic diarrhea was present in 60% and fecal blood loss in 18%; among minor criteria, 76% reported recurrent pain, 33% weight loss, 9% fistulas, 9% anemia, and 12% were relatives of IBD patients. Positivity of fCAL was seen in 13/55 patients (24%) and a final IBD diagnosis was made in 4/13 (31%). Sensitivity of fCal with a threshold of 70 mg/kg was 100% (95% CI: 44–100) and specificity was 93% (95% CI: 77–99). The positive predictive value (PPV) of fCAL was 60% (95% CI: 0.23–0.88) but the negative PV was 100%. (95% CI: 0.87–1.00)

Discussion/Conclusion: fCAL with a threshold set at 70 mg/kg seems to represent a potentially reliable and cost-effective negative test to be used in primary care settings for patients with symptoms suggestive for IBD. Training programs for GPs may increase early diagnosis of IBD patients.
Association between ulcerative colitis and polymyositis: An extraintestinal manifestation of ulcerative colitis or an intestinal sign of the polymyositis: A case report

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Introduction: Polymyositis belongs to the spectrum of inflammatory idiopathic myopathies. Polymyositis was rarely described as an extra intestinal manifestation of inflammatory bowel disease. We discuss the case of a patient diagnosed with polymyositis who develops an ulcerative colitis.

Methods: A 75-year-old women diagnosed with polymyositis 3 years ago, treated with 7.5 mg of prednisone daily. She was hospitalised for bloody diarrhea: 7 times a day for more than 3 weeks, associated with fever and abdominal pain. No abnormalities were detected during clinical examination. Biology tests revealed: increased leucocytes count: 11500/mm³ with neutrophilia, increased inflammation markers: CRP 173.5 mg/l and the sedimentation rate: 60 during the first hour. Parasitic stool tests and stool culture were negative. The coloscopy was realised and showed signs of an ulcerative colitis in the entire colon. Biopsy revealed a chronic colitis with signs of activity. The diagnosis of pancolic ulcerative colitis was confirmed. Under 1 mg/kg/day of prednisone we noticed a clinical and biological remission: the diarrhea disappeared and inflammation blood markers regained normal levels.

Discussion/Conclusion: In case of myalgia, muscle weakness and elevated muscle enzymes presented by a patient with ulcerative colitis, practitioners should evoke the diagnosis of polymyositis. Even though it is a rare complication, it should be recognized because of its impact on life quality.
Safety and effectiveness of long-term azathioprine maintenance treatment in inflammatory bowel disease

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Introduction: Azathioprine is the mainstay of conventional maintenance therapy in inflammatory bowel disease. Unfortunately, up to 40% of patients discontinue immunosuppressive therapy within 2 years due to intolerance or lack of efficacy. The aim of this study was to assess long-term maintenance effectiveness and tolerability of azathioprine therapy in inflammatory bowel disease patients.

Methods: This is a retrospective study conducted between January 2004 and June 2016 including patients with a chronic inflammatory bowel disease treated by azathioprine at a dose of 2 to 2.5 mg/kg/day. The lack of efficacy of azathioprine was defined as no response or recurrence of the disease after 6 months of treatment.

Results: Seventy patients of inflammatory bowel disease treated with azathioprine: 15 patients with ulcerative colitis and 55 cases of Crohn’s disease. They were 40 women and 30 men. The mean age was 54 years. Indication of treatment were respectively maintenance therapy after a severe relapse in 5 cases, 20 patients with steroids dependence, prevention of postoperative Crohn’s disease in 35 patients, 3 cases of upper gastrointestinal localisation and combotherapy in with anti-TNF-α in 7 cases. Remission was noted in 75% of patients. The prevalence of adverse events was 15% requiring discontinuation in 10% of cases. The median time of occurrence of side effects was two months. The most common side effects were: liver toxicity (13%), hematologic toxicity (9%) and acute pancreatitis in 3 patients. We didn’t found any correlation between side effects and the following factors: age, sex, type/or location of inflammatory bowel disease.

Discussion/Conclusion: Azathioprine is the most common drug used to maintain clinical remission in inflammatory bowel disease. This drug is also important as a steroid-sparing agent in steroid-dependent and chronically active inflammatory bowel disease. However, its use is not devoid of side effects that can be severe requiring discontinuation of the treatment.
Prevalence and clinical significance of hypergammaglobulinemia in inflammatory bowel disease patients

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Introduction: Hypergammaglobulinemia polyclonal in adult patients is related to infections, autoimmune diseases, chronic liver diseases, and malignancies. The significance of hypergammaglobulinemia in inflammatory bowel disease has not yet been evaluated; hence, whether elevated IgG levels at inflammatory bowel disease diagnosis simply is a consequence of an autoimmune process, or a feature of distinct phenotypic characteristics remains unexplored. The aim of our study was to evaluate the prevalence and clinical significance of hypergammaglobulinemia in inflammatory bowel disease patients.

Methods: We conducted a retrospective cross-sectional study including 80 inflammatory bowel disease patients referred to our Hospital in Sousse, between January 2015 and December 2016. Baseline characteristics included age at onset, sex, severity indices, laboratory data, extraintestinal manifestations and endoscopic findings. Hypergammaglobulinemia was defined as polyclonal increment of the gammaglobulins level above the normal laboratory value.

Results: Of 90 patients, 45 (50%) had Crohn’s disease and 40 (44.5%) had ulcerative colitis, and 5 (5.5%) had unclassified inflammatory bowel disease. Overall, 25 patients (27.7%) had hypergammaglobulinemia, including 11 (24.4%) with Crohn’s disease and 14 (35%) with ulcerative colitis. Hypergammaglobulinemia was associated with the extraintestinal manifestations (57% vs. 22%; p < 0.05) including articular manifestations, dermatological manifestations, and ocular disorders. In ulcerative colitis patients hypergammaglobulinemia was associated with a high pancolitis prevalence (p < 0.05).

Discussion/Conclusion: In the present retrospective study, hypergammaglobulinemia was not uncommon in inflammatory bowel disease patients, and it was associated with a higher prevalence of extraintestinal manifestation. Further large prospective studies are needed to confirm the presence of hypergammaglobulinemia in inflammatory bowel disease patients.
Factors associated with non-delayed surgery for intraabdominal abscesses complicating Crohn’s disease

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Introduction: Intraabdominal abscesses are often managed with antibiotics and percutaneous drainage and then evaluation for the need for delayed surgery, so the surgeon can resect and create a primary anastomosis. This strategy is not always possible and some patients require emergent surgery.

Aim: To identify predictive factors of resort to undelayed surgery in patients with intraabdominal abscesses complicating Crohn’s disease who initially underwent medical management.

Methods: We retrospectively identified patients with Crohn’s disease who had been diagnosed with spontaneous intraabdominal abscess from January 2002 to October 2017 and who underwent first-line medical antibiotics. Patients with postoperative collection were excluded. We recorded clinical, biological and imaging findings. We studied predictive factors of the need for undelayed surgery.

Results: Fifty patients were included. There were 22 (44%) females and 28 (56%) males. The median age was 32.16 ± 11.84. There were 5 (10%) patients treated with thiopurine, 2 (4%) with anti-TNF-α, 3 (6%) with mesalamine. Four (8%) patients were on oral steroids. Thirty-six (72%) patients had fistula. Thirty-two patients (64%) had simple abscess, 8 (16%) patients had multiple abscesses and 10 (20%) had multilocular abscess. The average size of abscess was 34.41 ± 16.99 mm. All were on broad-spectrum antibiotics. Sonographic or computed-tomography guided drainage was performed in 5 (10%) patients. Three (6%) patients had puncture-aspiration. Half of patients had undelayed surgery in a median delay of 21 days [8–45]: 2 (4%) had intestinal obstruction, 1 (2%) patient had peritonitis and 21 (42%) patients failing medical treatment. Multilocular abscess was strongly correlated with non-elective surgery (80% vs. 42.5% p = 0.037). Percutaneous drainage seemed to be a preventive factor of urgent surgery (0% vs. 55.55% p = 0.025). However, puncture aspiration didn’t prevent non elective surgery (66.66% vs. 51.06% p = 0.5). High serum C-reactive protein (36.9 vs. 9.25 p < 0.0001) and platelet count (405813.64 vs. 353545.45 p = 0.039) at day 10 of the course of antibiotics was significantly predictive of need for non-elective surgery. Underlying treatment, the size of collection and the existence of fistula were not identified as prognostic factors.

Discussion/Conclusion: Percutaneous drainage of intraabdominal abscess in Crohn’s disease seemed to prevent non-delayed surgery. Multilocular abscesses, elevated CRP and platelet count within the first 10 days of medical management predicted poor outcome.
Risk factors associated with high levels of fatigue in patients with inflammatory bowel disease in remission

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Introduction: Even in remission, fatigue is a common symptom faced by patients with inflammatory bowel disease (IBD). The aim of our study is to determine factors associated with high levels of fatigue in patients with IBD in remission and investigate its prevalence.

Methods: Known IBD outpatients in remission for at least 3 months were collected. Patients completed Functional Assessment of Chronic Illness Therapy-Fatigue score (FACITC-F). The Fatigue subscale (FS) was the main item used. Scores range from 0 to 52. Fatigue was determined as FS less than 40 points. A score of less than 20 points indicates severe fatigue. We used medical records to abstract demographic and disease characteristics of the participants.

Results: Seventy-four patients (85.1% Crohn’s disease (CD) patients and 14.9% ulcerative colitis (UC)) were included in this study. There were almost same number of man and female in our study (42% vs. 58%), with a median age of 26.7 years. The prevalence of fatigue in the analyzed group was 54.7%. Ten percent of patients had severe fatigue. Anemia (p = 0.2) and iron deficiency (p = 0.61) are not significantly associated with high levels of fatigue. Lower cholesterol level (p = 0.013) and higher C-reactive protein value (p = 0.04) were risk factors of increased fatigue. Multiple bowel resections presents strong associations with fatigue (p = 0.01). Extra-intestinal manifestations were significantly associated with fatigue (p = 0.008). We detected that perianal CD induces high fatigue (p = 0.022). We observed that 65% of patients with perianal CD did not answer sexuality item.

Discussion/Conclusion: Even in remission, IBD patients suffer from fatigue. Multiple bowel resections, extra-intestinal manifestations, high C-reactive protein and cholesterol level were risk factors of fatigue. Patients with perianal CD had greater fatigue levels, which allows us to think that their sexuality is significantly impaired.
Efficacy of intravenous steroids in moderate colitis refractory to oral steroids

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Introduction: Moderate colitis refractory to oral steroids should preferably be treated with anti-TNF combined to thiopurine which is an expensive strategy. Intravenous (IV) steroids is also an alternative but little is known about the results.

Aim: To evaluate the efficacy of IV steroids in patients with moderate colitis failing to oral steroids and to assess factors associated with a good response to this strategy.

Methods: We retrospectively investigated the medical files of patients between January 2007 and October 2016. Patients with moderate to severe colitis who had been treated with IV steroids after failure of oral steroids therapy were identified. Clinical, endoscopic and biological data were recorded.

Results: Twenty-one patients were included with a median age of 34.57. There was 13 (61.9%) ulcerative colitis and 8 (38.1%) Crohn’s disease. IV steroids was started after a median of 21.95 days of oral corticosteroids. 11 patients were on mesalamine and 3 on thiopurine while moderate flare occurred. Severe lesions at endoscopy were found in 16 patients (76.2%). Median length of course 9 days [3–15]). Initial response (defined as mild severity or inactive disease at day 7 after starting intravenous corticosteroids, without rescue therapy) was seen in 12 cases (57.1%), these patients were on oral steroids again and 10 of them started on thiopurine. 8 patients (38.1%) required cyclosporine as a medical rescue therapy and an emergency colectomy was needed in 1 patient. After a median follow up of 24 months, 3 patients (19%) underwent colectomy and 2 patients were on anti-TNF. Severe lesions at endoscopy were found to be a predictive factor for failure of IV steroids (59.25% vs. 0%, p = 0.016). Bloody stools were strongly associated with poor outcome (p = 0.005). Indeed, their number at the first day of IV therapy was negatively correlated to response to treatment (6.78 vs. 4.42, p = 0.026) and was predictive of colectomy (7.75 vs. 4.88, p= 0.033). Bloody stools at the third day of IV therapy also predicted colectomy (66.66% vs. 0%, p = 0.005). Thiopurine (while the flare occurring or after IV steroids) was protective against colectomy and need for anti-TNF (p < 0.05).

Discussion/Conclusion: IV steroids should be started for patients with moderate colitis who failed oral steroids as this permitted to avoid therapy escalation in 57% of cases. Severe endoscopic lesions and bloody stools predict poor outcome. Patients started on thiopurine have better results. This strategy may offer an alternative to a second line medical rescue therapy, it’s cheaper and more simply. Anti-TNF therapy can always be started in case of failure.
A change in ΔMCV predicts mucosal healing in patients with Crohn’s disease under combination therapy

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Introduction: Higher tioguanine (6-TGN) levels have been associated with better clinical and endoscopic outcomes in patients with inflammatory bowel disease under thiopurine therapy. Previous studies have suggested that an elevated erythrocyte mean corpuscular volume (MCV) can be a valid surrogate of adequate 6-TGN levels.

Methods: This was a retrospective study using a cohort of patients under combination therapy with Infliximab and azathioprine followed in a single-center. We evaluated the influence of a ΔMCV in major endpoints including: Clinical response (decrease of 3 points in Harvey-Bradshaw index), clinical remission (a Harvey-Bradshaw index ≤ 4), endoscopic response (improvement in endoscopic appearance) and endoscopic remission (absent of ulcers). In a subgroup of patients anti-TNF pharmacokinetics (serum levels and antibodies) were also evaluated.

Results: 143 patients with Crohn’s disease were included, 53.1% patients were male with mean age of 28 ± 11.5 years. MCV at baseline and at week 48 of treatment was 88.2 ± 15.8 fl and 89.7 ± 4.7fl. At the end of the first year of combination therapy, 87.4% patients achieved clinical response, 74.1% clinical remission, 83.9% endoscopic response and 43.4% endoscopic remission. Patients with higher variations in MCV were more likely to be in clinical remission (3.16 ± 4.94 vs. -0.95 ± 6.44, p < 0.001). Patients with endoscopic response and remission had higher ΔMCV (2.57 ± 3.70 vs. -3.38 ± 7.05, p < 0.001 and 3.17 ± 3.97 vs. -0.27 ± 5.74, p = 0.006). The area under the receiver-operating curve for predicting endoscopic remission, endoscopic response and clinical remission according to the ΔMCV was 0.665 (95% CI: 0.532–0.797, p = 0.025), 0.714 (95% CI: 0.545–0.883, p = 0.011) and 0.711 (95% CI: 0.616–0.806, p < 0.001). For each unit increase in MCV level there was an increase in the probability of achieving clinical remission – OR = 1.17 (95% CI: 1.07–1.27, p = 0.001), endoscopic response – OR = 1.29 (95% CI: 1.10–1.50, p = 0.001) and endoscopic remission– OR= 1.17 (95% CI: 1.027–1.326, p = 0.018). There was a negative correlation between C-reactive protein levels and – ΔMCV (spearman rho -0.254, p = 0.003). We found no significant association between ΔMCV and Infliximab pharmacokinetic.

Discussion/Conclusion: Our results suggest an association between ΔMCV and better outcomes in CD patients under combination therapy. Assessment of ΔMCV may be an alternative to 6-TGN dosing.
Ultrasonography and perianal involvement in inflammatory bowel disease

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Introduction: Ano-rectal ultrasonography (AR-EUS) is an accurate and well-tolerated method for assessing perianal complications of inflammatory bowel disease (IBD). The aim of this study is the characterization of AR-EUS findings in patients with IBD.

Methods: This was a retrospective cohort single-center study. Patients with IBD and perianal involvement confirmed by AR-EUS were included. Demographic, clinical and ultrasonographic data were collected.

Results: 113 AR-EUS were performed in 71 patients with IBD: 68 with Crohn’s disease (CD), 1 with ulcerative colitis (UC) and 2 with unclassified colitis. 62% were female with a median age of 28.1 years (range 17–60); 54% of the patients had perianal disease at time of IBD diagnosis. CD localization was ileal (L1) in 29.4%, colonic (L2) in 22.1% and ileocolonic (L3) in 48.5%. CD behavior was inflammatory (B1p) in 70.6%, stricturing (B2p) in 19.1% and penetrating (B3p) in 10.3% of the cases. All the patients were treated with anti-TNF therapy (infliximab: 70.4%, adalimumab: 29.6%) and 56 received combination therapy (azathioprine: 75% and methotrexate: 25%). All the AR-EUS were performed without sedation. In CD, 87 perianal fistulas were found (43 intersphincteric; 26 transphincteric, 7 suprasphincteric, 11 anovaginal); 43.7% were complex. Others ultrasonography findings were: 18 perianal abscesses, 24 anal fissures, 13 internal sphincter lacerations, 19 anal ulcers and 5 external sphincter lacerations. Cicatricial changes and superior anorectal strictures were present in 15 and 4 patients, respectively. In UC, cicatricial changes and 1 lateral anal fissure were evident on AR-EUS. Ultrasonography findings in UC patients were: 1 suprasphincteric fistula, 1 internal sphincter laceration and 1 anterior anal fissure. We found no significant association between the localization or behavior of CD and type of fistula (p = 0.85 and p = 0.89, respectively).

Discussion/Conclusion: Suppurative complications were the main perianal finding in ano-rectal ultrasonography. In our series, we also found a high prevalence of echostructural changes and sphincteric lacerations, most due to prolonged and recurrent suppurative processes and surgical complications. We consider that anorectal ultrasonography has excellent tolerability and should be used in the assessment of perianal disease in IBD patients.
Predicting outcome in acute severe ulcerative colitis: Comparison of the Oxford, Edinburgh, Lindgren and endoscopic Mayo scores

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Introduction: Up to one-third of patients with acute severe ulcerative colitis (ASUC) will fail intravenous corticosteroids (IVCT) treatment, requiring rescue therapy with Cyclosporin (Cy), Infliximab (IFX) or colectomy. Although several scores for predicting response to IVCT exist, formal comparison is lacking.

Methods: This was a retrospective cohort single-center study. The endoscopic Mayo score and the Oxford, Edinburgh and Lindgren scores were determined at admission and on the 3rd day of IVCT treatment, respectively. Outcomes included prediction of steroid refractoriness, need for rescue medical therapy and surgery.

Results: From 489 patients with ulcerative colitis, 112 presented with ASUC; 58% were male with a median age of 33.5 years (range 18–80). The median of Truelove and Witts score was 4 (range 2–5). 35% of patients showed an incomplete or absent response to IVCT, 28.6% received rescue medical therapy (IFX: 65.6%, Cy: 31.3%, sequential therapy with Cy and IFX: 3.1%) and 13.4% were colectomized up to 1 year from admission. The Lindgren score was superior to the Edinburgh score (AUC 0.856 [0.784–0.928] vs. 0.775 [0.682–0.869], p = 0.01) and the Mayo score (AUC 0.699 [0.597–0.801], p = 0.02), but not to the Oxford score (AUC 0.746 [9.651–0.841], p = 0.14) in predicting steroid refractoriness. The Lindgren score was superior to the Mayo (AUC 0.826 [0.749–0.902] vs. 0.637 [0.525–0.749], p = 0.002) and Oxford scores (AUC 0.719 [0.617–0.821], p = 0.03), but similar to the Edinburgh score (AUC 0.771 [0.678–0.865], p = 0.18) in predicting the need for rescue therapy. Finally, the Lindgren score was also a better predictor of the need of colectomy than the Edinburgh (AUC 0.836 [0.712–0.960] vs. 0.753 [0.608–0.897], p = 0.03) and Oxford scores (AUC 0.712 [0.587–0.837], p = 0.003), but not to Mayo score (AUC 0.782 [0.685–0.879], p = 0.47).

In multivariate regression analysis, the Lindgren score was an independent predictor for steroid refractoriness (OR 1.647 1.111–2.441, p = 0.013) and need for medical rescue therapy (OR 1.410 1.033–1.926, p = 0.03). A Lindgren score > 9 had a positive and negative predictive value for IVCT failure of 91.7% and 72.9%, respectively.

Discussion/Conclusion: In our series, the Lindgren score was superior to the Edinburgh, Oxford and endoscopic Mayo scores in predicting steroid refractoriness, need for rescue medical therapy and colectomy.
Efficacy of therapeutic drug monitoring of anti-TNF therapy in the control of patients with inflammatory bowel disease

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Introduction: Infliximab (IFX) and adalimumab (ADA) are effective drugs in the treatment of inflammatory bowel disease (IBD). Studies suggest that therapeutic drug monitoring (TDM) may allow optimization of drug treatment, but it remains unclear if this strategy is associated with greater therapeutic efficacy and better outcomes.

Methods: We compared clinical-based adjustment (CB) with drug-monitoring adjustment (DM) in patients with IBD under IFX and ADA on several outcomes including hospitalization, surgery, clinical remission and therapeutic failure at 48 weeks of treatment. We also determined the number of therapeutic adjustments, C-reactive protein (CRP) and fecal calprotectin (FC) values (negative < 0.5 mg/dl and < 50 ug/ml) at 48 weeks of treatment. Clinical remission was defined as absence of hospitalization, surgery and failure or switch of anti-TNF at 48 weeks of treatment.

Results: 117 patients were included: 98 with Crohn’s disease (CD) and 19 with ulcerative colitis (UC). 54.7% were male with a mean age of 29.1 years (range 7–65). 117 were allocated to the DM group and 101 to the CB group. Therapeutic escalation was more frequent in the DM group (47.0% vs. 10.9%, p < 0.001). DM was associated with longer time to relapse (8.74 ± 42 vs. 6.00 ± 3.1 months, p = 0.045) and, in patients with positive baseline CRP, with higher probability of clinical remission (p = 0.05). The number of patients with negative FC was higher in DM group (77.3% vs. 54.2%, p = 0.029). There was a trend for higher therapeutic failure in the CB group (5.9% vs. 1.7%, p = 0.097). There were no differences in the rates of surgery (p = 0.385), hospitalization (p = 0.593) or clinical remission (p = 0.258). Clinical remission (78.7% vs. 60.5%, p = 0.036) was more common in patients with higher drug serum levels (7.12 ± 7.34 vs. 4.56 ± 3.81, p = 0.018).

Discussion/Conclusion: Our results suggest some benefit from DM-based management. The rates of escalation were four times higher in the DM group.
A case report: Anti-VEGF agent bevacizumab in a patient with Crohn’s disease

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Introduction: Angiogenesis is an important component of pathogenesis of inflammatory bowel disease (IBD). The level of VEGF was found to be increased in serum of IBD patients. But little is known about determining the response in patients with Crohn’s disease (CD) who treated with bevacizumab (a humanized IgG1 monoclonal antibody to VEGF). We report on a patient with CD who received bevacizumab for refractory symptoms.

Case report: 34-year-old woman with an 8-year history of CD and 7-year history of ankylosing spondylitis who had taken 5-aminosalicylate, azathioprine and oral corticosteroids but didn’t respond to conventional therapy. Then she was treated by infliximab for two years until an anaphylactic reaction was developed to infliximab and because of that infliximab was discontinued. As adalimumab is the second biologic therapy approved for the treatment of patients with moderately to severely active CD, she was then started on adalimumab. Three years later, there had been no significant improvement so we switched to bevacizumab treatment. The patient received bevacizumab subcutaneously and treatment repeated every 14 days for 7 months in the absence of unacceptable toxicity. Importantly, no acute CD outbreak was observed while the patient was under bevacizumab therapy and she achieved a full remission, confirmed colonoscopically. Before administration bevacizumab; colonoscopy showed multiple aphthous ulcers in terminal ileum and extensive ulcerations were noted in the ascending colon, after 7 months of bevacizumab therapy repeated colonoscopy revealed no abnormalities in terminal ileum and colon.

Discussion/Conclusion: It is widely known and shown an increased risk of serious infection and malignancy in patients receiving anti-TNF therapy. If TNF blockers are contraindicated or refractory, beyond TNF blockers, VEGF inhibitors appear to be one of the most promising drug class in CD.
Is azathioprine effective in the treatment of Crohn’s disease?

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Introduction: Azathioprine (AZA) is a well-established therapy in the treatment algorithm of Crohn’s disease (CD) and has been shown to be effective in the induction of and maintenance of remission of CD in several prospective, randomized controlled trials. However, up to 50% of patients discontinue immunosuppressive therapy within 2 years due to intolerance or lack of efficacy. The aim of this study is to assess the effectiveness and the tolerability of thiopurine therapy in patients with intestinal bowel disease.

Methods: A total of 158 patients with Crohn’s disease in the Department of Gastroenterology of Sahloul treated with azathioprine were retrospectively analyzed between January 2010 and December 2016. The lack of efficacy of AZA was defined as no response or recurrence of the disease after 6 months of treatment.

Results: 83 men and 77 women were included, with a mean age of 33 years. Limited terminal ileal involvement was noticed in 23% of patients, ileocecal localization in 54% of cases and an exclusive colonic involvement was observed in 21% of cases. Azathioprine was prescribed for: maintaining remission after corticosteroid therapy in the first attack (36%), after acute severe colitis responding to corticosteroids (24%), after surgical treatment (26%), for anoperianal lesions (7%), and a failure of response to aminosalicylates (7%). 26% of patients treated with AZA developed new attacks within a median time of 22 months. 85% of these patients required surgery, and 15% received anti-TNF therapy. 26% of patients developed side effects due to AZA therapy within a median time of 7 months: Liver toxicity in 13% of cases, one case of nodular regenerative hyperplasia and one case of liver cirrhosis. Hematologic toxicity was observed in 8% of patients including 5 cases of thrombocytopenia. 5 patients developed acute pancreatitis. One case of lymphoma was diagnosed after 3 years Imurel. In regards to these side effects, 20% of patients stopped AZA.

Conclusion: Azathioprine is an effective and steroid-sparing agent for refractory CD. Its side effects are generally mild and tolerable.
Six-year efficacy and safety of azathioprine treatment in the maintenance of steroid-free remission in inflammatory bowel disease patients

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Introduction: Azathioprine (AZA) is widely used for induction and maintenance of remission in steroid dependent patients with inflammatory bowel disease (IBD).

Methods: We investigated its efficacy and safety in maintaining steroid-free remission in steroid dependent IBD patients six year after the institution of treatment. Data from consecutive IBD outpatients referred in our Institution (between 1985–2015) were reviewed and all patients treated with AZA were included. AZA was administered at the recommended dose of 2–2.5 mg/kg.

Results: Out of 2722 consecutive IBD outpatients visited in the index period, AZA was prescribed to 415 patients, 227 (54.7%) were affected by Crohn’s disease (CD) and 188 (45.3%) by ulcerative colitis (UC). One hundred and fifty-eight patients with a follow-up < 72 months were excluded from the study. Two hundred and fifty-seven patients were evaluated, 143 (55.6%) with CD and 114 (44.4%) with UC. One hundred and forty-two (55.2%) were male and 115 (44.8%) female (average age of 35.68 ± 14.22 SD years, range 14–74 years). Six years after the institution of treatment, 130 (50.6%) patients still were in steroid-free remission (85 CD vs. 45 UC, 59.5% and 39.5%, respectively, p = 0.0017), 71 (27.6%) had a relapse requiring retreatment with steroids (29 CD vs. 42 UC, 20.3% and 36.8%, respectively, p = 0.0048), 56 (21.8%) discontinued the treatment due to side effects (29 CD vs. 27 UC, 20.2% and 23.7%, respectively). Loss of response from 1st to 6th year of follow-up was low, about 20%.

Discussion/Conclusion: Six year after the onset of treatment 50.6% of patients did not require further steroid courses. After the first year loss of response was low in five subsequent years. In the present series the maintenance of steroid-free remission was significantly higher in CD than in UC patients. The occurrence of side effects leading to the withdrawal of AZA treatment has been low.
Mesalazine monotherapy for maintenance of remission in ulcerative colitis patients in Turkish population

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Introduction: Newer formulations of salicylates based drugs have fewer side-effects and are free of the sulphur component. Mesalazine is one of them and it has been used for over 30 years in the treatment of inflammatory bowel disease (IBD). The aim of this study was to analyze the role of the mesalazine in the remission of ulcerative colitis (UC).

Methods: A total of 392 adult outpatients and inpatients with a previously confirmed diagnosis of UC were enrolled at the Departments of Gastroenterology of the Ankara University between 2009 and 2017. They were diagnosed on the basis of standard clinical, endoscopic, and histologic criteria. Disease activity was evaluated using the Rachmilewitz Endoscopic Index (REI) and the Mayo score. Remission is defined as ≤ 1 point by Mayo score and ≤ 4 points by REI.

Results: Just over half of the patients (58%) were male, and the median age of the study population was 44 year. 45.4% of patients had their UC disease limited to the left side of the colon while 42.8% had pancolitis. 93.3% of all the patients were treated with mesalazine as a first line agent. Mesalazine has been shown to be effective in the maintenance of remission in 45% of patients with UC who were under monotherapy with mesalazine.16.3% of patients receiving corticosteroids and mesalazine achieved remission compared to 23.4% of patients receiving azathioprine and mesalazine. 11% of all the patients who failed to maintain remission with mesalamine and azathioprine received anti-TNF therapy. This study presented that 71% of all the patients on mesalazine maintained remission.

Discussion/Conclusion: Mesalazine is shown to be significantly superior to other therapies for maintenance of remission as a first-line therapy.
Prevalence of effective vaccination for hepatitis B in patients with inflammatory bowel disease

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Introduction: Hepatitis B immune status in IBD patients is important due to the risk of reactivation of hepatitis B virus (HBV) infection, especially in patients starting anti-TNF therapy. Vaccination with an accelerated double-dose of rHBAg 20 µg at 0, 1, 2 months has demonstrated a good efficacy with a seroconversion rate of 60–70%.

Methods: We studied retrospectively 35 patients with IBD, evaluated in a tertiary medical center in North-East of Romania, during 2016–2017 for initiation of anti-TNF therapy. None of the patients had been previously vaccinated for HBV. All patients were tested for hepatitis B surface antigen (HBs Ag), hepatitis B core antibodies (anti-HBc) and antibodies to hepatitis B surface antigen (anti-HBs). Seronegative patients were vaccinated with an accelerated double-dose of Engerix-B at 0, 1, 2 months. Serological response was assessed at 2 months after the last dose of vaccination.

Results: 35 patients with IBD (29 with ulcerative colitis and 6 with Crohn’s disease), aged between 29 and 60 years (median age 35 years) were enrolled. All patients were HBs Ag negative. 3 patients that tested positive for anti-HBc were excluded because of possible occult HBV infection. Seroconversion at 2 months after vaccination occurred in 75% of patients with titers > 100 UI/ml in 28.5%.

Discussion/Conclusion: Vaccination with an accelerated double-dose of Engerix®-B at 0, 1, 2 months is efficient in IBD patients starting anti-TNF therapy demonstrating a high seroconversion rate.
Prevalence of hepatitis B virus infection markers in patients with inflammatory bowel disease in a hepatitis B endemic region

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Introduction: Patients with inflammatory bowel disease (IBD) are considered to have a higher risk for hepatitis B virus (HBV) infection. Although recent studies have shown that the frequency of HBV infection in IBD patients does not differ from the general population, HBV infection prevalence in endemic areas such as Romania remain of particular interest.

Methods: We studied retrospectively 75 patients diagnosed with IBD, evaluated in a tertiary medical center in North-East of Romania during 2015–2017 before initiation of either immunomodulator or anti-TNF therapy. Screening for hepatitis B infection was performed by testing for hepatitis B surface antigen (HBs Ag), hepatitis B core antibodies (anti-HBc) and antibodies to hepatitis B surface antigen (anti-HBs). HBV DNA was assessed in patients with positive markers for HBV infection.

Results: A total of 75 patients with IBD (55 with ulcerative colitis and 20 with Crohn’s disease), aged between 35 and 65 years (median age 44 years) were enrolled. All patients tested negative for HBs Ag. Anti-HBc were present in 13.3% (10 patients). 1 patient had detectable HBV DNA. Anti-HBs in titers > 10 IU/ml were present in 5.33% (4 patients).

Discussion/Conclusion: HBV infection has a high prevalence in IBD patients in hepatitis B endemic regions such as Romania and this should be taken into consideration when starting immunosuppressive therapies, especially anti-TNF agents, due to the risk of HBV reactivation.
The effect of 1-year therapy with anti-TNF-α monoclonal antibodies on the lipid profile in patients with inflammatory bowel disease

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Introduction: Tumor necrosis factor α (TNF-α) is considered one of the key cytokines involved in the pathogenesis of both atherosclerosis and inflammatory bowel disease (IBD). Although anti-TNF-α monoclonal antibodies have markedly revolutionized the treatment of IBD, the long-term effects of these drugs on the lipid profile are still controversial. The aim of our study was to assess the effect of 1-year therapy with anti-TNF-α monoclonal antibodies on the lipid profile in patients with IBD.

Methods: We have conducted a clinical retrospective study. Inclusion criteria were: IBD patients undergoing treatment with standard doses of infliximab or adalimumab, in clinical remission for at least six months. Exclusion criteria were: Patients who have changed their basal treatment regimen (including corticosteroids) or patients who have taken medications (other than anti-TNF-α) that alter the lipid profile. Demographic, clinical characteristics and laboratory findings were collected from medical records. Total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and atherogenic index (AI) were measured at baseline and at 4, 8 and 12 months.

Results: 98 patients were included: Crohn’s disease (CD)/ulcerative colitis (UC): 56/42; mean age 49.9; male/female: 61/37; infliximab/adalimumab: 63/35. During the follow-up period, 18 (18.3%) patients underwent a relapse (Harvey-Bradshaw score > 4 in patients with CD and Mayo score > 3 in patients with UC). Following anti-TNF-α treatment, the mean levels of TG were 89 ± 32 mg/dL at baseline and increased to 98 ± 35 mg/dL at 4 months (p < 0.003), 112 ± 29 mg/dL at 8 months (p < 0.001) and 128 ± 30 (p < 0.001) at 12 months. Mean levels of HDL cholesterol were significantly higher than basal levels after 4, 8 and 12 months of treatment (p < 0.05). There was no statistical significant difference for TC, LDL cholesterol and AI. No statistical significant differences in TC, TG, LDL cholesterol, HDL cholesterol and AI were found in patients underwent a relapse.

Discussion/Conclusion: One-year therapy with anti-TNF-α monoclonal antibodies might affect lipid profile in patients with IBD despite a good control of the chronic inflammatory state.
Transfer of responsibility for self-care from the pediatric to the adult patient with Crohn’s disease: Case report

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Introduction: Children with Crohn’s disease (CD) often present with a more complicated disease course compared to adult patients. Data on the transition and transfer of care in children/adolescents with CD are scarce.

Results: We present the case of a young female patient, diagnosed in early childhood with ulcerative colitis (UC). She was admitted to the Institute of Gastroenterology and Hepatology at 19 years of age with a history of chronic abdominal pain for 2 years, localized in the right lower quadrant, and associated with diarrhea (4–7 episodes per day). At the time of admission, the patient was not dependent on particular medications. On clinical examination, the skin and mucosa were pale, the abdomen was distended and tender. The CT scan and the magnetic resonance enterography showed an enlarged enhancing appendix, mesenteric inflammation, an inflammatory mass in the right lower quadrant associated with thickening of the wall and narrowing of the lumen of the cecum and ascending colon. An exploratory laparoscopy was performed and the macroscopic cobblestone was consistent with CD. Induction therapy using intravenous corticosteroids was initiated, and except for two episodes of Clostridium difficile infection effectively treated with oral Vancomycin, the overall outcome was favorable.

Discussion/Conclusion: A change in diagnosis form UC to CD occurs in about 5% of cases. Bridging the gap between the pediatric and adult services is of the utmost importance especially in the regards to the changing phenotype of inflammatory bowel disease spectrum.
Outcomes following anti-TNF discontinuation and the risk of relapse in inflammatory bowel disease: A single-centre experience

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Introduction: Crohn’s disease (CD) and ulcerative colitis (UC) are chronic inflammatory bowel (IBD) conditions that result in fluctuations of disease activity. Infliximab and adalimumab are well-established agents associated with inducing and maintaining remission in IBD. Long term use of this agent has an associated risk profile and significant healthcare budget implications.

Methods: A single-centre retrospective review was performed of our 1000 IBD patients. We reviewed IBD cohort on Anti-TNF therapy. Analysis of colonoscopy findings and patient symptoms at time of discontinuation was performed and subsequent clinical follow following withdrawal of therapy.

Results: We identified 71 patients on Infliximab. 43 (60%) have ulcerative colitis and 28 (39.4%) have Crohn’s disease. Following a mean treatment interval of 48 months Infliximab therapy was discontinued in 23 (32.3%) patients. Of the discontinuation cohort 13 (56.5%) patients had UC, 8 (34.7%) had CD 2 (8.6%) were indeterminate colitis. During a follow up of 44 months 22 (95%) remained in clinical remission, while 1 (5%) relapsed. We identified 224 patients on Adalimumab in our cohort for treatment of CD. Of this cohort 3 (1.3%) were discontinued as they were in clinical remission. The follow up for this arm was 50 months. There have been 2 (66%) relapses in this group.

Discussion/Conclusion: Successful remission was achieved in 95% of our Infliximab cohort and 33% of our Adalimumab cohort resulting in fewer hospital admissions, improvement in patient quality of life and decreased healthcare costs that are associated with provision of both maintenance and rescue therapy for flares of disease.
Can we avoid surgery in Crohn’s disease with spontaneous abdominal abscesses?

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Introduction: Crohn’s disease (DC) can be complicated by intra-abdominal abscesses (IAA) in 10–30% of the patients. The antibiotic therapy (ABT) with or without percutaneous drainage (PD) has become the first line therapy in order to prevent surgical intervention or to improve surgical outcomes.

Objectives: To evaluate the rate and predictive factors of medical treatment (ABT ± PD) success in DC-related IAA.

Methods: Retrospective analysis of patients admitted to our Gastroenterology Department due to newly or known DC complicated by IAA between January 2007 and October 2017. Socio-demographic and clinical data were collected through the electronic medical records. Treatment success was defined as imageological (CT or MR) abscess resolution and non-reappearance within 1 year of follow-up. The association between the socio-demographic and clinical variables and medical treatment success was determined by univariate and multivariate analysis.

Results: A total of 43 patients (55.8% males) with 32 ± 11 years were analyzed. DP was performed in 16 patients (37.2%). Within one year of follow-up surgery was needed in 30 patients (69.8%). The overall medical treatment success rate was 30.2%. The medical treatment resulted in abscess resolution in 17 patients (39.5%), but in 4 patients (9.3%) the abscess recurred within 1 year. Active CD at abscess diagnosis (p = 0.002) was associated with overall medical treatment failure. Active CD at abscess diagnosis (p = 0.002) and abscess > 4 cm (p = 0.002) were associated with abscess non-resolution and recurrence after medical treatment, respectively.

Discussion/Conclusion: The large majority of patients with CD-related IAA need surgery in the short-term. Only in patients with inactive luminal disease and small abscess may we avoid surgery in the short-term.
Changing natural history in IBD – Steroid-free remission and surgery in two cohorts (≤ 2009 and > 2009): An interplay between disease pattern, biologics and adherence

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Introduction: With the more frequent use of biologics (BIO) a change in disease outcome for both, Crohn’s disease (CD) and ulcerative colitis (UC), is expected but studies yield conflicting results. The aim of the present study was to investigate changes of therapeutic approach, patients’ adherence, and disease outcomes, i.e. steroid-free remission and surgery rates, in two IBD cohorts.

Methods: We retrospectively assessed demographic and disease-related data (disease, age at diagnosis, Montreal classification of IBD, disease pattern (DP) (1: onset and subsequent mild course, 2: relapsing, 3: chronic active), type and start of therapy, surgery rates, steroid free remission at 1 and 2 years after taking in charge, and patients’ adherence) of patients followed at our IBD-UNIT. The patients were divided into two cohorts those taken over ≤ 2009 and those taken over after 2009.

Results: Cohort 1: 129 UC, 154 CD; Cohort 2: 200 UC, 170 CD. In cohort 2, compared with cohort 1, there was an increase in steroid-free remission at year 1 (p < 0.008) and 2 (p < 0.041) in CD and in UC (p < 0.022 and 0.048, respectively). In CD, there was a reduction in surgery rates (19% vs. 11%, p < 0.006). UC colectomies were very low in both cohorts. While the use of immunomodulators (IMM) was comparable in both cohorts, BIO were earlier employed in cohort 2 (log-rank: p < 0.0001). By multivariate analysis, steroid free remission at 1 year was associated with DP-1 (p = 0.047) and adherence (p = 0.03), whereas steroid free remission at year 2 was associated with BIO use (p = 0.000) and DP-1 (p = 0.048). Adherence was associated with the use of IMM (p = 0.012), BIO (p = 0.000), and DP-1 (p = 0.01).

Discussion/Conclusion: Adherence, BIO, and disease pattern were associated with steroid-free remission at year 1 and 2. Reaching early benefit may influence patients’ confidence and, thus, adherence. This in turn leads to better long-term results at least in patients with milder disease patterns.
MaRIA score in the assessment of disease activity in patients with ileocolonic Crohn's disease: The correlation between radiological, clinical and endoscopic scores

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Introduction: Adequate disease assessment in Crohn's disease (CD) is crucial for therapeutic strategy. It includes evaluation of disease extension and activity. In this study we correlated MR findings in patients (pts) with ileocolonic CD assessed my MaRIA score with endoscopic SES-CD index and Crohn's disease index of activity (CDAI).

Patients and methods: We evaluated 40 pts with more severe ileocolonic CD phenotype classified according to Montreal classification. MR index of activity (MaRIA) was calculated according to further formula: 1.5 x wall thickness (mm) + 0.02 x relative contrast enhancement + 5 x edema + 10 x ulceration and evaluated as follow: 0–7 points remission, 7–11 mild disease, > 11 points severe disease. SES-CD was calculated for each segment of ileocolonoscopy finding for further variables: presence of ulcers, ulcerated surface and affected surface, presence of stenosis and number of affected segments. CDAI was calculated in standard manner; < 150 points remission; 150–450 points mild and moderate disease; > 450 points severe disease.

Results: 40 pts (23 female, 17 male) with ileocolonic CD, average age 40 yrs were evaluated. The average CDAI was 351. Further variables were correlated: MaRIA score, CDAI and SES-CD. For statistical analysis Pearson and Spearman coefficient for categorical variables with level of significance 0.01 were used. According to MaRIA score 70% of pts had severe disease, 15% mild disease, 15% remission. MaRIA score ranged from 4.5–30 and correlated positively with CDAI (Spearman 0.459, p = 0.003, Pearson 0.468, p = 0.002). Correlation of CDAI with single MR variables showed that lymph node involvement and fibrosis positively correlated with CDAI (Pearson 0.245; Spearman 0.169). MaRIA and SES-CD correlated also strongly positive (Spearman 0.542, p < 0.001, Pearson 0.494, p = 0.001).

Conclusion: MaRIA score as a MR index of activity in CD patients presents very good and valuable score for assessing disease extent and activity, especially in patients with more-severe forms of disease. Our study showed positive correlation of MaRIA score with most frequently used clinical (CDAI) and endoscopic indexes (SES-CD) in CD patients.
Experimental model of fistulizing Crohn’s disease: Beneficial effect of topical application of adipose tissue-derived mesenchymal stromal cells

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Introduction: Penetrating phenotype usually constitutes a critical issue in Crohn’s disease (CD). We investigated the potential therapeutic effect of the topical administration of adipose tissue-derived mesenchymal stromal cells (AT-MSCs) in a new model of penetrating CD.

Methods: Wistar-specific pathogen-free rats with trinitrobenzene sulfonic acid (TNBS)-induced colitis were submitted to a transversal section of the descending colon 4 cm above the peritoneal pelvic reflection, preserving the blood supply, and followed by end-to-end anastomosis at day 7. Immediately after the procedure, either 2 x 10^6 AT-MSCs or cell culture medium was instilled onto the anastomosis. Two groups of animals not receiving TNBS served as additional sham and control groups, respectively. Euthanasia was performed at day 14 and the abdominal cavity surveyed for macroscopic abnormalities. The area of anastomosis was removed for the histologic analysis, myeloperoxidase activity, fibrosis epithelial integrity, activation of intracellular pathways; inflammatory cytokines from explant cultures, and tissue expression of extracellular matrix-related genes.

Results: Compared to animals treated with culture medium, the group receiving AT-MSCs had a lower mortality rate (50% versus 16%), and fewer macroscopic complications such as fistula, abscess, phlegmon, and adhesions (80% versus 25%). Treatment with AT-MSCs resulted in lower histopathologic scores (p < 0.003), reduction of myeloperoxidase activity (p < 0.02), collagen deposition (p < 0.004), and goblet cells preservation (p < 0.04). The therapeutic effect was mediated by reducing the accumulation of inflammatory cells, rates of epithelial apoptosis, levels of Th1/Th17 cytokines, and NF-kappa B activation. Changes in extracellular matrix–related genes have been detected, with probable involvement in the tissue remodeling observed in the model.

Discussion/Conclusion: This novel experimental model of fistulizing CD is effective and reproducible. Topical instillation of AT-MSCs remarkably attenuates the inflammation in this model, probably due to a paracrine anti-inflammatory action. These results support the use of AT-MSCs as a promising therapy for a disabling CD phenotype.
Anxiety and depression in inflammatory bowel disease

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Psychosocial issues are an important dimension of inflammatory bowel disease, evaluation of phenomenon of "living with inflammatory bowel disease, showed a bad influence of the disease on quality of life.

Introduction: Young age, periods of activity, associated pathologies and treatment these diseases affect patients not only physically, but also by limiting social and emotional life.

Methods: We evaluated retrospective prevalence of depression and anxiety at patients with inflammatory bowel disease. The presence of anxiety and depression was determined by diagnosis through psychiatric interview or using report health questionnaires. Patient demographics, disease characteristics, and medication information were also collected. Multivariable analysis was used to determine associations between patient factors and depression and anxiety.

Results: We evaluated 72 patients with inflammatory bowel disease (34 patients with Crohn’s disease and 38 with ulcerative colitis). 32.3% of patients with Crohn’s disease suffering from anxiety and 14.7% with depression, and also we found 31.5% with anxiety and 23.6% with depression at patients with ulcerative colitis. Disease activity was found to be significantly associated with depression and/or anxiety (p = 0.01). Females were more likely to have anxiety (p = 0.001).

Discussion/Conclusion: A significant proportion of inflammatory bowel disease patients suffer from depression and/or anxiety. Patients with active disease are particularly at risk for depression anxiety.
Treatment and quality of life in inflammatory bowel disease

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The treatment of inflammatory bowel diseases includes several classes of drugs, from classical 5-aminosalicylic derivatives and corticosteroids, to immunomodulatory agents and biological therapy, which practically revolutionized the evolution and prognosis of inflammatory bowel disease.

Introduction: The type of medication is recommended depending on disease activity, location and the behavior of the disease and, of course, preferably to each patient.

Methods: In the study was enrolled 82 patients diagnosed with inflammatory bowel disease. The inclusion criteria in this study were: age > 18 years, informed consent of the patient and clinical, biologically, endoscopically and histologically confirmed diagnosis. The study results are represented only by the data recorded at the time of inclusion in the study without being quantified in evolution.

Results: Most patients were treated with 5-ASA derivatives (64.6%). Also the number of patients undergoing corticosteroid therapy was significant (21.9%). Only 13.5% patients were treated with biological agents (adalimumab 40% and infliximab 60%). Also patients who were treated with 5-ASA derivatives showed higher values of the quality of life score. Corticotherapy has been found to be higher in patients with ulcerative colitis being indicated in severe forms. The patients treated with Infliximab presented higher values of quality of life through gastrointestinal and systemic manifestations. Aspects of social life and emotional functions were less affected in patients treated with adalimumab.

Discussion/Conclusion: For both diseases corticotherapy administered during periods of activity of the disease was associated with lower quality of life scores, while patients in biological therapy had a higher quality of life score.
Cerebral venous thrombosis is a rare complication of ulcerative colitis – Case report

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Introduction: Ulcerative colitis (UC) is a chronic inflammatory bowel disease. The incidence of extraintestinal manifestations and/or complications in inflammatory bowel disease in children is around 6% at the beginning of the disease with prevalence gradually increasing with age. The most common are arthritis, aphthous stomatitis and osteopenia. Cerebral venous thrombosis (CVT) is a rare but serious complication of UC. The prevalence of CVT correlates with activity of primary disease and ranges, depending on the study, from 0.5% to 7.5%.

Methods: We present a case of patient with cerebral venous thrombosis as complication of ulcerative colitis. Patient was diagnosed with UC at the age of 13 and partial remission was achieved with combination of corticosteroids, mesalazine and azathioprine. Two years later he was admitted to the hospital due to relapse of UC and partial remission could not be achieved with high doses of corticosteroids. During hospitalization patient developed acute progressive headache with minimal neurological deficits and diagnosis of CVT was considered. Cerebral MR venography showed absence of normal flow void in sagittal sinus, left sigmoid and transverse sinus and also paramedian cerebral venous infarction. Subcutaneous low molecular weight heparin was given along with biological therapy (infliximab) for the treatment of UC. This therapeutic approach led to recovery in neurological examination and control brain MR venography showed partial recanalization.

Conclusion: Awareness of this rare complication may contribute to early detection and treatment of this serious and often deadly condition.
Status of vitamin D in patients with inflammatory bowel disease: A study in a tertiary care center from Northeastern Romania

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Introduction: Vitamin D (VD) deficiency is more common in those diagnosed with inflammatory bowel disease (IBD) as compared to the general population. The purpose of the study is to assess the prevalence of VD deficiency in our patients with IBD, to determine the factors that predict this deficiency and to establish its link with disease activity and extent.

Methods: We performed a retrospective study, during a period of 24 months (January 2014–January 2016). Exclusion criteria were: age under 18, patients with incomplete medical history or with other known causes of VD deficit. Clinical data and laboratory parameters were collected.

We have interpreted serum levels of VD as according to the 2015 Endocrinology Guidelines which defined deficit as a 25-(OH)-D below 20 ng/ml (severe < 10 ng/ml) and insufficiency: 25-(OH)-D levels between 21–29 ng/ml. We considered adequate levels of VD values ≥ 30 ng/ml.

Results: We included 76 patients (56% men, median age: 33 ± 6 years). 54 with ulcerative colitis (UC)-lot A and 22 with Crohn’s disease (CD)-lot B. Of 76 patients, 55 (72.3%) had VD deficiency (20 with CD and 35 with UC, p < 0.01), 19 had insufficient levels of VD and only 2 had adequate levels.

Furthermore, 64.8% (35/54) of the patients with UC and 90.9% (20/22) of the ones with CD had low VD levels.

Regarding the lot A, VD deficiency was found in 66% of patients with pancolitis and in half of the patients with left-sided colitis. Concerning the Mayo score, the deficit of VD was found as follows: 57% of those having Mayo score > 6 (19/33) and 47% Mayo < 6 (10/21).

In lot B, 82% of those having B1 phenotype had VD deficiency and 94% of patients with B2 phenotype. 91% of the patients with Crohn’s Disease Activity Index (CDAI) < 150 and all of those who had CDAI > 150 were deficient in VD. In this group we found an association between low levels of VD and higher values of CRP (p = 0.028), younger patients (p = 0.032) and lower BMI (p < 0.001).

No link was found between levels of VD and gender, disease location, phenotype, disease activity (Mayo and CDAI) or smoking habits.

Discussion/Conclusion: In patients with IBD, there is a high prevalence of inadequate levels of VD, especially deficiency (72.3%). Therefore, patients with this condition should be investigated and treated if this deficiency is present.
Particularities of treatment in elderly people with inflammatory bowel disease: A study in a tertiary care center from North-eastern Romania

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Introduction: Inflammatory bowel disease (IBD) among the elderly is common, with increasing rates of incidence and prevalence. Even though the principles of managing IBD elderly patients are the same as in other age groups, given the fact that most of the studies were performed on young patients, there are limited data regarding the therapeutic options and adverse events in elderly people with IBD.

Methods: We conducted a single-center retrospective study during a period of 36 months (January 2013–January 2016) at the Institute of Gastroenterology and Hepatology Iasi. Demographic characteristics, therapies and outcomes were analyzed. Elderly was defined as patients over 60 years.

Results: 128 patients were included (59% men): 91 (71%) – Ulcerative colitis (UC), 37 (29%) – Crohn’s disease (CD). Mean age at diagnosis was 37 years, 17 (13.2%) had elderly-onset IBD and 48 (37.5%) were ≥ 60 years at the time of the study analysis. Charlson comorbidity index (4.8 ± 1.2 vs. 0.9 ± 1.5, p < 0.001) and the number of daily medications (4.7 ± 3.9 vs. 1.9 ± 1.9, p < 0.001) were significantly higher in patients ≥ 60 years. The elderly people received more often 5-aminosalicylates (88.4% vs. 76.2%, p = 0.001) and less frequently azathioprine (23.4% vs. 55.7%, p = 0.000) or biological therapy (9.7% vs. 27.2%, p = 0.000). Regarding the global incidence of adverse events there was no significant difference between the two groups (18.4% – elderly people vs. 23.7%, p = 0.256) and also in terms of surgery. Concerning infections, the statistical analysis reported no significant difference in patients over 60 years.

Discussion/Conclusion: Even though the use of immunosuppression was higher in the non-elderly group, the safety profile of these drugs is accurate, with similar rates of adverse events in older and younger patients.
Prevalence of anemia in patients with inflammatory bowel diseases (IBD) in a tertiary center in Romania

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Background: Anemia is the most frequent extradigestive manifestation in patients with IBD. Up to 74% patients develop anemia during life time.

Aim: To evaluate the prevalence and the risk factors for anemia in patients with IBD hospitalized during two years.

Methods: We conducted a prospective study, that took place during 2 years (between 1st January 2015–31st December 2016) which enrolled 187 patients with ulcerative colitis (UC) and 85 patients with Crohn’s disease (CD). A complete clinical and biological examination was performed to each patient. The diagnosis was established by colonoscopy and biopsy. The localization of lesion and the behavior of the disease was classified according to Montreal classification. The activity of the disease of the disease was established by using UCDAI (ulcerative colitis disease index) for UC and CDAI (Crohn’s disease activity index) for CD. We define anemia according to OMS definition: < 13 g/dl for men, < 12 g/dl for women.

Results: The prevalence of anemia was 32.08% in UC and 36.4% in CD. The most frequent form of anemia was iron-deficiency anemia (79.66% of patients with UC and 80.64% of patients with CD). Factors associated with anemia were similar for those with CD and UC and included extended forms of the disease, more severe forms of the disease, a longer period from diagnosis and smoking.

Discussion/Conclusion: The prevalence of the anemia is still important, one third of the patients with IBD developed anemia. The most frequent form of anemia was iron-deficiency anemia. Incorporation of screening for anemia and, in particular, iron deficiency, should be a component of monitoring and treatment of these patients.
Metastatic vulvar Crohn’s disease: A rare entity

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Introduction: Crohn's disease is an inflammatory bowel disorder with several well-known extraintestinal manifestations, such as erythema nodosum, uveitis, and arthritis. Less commonly observed are cutaneous, so-called metastatic lesions of the vulva, which represent a diagnostic and therapeutic dilemma and require a multidisciplinary approach. The objective of this study was to report a case series of patients with vulvar Crohn’s disease (VCD), describe its clinical features, histopathologic characteristics and therapeutic management.

Methods: In this retrospective study, we reviewed all cases of VCD seen in our department between 2008 and 2016. Data concerning age at diagnosis of VCD, vulvar symptoms at presentation, histologic findings, and different treatment modalities were recorded. Only patients with both clinical features of VCD [knife-cut fissures, edema, ulceration] and histologic confirmation were included. A total of 3 cases were identified among 106 female patients with CD.

Case 1: A 58-year-old patient, presented with a 4-year history of vulvar pain and itching. She had no bowel complaints. Clinical examination revealed hypertrophic exophytic lesions associated with linear ulcerations involving the vulva. A biopsy from the lesional skin showed non-caseating gigantocellular granuloma. In view of the clinical and histopathological features, a diagnosis of Crohn’s disease of the vulva was made. Anti-TNF treatment with adalimumab was started, resulting in a significant regression of the lesions.

Case 2: A 47-year-old patient presented to our department with complaints of painful, persisting vulvar ulcers, and resulting dysperunia for 2 years. On clinical examination she had unilateral vulvar edema with multiple “knife-cut” linear ulcers. A skin biopsy was done which revealed dense inflammatory lymphocytic infiltrate with non-caseating granulomas. Treatment with adalimumab was initiated. An improvement of symptoms was noted.

Case 3: A 16-year-old patient with no remarkable medical history, presented with a 2-year-history of persistent cheilitis and vulvar pain. Clinical examination of the external genitalia revealed ‘knife-cut’ vulvar fissures with important bilateral labial swelling and multiple papules on the surrounding skin. Histological analysis showed chronic inflammatory infiltrate with non-caseating tuberculoid granulomas. Anti-TNF treatment with infliximab was started with partial regression of lesions.

Discussion/Conclusion: Our findings highlight the importance of keeping VCD on the differential diagnosis when faced with a range of vulvar symptoms. Anti-TNF agents seem to be an efficient treatment strategy for this particular localization.
Prevalence of chronic hepatitis B in Tunisians patients with inflammatory bowel disease

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Introduction: Patients with inflammatory bowel disease (IBD) have long been considered at increased risk of hepatitis B and C. Moreover, recent epidemiological studies reported similar and even lower prevalences of chronic hepatitis B than in the general population. The aim of this study is to assess the prevalence of HBV markers in Tunisians patients with IBD.

Methods: We enrolled a retrospective study including 210 patients treated for IBD between January 2010 and November 2017. All our patients were tested for hepatitis B antigens and antibodies. DNA levels were requested in case of positive HBsAg or positive anti-Hbc with negative anti-HBs.

Results: We included 210 IBD patients (124 Crohn's disease [CD] and 86 ulcerative colitis [UC]) with the mean age of 39 years. The mean follow-up was 19 months. We found that 2.3% of patients had positive HBsAg, 21% had positive anti-HBs, and 22.8% had positive anti-Hbc. The viral load performed in 8 patients was detectable only in 3 patients. Five patients received preemptive antiviral treatment before starting immunosuppressive therapy. One patient had a viral load > 2000 UI / ml with a Metavir scoring A2F2 on liver biopsy requiring antiviral treatment. The two other patients did not need any immunosuppressive therapy or antiviral treatment during follow-up.

Discussion/Conclusion: Prevalence of HBV infection in IBD is lower than that of the general population of reference. It is crucial to screen for HBV immunity and to implement a meticulous vaccination strategy for IBD patients.
Introduction: Increasing numbers of patients with inflammatory bowel disease (IBD) are being treated with anti-TNF agents. Due to their immunosuppressive action, these treatments may lead to the reactivation of latent tuberculosis (LTB). Therefore, screening for LTB is mandatory before initiating any anti-TNF therapy. In this study, we aimed to identify the prevalence of LTB among patients with IBD treated with anti-TNF drugs.

Methods: In this retrospective study, all patients with IBD treated with anti-TNF between 2008 and 2016 were enrolled. Recommended studies for screening TB (clinical history, chest X-ray, tuberculin skin test (TST), Quantiferon Gold Assay [QFT-G]) performed prior to therapy were revised. LTB was determined by positive TST (> 5 mm) and/or positive QFT-G.

Results: A total of 65 patients (53 with Crohn’s disease and 12 with ulcerative colitis) were enrolled. None of the patients had medical history of tuberculosis. LTB was diagnosed in 14 patients (21.5%) with either positive TST (n = 3) or QFT-G (n = 11). They were 9 males and 5 females with a mean age of 34 years. Chest X-rays showed suggestive lesions of tuberculosis in 2 patients which were considered as sequelae at computed tomography. Ten patients were treated with azathioprine and 3 with corticosteroids at the moment of the screening. Anti-tuberculosis prophylaxis with isoniazide and rifampicine was started in all patients, 3 weeks before initiating anti-TNF therapy and maintained for 3 months. After a median follow-up of 18.4 months, none of these patients developed active tuberculosis.

Discussion/Conclusion: The overall prevalence of LTB was 21.5% in our series. Chemoprophylaxis and rigorous follow-up were needed in order to avoid the development of a potentially life-threatening infection.
Can we predict the efficacy of anti-TNF agents?

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Introduction: The use of anti-TNF treatments has revolutionized the therapeutic management of inflammatory bowel diseases (IBD). However, despite their proven efficacy, primary non-response or loss of response to these treatments is a frequent concern in IBD patients. Thus, the identification of predicting factors of efficacy is crucial to allow clinicians to efficiently use these therapies. The aim of this study is to identify predictive factors of the efficacy of anti-TNF agents in IBD patients.

Methods: This was a retrospective study in which we included all patients diagnosed with Crohn’s disease (CD) or ulcerative colitis (UC) and treated with anti-TNF (infliximab or adalimumab) from 2008 to 2016. The disease activity was assessed by the Crohn’s Disease Activity Index (CDAI) in CD and Mayo score in UC. Clinical remission was defined as a CDAI < 150 or a Mayo score ≤ 2. The efficacy of anti-TNF treatment was attested by a sustained steroid and surgery-free clinical remission. Univariate analysis was performed to identify potential predictive factors of efficacy.

Results: Sixty-five patients were included with a median age of 39 years, 30 (46.1%) of them were males. Fifty-three had CD and 12 had UC with a median follow-up period of 82 months. Forty patients were treated with infliximab (61.5%) while 15 received adalimumab (61.5%). Combotherapy with azathioprine was prescribed in 59 (90.7%) cases. The commonest indication of anti-TNF treatment was refractoriness to immunosuppressors (53.8%). Sustained surgery and steroid free clinical remission was obtained in 65.2% of patients. In univariate analysis, disease duration < 24 months before the initiation of anti-TNF treatment was the only predictor of treatment efficacy.

Conclusion: In our cohort, shorter disease duration before the start of anti-TNF therapy was associated with increased efficacy and better outcomes. This highlights the importance of selecting patients who should benefit from an early use of an anti-TNF agent.
Impact of endoscopic remission on the ulcerative colitis evolution

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**Aims:** To specify the impact of endoscopic remission obtained after a first attack treatment on the evolution course of patients with ulcerative colitis (UC).

**Materials and methods:** We retrospectively included inpatients for a first RCH flare, put into remission by medical treatment and in whom a colonoscopy check at the end of the attack treatment was performed. Endoscopic remission was defined by the restitution of a colonic mucosa appearance (Mayo score: 0–1). The parameters evaluated during the follow-up were the occurrence of a subsequent relapse, the extension of colonic and the occurrence of a severe acute colitis.

**Results:** We included 46 patients. Endoscopic remission was observed in 33 patients (71%). After an average follow-up of 41 months, relapse rates and a severe acute colitis were similar when comparing patients with or without endoscopic remission (respectively 51% vs. 46%, p = 1 and 0% vs. 16%, p = 0.2). The colonic lesion extension rate was lower in patients obtaining an endoscopic remission with a difference at the borderline of statistical significance (11% vs. 50%, p = 0.08).

**Conclusion:** Obtaining endoscopic remission during the course of UC should be a therapeutic goal. A better evaluation of its impact on our patients must be carried out over a longer period of follow-up and by a use probably a Mayo clinic score 0 to confirm endoscopic remission.
Long-term outcome of patients with Crohn’s disease treated with corticosteroids: A retrospective comparative study

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Introduction: Crohn’s disease patients with moderate to severe flares are often effectively treated with corticosteroids (CS). However, early and frequent use of CS may reflect severe engineering of CD. The aim of our study was to assess long-term outcome of CD patients treated with CS regarding immunosuppressive use, biotherapy use and need for surgery.

Material and methods: A retrospective study including hospitalized CD patients was conducted. Epidemiologic, clinical and therapeutic characteristics were determined. Patients who had at least one course of CS (group A) were compared to patients who have never been treated with CS (group B). Statistical analysis was performed with SPSS software version 20.0.

Results: Two hundred seventy-five patients (143 males and 132 females) were collected. Mean age at onset of CD was 31.8 years old (8–65 years). 159 patients received at least one course of CS (57.8%) (group A). Characteristics of both groups are shown in the table below:

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset of CD (%)</td>
<td>A1/A2/A3</td>
<td>10/70/20</td>
<td>1/72/27</td>
</tr>
<tr>
<td>Location of CD L1/L2/L3</td>
<td>24/40/36</td>
<td>39/29/32</td>
<td>0.025</td>
</tr>
<tr>
<td>L4 (%)</td>
<td>12.5</td>
<td>1.2</td>
<td>0.003</td>
</tr>
<tr>
<td>Phenotype (%) B1/B2/B3</td>
<td>67/20/13</td>
<td>42/25/33</td>
<td>0.0001</td>
</tr>
<tr>
<td>Perineal lesions</td>
<td>32</td>
<td>29</td>
<td>0.3</td>
</tr>
</tbody>
</table>

After a mean follow-up of 23.3 months (6–182 months), immunosuppressives (thiopurines/methotrexate) were more commonly used in patients of group A (66.6%) than those of group B (28.4%) (p = 0.0001) mainly thiopurines (respectively 65% vs. 27%, p = 0.0001). Use of biotherapy was similar in both groups (9.4% in group A vs. 8.8% in group B, p = 0.5). Bowel resection surgery was less frequently performed in patients of group A (27%) than in patients of group B (45%) (p = 0.001).

Conclusion: Corticosteroids are more often used in young CD patients having colonic location, inflammatory phenotype and upper gastrointestinal tract involvement. CS treatment seems to be associated with more common use of immunosuppressives resulting probably in less need for surgery in such patients.
Sicily (Italy) confirms a high prevalence of inflammatory bowel disease (IBD) – A population-based study in the Province of Messina

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Introduction: In the absence of a national registry, the prevalence of IBD in Italy is largely underestimated. From former reports it appears that Sicily represents a region with a high prevalence of these diseases but data date back to 1990. The aim of the present study was to establish prevalence and clinical features of IBD in the province of Messina.

Methods: Databases of General Practitioners (GP) were analyzed by matching ICD-9 codes with medical care cost exemption codes (009), together with prescription of mesalazine (in any form). Disease specific data and demographic data were extracted. Reliability of diagnosis was checked on the base of clinical, endoscopic, and histologic data.

Results: Ninety-nine GPs participated at the study covering a study population of 110,941 people. A total of 429 patients with IBD were identified (Crohn’s disease [CD]: 148, 85 males; ulcerative colitis [UC]: 261, 139 males; inflammatory bowel disease-unclassified [IBDU]:16, 6 males). Mean age at diagnosis was 38 ± 13 years with an average duration of symptoms of 8 months before diagnosis. Eighty-three patients (20%) presented with extraintestinal manifestations (EIM). The most frequent EIM were spondiloarthritides (58; 13%) followed by cutaneous EIM (11; 2.5%). The total prevalence of IBD was 386/105 (UC: 235/105, CD: 133/105, IBDU: 14/105); 57% was on mesalazine monotherapy or in combination with steroids (16%) or immunomodulators (6%). Only 6% of patients did receive biologic therapies. Only 24% of patients followed an integrated therapeutic approach between GP and IBD specialist. The incidence rates, calculated in 5-years periods, showed a constant increase over the last 30 years.

Discussion/Conclusion: Our data confirm a high prevalence of IBD in Sicily in socially active subjects. Data extrapolated from medical care exemption codes do not reflect the real dimension of the problem. Time to diagnosis is still a problem, thus, realization of regional/national programs for early diagnosis are warranted.
Short-term efficacy of the biosimilar CT-P13 in Greek patients with ulcerative colitis: A retrospective single-center study

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Introduction: Biosimilar infliximab CT-P13 is approved for the treatment of ulcerative colitis (UC) in Europe. We aimed to assess the short-term efficacy and safety of CT-P13 in a cohort of UC patients treated in a Greek tertiary Inflammatory Bowel Disease (IBD) referral hospital.

Methods: Retrospective analysis of prospectively acquired data from biologic-naïve and anti-TNF experienced UC patients receiving CT-P13 induction and maintenance therapy according to treatment guidelines from Jan 2016 till Jan 2017. A partial response was defined as a 2-point decrease from baseline in partial Mayo score (pMS) and remission as a total score on the pMS of 2 at week 6 and 14. The type and severity of adverse events (AEs) were also recorded.

Results: Fourteen UC patients were treated with CT-P13 [8 males, age (mean ± SD): 40 ± 13 years]. Disease extent was E2 in 3 patients and E3 in 11 (Montreal classification). Four individuals were ex- or current smokers. Eight patients were biologic-naïve and 6 biologic-experienced (golimumab = 4, adalimumab = 2). Indications for treatment were steroid-refractory UC (n = 6), azathioprine failure (n = 2) and anti-TNF failure (n = 6). At week 6, 8/14 patients were clinical responders and 1/14 in remission. At week 14, 11/14 patients demonstrated clinical response, whilst 2/14 exhibited remission. Interestingly, from the 8 patients who had had previously failure to azathioprine and/or anti-TNF factors, 6 exhibited clinical response at week 14. Patients who relapsed under CT-P13 treatment were additionally treated with corticosteroid (n = 3), azathioprine (n = 2), and surgery (n = 1). In total, seven AEs were recorded but only one was graded as moderate (infusion reaction).

Discussion/Conclusion: CT-P13 appears to be safe and effective in both biologic-naïve and experienced UC patients. Prospective studies in larger cohorts are needed to confirm these results.
BAFF, its homologue APRIL and BAFF-R and infliximab therapy in patients with inflammatory bowel disease

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Introduction: BAFF has been suggested to be associated with inflammatory bowel disease (IBD) by regulating the inflammatory process. It is known that BAFF became induced after B-cell depletion, and in Crohn’s disease improvement is indicated by normalization of the elevated circulating transitional and natural effector B cells in response to infliximab treatment. The aim of this study was to assess BAFF, APRIL, and BAFF-R in biologic-naïve IBD patients and evaluate its levels in response to infliximab treatment.

Methods: Intestinal BAFF, APRIL and BAFF-R expression was analyzed in biopsies obtained from 26 Crohn’s disease patients (14 responders to infliximab therapy and 12 non-responders) and 12 healthy controls. The expression levels, were detected by real-time reverse transcriptase-polymerase chain reaction (RT-PCR). Clinical and endoscopic response to IFX was evaluated by ileocolonoscopy performed at baseline and after 12–20 weeks of therapy with patients classified as either responders or non-responders.

Results: The BAFF, APRIL and BAFF-R expression was significantly increased (1.13 ± 0.48, 3.34 ± 1.24 and 2.16 ± 0.67) in biopsy specimens from IBD patients compared to healthy controls. After Infliximab treatment the BAFF levels were approximately 3-fold lower in infliximab non-responders compared to responders. However, APRIL levels were significantly increased (approximately 1.84-fold) in non-responders compared to responders. Regarding BAFF-R levels were found elevated (approximately 2.53-fold) in non-responders compared to responders.

Discussion/Conclusion: High intestinal levels of BAFF, APRIL and BAFF-R detected suggest that might be involved in the Crohn’s disease pathogenesis. Infliximab appear to affect BAFF levels may be due to anti-apoptotic effect of BAFF since TNF-α enhances BAFF-stimulated cell viability/survival. APRIL and BAFF-R levels seems to be predictive of resistance to infliximab therapy.
Extraintestinal manifestation in inflammatory bowel disease and the relationship between bone mineral density, disease activity and remission maintenance therapy

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Introduction: We determined the prevalence and the types of extraintestinal manifestation in IBD and identified possible relationships between the bone mineral density (BMD) and the localization and activity of disease, the long term therapy with steroids drugs or immunosuppressant treatment in remission maintenance of IBD.

Methods: We investigated 32 patients with IBD: 22 patients with ulcerative colitis (UC) and 10 patients with Crohn’s disease (CD). The therapy for induction of remission consist of mesalazine (Salofalk® 2–3 g/day) associated with Budesonide (3 x 3 mg/day) and all patients follow-up immunosuppressant therapy for maintenance of remission. BMD was measured by dual energy x-ray absorptiometry (DEXA) of the femoral neck and lumber spines. The osteoarticular manifestations were clinical, radiological and biochemical investigated. Also, we identified dermatological manifestation, ophthalamic involvement and hepatobiliary manifestation.

Results: The rheumatic manifestations of UC patients were: pauciarticular peripheral arthropathies (7 cases), polyarticular peripheral arthropathies (3 cases) and only one patient was diagnosed with ankylosing spondylitis. CD patients present polyarticular peripheral arthropathies in 2 cases (20%) and ankylosing spondylitis in one case. We identified 5 cases with cutaneo-mucosal lesions (3 cases with oral apthosis and 2 cases with erythema nodosum), 4 patients with ophtalmologic involvement (uveitis in 2 case and scleritis in 2 cases) and only one cases with primary sclerosing cholangitis. More patients had multiple extraintestinal manifestations (4 cases). The incidence of osteoporosis was significant higher in UC patients (36.36%) comparative with CD patients (20%). We have not found a correlation between BMD and ages, gender or severity of IBD activity, but T-score was correlated with C reactive protein and hypocalcemia. History of long term treatment with corticosteroids (in the last 3 years) was associated with less than minus -2.5 values of T-score. The localization of IBD and values of clinical disease activity index (CDAI in CD and Powell Tuck Index in UC) were not significantly correlated with T-score, but osteoporosis was present more frequent in patients with CDAI > 220 or large extension of disease.

Discussion/Conclusion: The extraintestinal manifestations and especially the osteoarticular and cutaneous-mucosal implications are common in patients with IBD and may occur before and after IBD diagnosis. The low BMD, common in both CD and UC patients, uncorrelated with the localization, duration and severity of disease, remain an important problem in IBD management.
Combined therapy versus monotherapy in the treatment of severe steroid-refractory Crohn’s disease

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Introduction: Aim of this study was to evaluate the efficacy and to monitor the adverse events of the infliximab-azathioprine combined therapy comparative with other therapeutic options in treatment of severe steroid refractory Crohn’s disease (CD).

Methods: We monitored 42 patients with moderate to severe steroid refractory CD. In 11 cases CD was associated with fistulae. The study was performed on three groups: 19 patients (A group) were received combined therapy with oral mesalazine and azathioprine (Salofalk® 3 g/day and azathioprine 2.5 mg/kg/day), 10 patients (B group) were received infliximab (5 mg/kg at 0, 2, 6 weeks) and 13 patients (C group) treated with combined therapy with infliximab and oral azathioprine (2.5 mg/kg/day). We monitored the disease activity and we evaluated the response of the therapy. CDAI scores were determined within one week before infusion and after infusion at weeks 2, 4, 8 and 12.

Results: After two weeks, clinical response (defined as a decrease in CDAI more 75 points) was observed only in B and C groups. In B group, 2 patients (20%) responded after a single intravenous infusion of Infliximab. After second infusions 2 patients had complete response and 4 patients had partial response. Also, in B group two patients developed pneumonia and two patients present the reactivation of the tuberculosis. Comparatively, in the C group five patients (38.47%) had rapid response (complete response after two weeks) and 8 patients (61.54%) present complete remission after 4 weeks. Early relapse, defined as clinically relevant picture of CDAI in a period of < 3 months after achieving remission, was present in two cases (10.53%) in the A group. One patient with fistulizing CD developed delayed hypersensitivity reaction, after second infusion. After 12 weeks complete remission was observed in 11 patients (57.9%) in group A, in 7 cases (70%) in B group and in 11 cases (84.62%) in C group. The relation between endoscopic activity and C-reactive protein positivity was significant. CRP level was correlated with clinical response and decreasing of CDAI score.

Discussion/Conclusion: Combined therapy with infliximab and azathioprine remain the most effectiveness option in patients with severe steroid refractory CD. In induction of remission of the severe CDAI, the combination therapy with infliximab and azathioprine is more effective than either mono-therapy alone. The main side effects were allergic reactions and tuberculosis reactivation.
Clinical course of Crohn’s disease followed-up in a period of six years in one reference center

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The late diagnosis is related to the development of complications and poor prognosis for Crohn’s disease (CD).

The aim of our study is to perform a retrospective analysis of the clinical course of CD in patients hospitalized in one reference clinical center for a period of 6 years.

140 patients were divided into two groups: group I: 108 (77.10%) diagnosed within one year of the onset of complaints and group II: 29 (20.70%) who were diagnosed 24 months after of the onset of complaints. There was a follow-up of the clinical course of CD, the occurrences of extraintestinal manifestations (EIM), intestinal complications (IC) and the therapy performed.

There is no significant difference between the two groups in terms of CD activity, the extent, the received treatment, the IC and the surgical interventions. A significant difference was found with respect to the average number of hospitalizations (4/group I and 6/group II, p < 0.05), the EIM frequency (group II prevalence: 95.8%), the course of the disease and perianal disease.

In group I 35% of patients with colon localization on debut progressed in the first year to ileocolonic. In the first year, perianal disease increased to 21% and in the 6th year it reached 70%. The penetrating and stricturing form of the disease reached 21% in the first year, while in the 6th year it was already 60.7%.

In group II there was a constant trend of increase of the perianal disease – year 1: 9.1%; year 3: 63.40% and year 6: 61.9%.

Regardless of the equally applied treatment in late-diagnosed patients, an increased number of hospitalizations, EIM, increasing progression in the occurrence of perianal disease, penetrating and stricturing form of CD are being observed.
The transcription factor NFATc3 promotes intestinal inflammation by suppression of regulatory T cells

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Introduction: The transcription factor NFATc3 (Nuclear factor of activated T cells) belongs to a transcription factor family of five members. NFATc3 plays an important role in the activation and function of T cells regulating cytokine expression and cell proliferation. High numbers of NFATc3+ cells in the lamina propria of patients suffering from inflammatory bowel disease (IBD) point out the regulatory role of this transcription factor in mucosal inflammation and led us to investigate its function in colitis.

Methods: NFATc3 KO mice were treated with oxazolone to induce colitis. Additionally, transfercolitis studies have been performed. Miniendoscopic analysis has been done to monitor the manifestation of colonic inflammation. The inflamed colon was used for isolation of LPMCs and histological sections were taken out for immunofluorescent staining.

Results: Deficiency of NFATc3 in the oxazolone-induced colitis model suppressed induction of intestinal inflammation. Staining for Caspase3 showed less proapoptotic cells in the colon of NFATc3 KO mice whereas apoptotic cells were significantly increased. Additionally, we found a higher number of FoxP3+ T cells in the colon of NFATc3 KO mice suggesting that NFATc3 controls regulatory T cells. As Tregs have been shown to prevent and cure intestinal inflammation caused by the adoptive transfer of naïve T cells in immunodeficient RAG1 knockout mice, we next analyzed the relation between Tregs and NFATc3 in this colitis model. Mice receiving NFATc3-deficient naïve T cells had a later onset of inflammation than mice reconstituted with wild-type T cells. Moreover, the adoptive transfer of NFATc3-deficient T cells was associated with an increased number of CD3+ FoxP3-expressing Tregs.

Conclusion: In summary, the transcription factor NFATc3 crucially promotes intestinal inflammation by affecting FoxP3 expression and therefore serves as a potential target for therapy in IBD.
Hepatic manifestations associated to inflammatory bowel diseases

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Introduction: Inflammatory bowel diseases are associated with various hepatobiliary disorders, reported both in Crohn’s disease and ulcerative colitis. They may occur at any moment in the natural course of the disease. The prevalence of liver dysfunction rises from 3% to 50% accordingly to definitions used in different studies. Fatty liver is considered as the most common hepatobiliary complication in inflammatory bowel diseases while primary sclerosing cholangitis is the most specific one. The aim of our study was to determine the prevalence of liver pathological abnormalities (LBA) in IBD patients, and to identify the different etiologies responsible for these abnormalities.

Material and methods: We conducted a retrospective study of all patients followed for IBD between January 2014 and June 2016. LBA were defined by an increase in alkaline phosphatase, gamma-glutamyl transferase or transaminase activity greater than 2-folds.

Results: Our study included 101 patients (64 women, 37 men) with IBD: 54 patients with Crohn’s disease (CD) and 47 patients with ulcerative colitis (UC). The average age was 37.7 years (18–81 years). The localization of CD was ileal in 39%, colic in 26%, and ileocolic in 35% of patients. The localization of the UC was rectal in 21.3%, left in 44.7% and extensive in 34% of the cases. Twenty patients (20%) were in remission. 23% had a complicated disease.

The abnormalities of liver tests were found in 12 patients (CD n = 6, UC n = 6): cholestasis (n = 6), cytolysis (n = 3) and mixed (n = 3). LBA were transient in 3 cases. In the remaining patients, the different etiologies were acute hepatitis B in 3 cases, primary sclerosing cholangitis in 2 cases, hepatic steatosis, autoimmune hepatitis, regenerative nodular hyperplasia secondary to azathioprine and drug toxicity to sulfasalazine in one case each. There was no association between these abnormalities and the age, the gender, the extent and the activity of the disease.

Conclusion: In our series, 12% of patients had LBA. These abnormalities were transient in the quarter of patients. Acute hepatitis B, which is independent of IBD, was the most common etiology.
Colectomy rate in acute severe colitis responding to rescue medical therapy

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Introduction: Acute severe colitis (ASC) is a serious and potentially life-threatening complication of chronic inflammatory bowel disease (IBD). Due to advances in medical therapy, the mortality rate has dropped to less than 2% over the past 30 years, but the colectomy rate reaches 30%. The purpose of this work is to evaluate short-and long-term colectomy rates in patients with ASC who responded to intensive medical treatment in the era of biological treatment.

Materials and methods: We have included all patients admitted in our department of Gastroenterology for ASC, according to Truelove and Witts criteria, and who responded to intensive medical treatment between January 2006 and December 2016. The score used to assess the severity was Truelove and Witts score. Epidemiological and clinical data were analyzed.

Results: Eighty-six patients who presented with ASC were registered. The median follow-up was 30 months [6–60 months]. Twenty-eight (40%) were males and forty-two (60%) were females. The average age was 36 years. Twenty-four patients (34.3%) had Crohn’s disease and forty-six (65.7%) had ulcerative colitis. Seventy cases (81.4%) responded to intensive medical treatment. Response to intravenous corticosteroids was observed in 39 cases (55.7%). In the non-responders group; 29 patients were treated with cyclosporine and only two patients with anti-TNF-α. As a maintenance therapy, thiopurines were prescribed in 55 patients (78.6%), anti-TNF-α in 9 cases (12.9%) and six patients received 5-aminosalicylic acid (5-ASA). At the end of the follow-up, clinical remission was maintained in 27 cases (38.5%). Eighteen patients presented recurrent episodes of ASC (at least one), requiring colectomy in 10 cases (14%).

Conclusion: Surgery continues to play an important role in acute severe colitis. Infliximab can avoid urgent colectomy in steroid-refractory patients but the risk of elective colectomy, in the long-term, is still relatively high (14% in our study).
Is it possible to prevent clinical recurrence of Crohn’s disease after surgical resection?

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Introduction: The natural history of Crohn’s disease (CD) is characterized by recurrent episodes of flares followed by complications leading to surgery. As surgery in CD is not curative, clinical recurrence after surgical resection is a significant problem, with reported rates up to 55% at 5 years. We aimed to determine clinical and endoscopic postoperative recurrence rates in CD and to assess the factors influencing this recurrence.

Methods: We conducted a retrospective study, including all patients with Crohn’s disease, followed in our department, who underwent ileocecal resection between June 2011 and June 2016.

Results: From a total of 240 Crohn’s disease patients, 86 (35.8%) underwent ileocecal resection, with a mean follow up of 5.8 years (2–13 years). There were 26 women and 60 men with an average age of onset of 32.95 years (16–69 years). All patients were regularly monitored and 68 patients (79.1%) had postoperative medical treatment, after an average period of 33 days (4–116 days) of the surgery. 19 patients (22.1%) received 5-ASA therapy. Azathioprine was prescribed in 47 cases (54.7%), and anti-TNF in 2 patients (2.3%). 18 patients (20.9%) received no treatment, with a favorable outcome.

During follow-up, cumulative clinical recurrence rates were 9.3% at 1 year and 20.9% at 5 years. In multivariate analysis, the absence of postoperative smoking cessation, a period of time between diagnostics and surgery < 9.5 month and resection margins < 2 cm, were independent factor for clinical postoperative recurrence.

Conclusion: Postoperative recurrence rates in Tunisian patients with CD are high. Based on this study, special attention should be paid in the preoperative phase to patients with smoking habits. An early start of appropriate medical prophylaxis should be taken into consideration for preventing postoperative recurrence in CD.
Terminal ileitis is not always Crohn’s disease: Correlation between endoscopic and histological findings

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Introduction: Ileitis, inflammation of the ileum, is commonly related to Crohn’s disease (CD). However, it may be caused by a wide variety of other diseases including non-steroidal anti-inflammatory drug (NSAID) intake, lymphoid hyperplasia, intestinal infections, eosinophilic enteritis, intestinal tuberculosis (ITB), and lymphoma. The aim of this study was to assess the correlation between endoscopic and histological features in diagnosis of terminal ileitis (TI).

Materials and methods: Retrospective study including all patients diagnosed with TI at imaging (abdominal computed tomography scan or ultrasound) from January 2006 to December 2016 in our Department of Gastroentrology. All patients had ileocolonoscopy with ileocolic biopsy. Correlation between visual endoscopic finding and histology was assessed.

Results: Eighty-nine patients were included, 52 were males and 37 were females (sex-ratio M/F = 1.4). The average age was 38 years [16–79 years]. Right iliac fossa pain was the cardinal symptom (86.5%). Biologic inflammatory syndrome and anemia were found in 97.7% and 49.4%, of patients respectively. Based on the imaging, thickened terminal ileum wall associated to thickened cecal wall was observed in 65% of cases. The endoscopic examination revealed: ileal erythema and ulcers in 44 cases (49.4%), ileocecal valve stenosis in 23 patients (24.7%), cobblestone appearance in the terminal ileum in 12 patients (12.3%), deformed and retracted cecum in 8 cases (9%) and polypoid lesion in the cecum only in two patients. Histopathological findings concluded to CD in 56 cases (63%), ITB in 22 cases (24.7%), infectious ileitis in 10 cases (11.2%) and only one case of adenocarcinoma. The concordance between endoscopic appearance and histological findings in TI diseases was found in 74.5% of cases. The positive predictive value and negative predictive value were 77% and 68% respectively for the diagnosis of CD vs. 58% and 52% respectively for diagnosis of ITB.

Conclusion: The inflammation of the ileum may occur due to leading to difficulties in the diagnosis. Complete colonoscopy with ileoscopy and terminal ileum biopsies are of key importance in such cases.
Adherence to medical treatment in patients with inflammatory bowel disease

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Introduction: Non-adherence to medical treatment is a real problem in patients with inflammatory bowel disease (IBD) and has a negative impact on disease outcome. The aim of our study was to assess the frequency of non-adherence to treatment among patients with IBD and evaluate which factors could be related.

Methods: A monocentric retrospective study including patients with IBD between and January 2007 and March 2017 was conducted. Information about demography, type of IBD, duration of the disease, specific therapy for IBD and adherence to treatment were analyzed. Categorical variables were compared with Fisher's exact test. A p value < 0.05 was considered statistically significant.

Results: A total of 175 patients were included: 87 ulcerative colitis (UC), 88 Crohn’s disease (CD). The mean age was 40.1 (19–65 years) and the sex-ratio was 0.96 (M/F = 86/89). Medical treatment was based on salazopyrin (n = 53, 30.2%), aminosalicylates (n = 35, 20%), azathioprine (n = 35, 20%) and biotherapy (n = 52, 29.7%). Non-adherence to medical therapy was observed in 27.4% of patients (n = 48): 28.4% (n = 25) in CD and 26.4% (n = 23) in UC with no significant difference (p = 0.92). Two thirds (66.6%, n = 32) of non-adherent patients were females (p = 0.04). Non-adherence to therapy was observed in patients aged ≤ 40 years in 70.8% of cases. It was statistically associated with young age (p = 0.01) and topical aminosalicylates (p = 0.03).

Conclusion: Non-adherence to therapy is one of the main causes of treatment failure in patients with IBD, especially in young female under topical aminosalicylates. Therefore, gastroenterologists have a major role in promoting education.
Predictive factors of a clinical severe course of Crohn’s disease: A monocentric study

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Introduction: Crohn’s disease (CD) is a heterogeneous entity with an unpredictable course. Categorizing patients into high and low risk of severe course of CD would enable clinicians to adapt treatment strategy (top-down or step-up) for a better outcome. The aim of this study was to assess the predictive factors of severe disease at presentation.

Methods: A retrospective study, including all patients diagnosed with CD in our Gastroenterology Department between January 2007 and June 2017. A severe disease was defined by: three or more moderate to severe flares per year necessitating oral or intravenous corticosteroid therapy, need for surgery for a complication after diagnosis (ileocecal resection for localized non-complicated disease was excluded) and presence of perianal disease at diagnosis.

Results: One hundred and twelve patients with CD were enrolled. Mean age of our patients was 42 years old (17–52). Fifty-one patients (45%) had non-stricturing non-penetrating disease, 31 (28%) had stricturing disease, 20 (18%) patients had fistulizing disease and 10 (9%) had stricturing and penetrating disease. Eighty-five patients (76%) presented with no severe disease and 27 (24%) had a severe course of CD. Patients with severe course of the disease had younger age at first diagnosis (p = 0.02). In univariate analysis, independent predictive risk factors for a severe course of CD were: complicated disease at diagnosis (stricturing or fistulizing) (p = 0.01), active smoking (p = 0.012), disease extent at diagnosis > 50 cm (p = 0.04) and severe flare inaugurating the disease (p = 0.04). Nineteen patients (70%) with severe disease had surgery after a mean follow-up of 22.4 months and they all had an age < 30 years old with at least one of the four independent risk factors of severe disease.

Conclusion: Our study confirms that the course of CD might be predicted. Thus, treatment strategy can be adapted to the severity of the disease. Independent risk factors of an aggressive disease at diagnosis were: complicated disease at diagnosis, active smoking, disease extent at diagnosis > 50 cm and severe flare inaugurating the disease.
Prevalence and risk factors for non-alcoholic fatty liver disease in Crohn’s disease

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Introduction: Non-alcoholic fatty liver disease (NAFLD) is responsible for up to 40% of hepatic alterations diagnosed in inflammatory bowel diseases (IBD). We aimed to evaluate the prevalence and risk factors for NAFLD in patients with Crohn’s disease (CD).

Methods: This is a comparative retrospective study of 86 cases of CD (42 men and 44 women, sex-ratio of 0.95) with a mean age of 42.47 years (18–88 years). We used as a control group, 50 patients consulting for an intestinal functional disorder (29 women and 21 men) whose average age was 42 years. In both groups, hepatic steatosis was sought by abdominal ultrasound as well as calculation of the HSI score (Hepatic Steatosis Index). Patients with chronic liver disease whose etiology is different from NAFLD, or daily alcohol consumption greater than 20 g/day for women and 30 g/day for men were excluded.

Results: We collected 86 patients followed for CD, the median duration of follow-up was 54 months; 44.2% (36) of patients were smokers, 12% had a family history of CD, 25.6% (22) were overweight with an average BMI of 22.45 kg/m² (15–30.47kg/m²), 44.2% (38) had ileal disease, 14% (12) a colonic disease and 38.6% (33) ileocolic localization. CD was inflammatory in 38.4% of cases, stenotic in 34.9% of cases, fistulizing in 7% of cases and both stenosing and fistulizing in 17.4% of cases. NAFLD based on abdominal ultrasound data and HSI score calculation was observed in 21 (24.7%) patients with CD versus 8 cases in the control group (16%) (p = 0.04). The prevalence of diabetes and overweight was comparable between the two groups. Among patients with CD, those with NAFLD were more likely to be women (14 women versus 7 men) with an average age greater than 45 years. BMI was higher in patients with hepatic steatosis. Factors associated with the presence of hepatic steatosis during CD were overweight (BMI > 25 kg/m²) (p = 0.026), smoking (p = 0.006), and corticosteroid therapy (p = 0.032). There was no significant association between history of surgery and the concept of fatty liver.

Conclusion: Hepatic steatosis is the most common hepatobiliary event during CD. Its screening should be systematic in order to introduce preventive measures avoiding its progression towards fibrosis.
Predictors of negative C-reactive protein in active Crohn’s disease

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Introduction: Due to its wide accessibility, fast availability and proven correlation with disease activity, C-reactive protein (CRP) remains an essential tool in the management of Crohn’s disease (CD). However, the correlation of CRP with CD activity is not perfect. It is therefore of great importance to identify the group of patients with active disease and negative CRP.

Methods: We performed a retrospective case-control study, with inclusion of CD patients with proven active disease as demonstrated by endoscopic and/or radiologic examinations. The CRP’s cut-off value used to separate patients in two groups (cases and controls) was 1 mg/dl. Demographic, phenotypic and clinical characteristics were collected. Statistical analysis was performed with SPSS 20.0.

Results: We included 77 patients (38 men, 39 women) with a mean age of 40.21 years (18–88 years) and median duration of disease of 58 months (24–310 months). Twenty seven (35%) of these patients had negative CRP. There weren’t statistically significant differences in CD activity between cases and controls, as evaluated by Best index. Upon exploratory analysis, there were statistically significant differences regarding gender as 47.36% of men vs. 23.07% of women had a negative CRP (p = 0.04). Even though location was not a significant predictor, all patients with a negative CRP had ileal involvement. On multivariate analysis, gender remained a significant predictor (p = 0.02). There was also a tendency to a higher probability of negative CRP in isolated ileal disease (p = 0.058). There were no differences in age, behaviour, disease duration, previous abdominal surgery or smoking status.

Conclusion: Despite being a useful tool, CRP has some limitations and it can be negative in cases of active disease. In patients with the identified characteristics: men with ileal disease, other methods should be used to exclude with confidence the presence of inflammatory activity.
Extraintestinal manifestations of inflammatory bowel disease: Prevalence and risk factors

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Introduction: Extraintestinal manifestations (EIM) in inflammatory bowel disease (IBD) are frequent and may occur before or after IBD diagnosis. EIM may affect the quality of life for patients with IBD and require specific treatment depending on the affected organ(s). The aim of the study is to determine the frequency of EIM in in Crohn’s disease (CD) and ulcerative colitis (UC), to identify the factors associated with the development of these manifestations, especially the role of smoking.

Methods: We performed a monocentric retrospective study including patients with IBD between January 2007 and March 2017. The frequencies of arthritis/arthralgia, primary sclerosing cholangitis (PSC), ocular and cutaneous EIMs were determined.

Results: A total of 175 patients were included (87 UC, 88 CD). The mean age was 40.1 (19–65 years) and the sex-ratio 0.96 (M/F = 86/89). Smoking was noted in 37.1% of patients; 42.3% of patients (n = 74) had ≥ 1 EIM: arthritis/arthralgia (n = 33, 18.8%), hepatobiliary manifestations (n = 26, 14.8%), ocular (n = 6, 3.4%) and cutaneous (n = 6, 3.4%) manifestations. The prevalence of EIM was 41.3% in UC and 43.1% in CD (p = 0.9). Active smoking increased the risk of EIM in CD patients (p = 0.009), but notably not of UC patients (p = 0.84). In addition, young age at first diagnosis as well as active disease were identified as risk factors for the development of an EIM in CD patients (p = 0.01, p = 0.032 respectively). No factor which increased the risk of development of an EIM was identified in UC patients.

Conclusion: In our study, we found a high prevalence of EIM in both UC and CD. In patients with CD, smoking, young age and active disease were risk factors for the development of an EIM. No risk factors were indentified for UC.
Results from a retrospective analysis of colonoscopies for inflammatory bowel disease and colorectal polyposis in a Tunisian center care

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Introduction: Colorectal polyposis is a major risk factor for colorectal cancer, especially among patients with inflammatory bowel diseases (IBD). This study evaluated the situation of IBD and colorectal polyposis at endoscopy unity in in a Tunisian center and compared prevalence and characteristics with general population.

Methods: Eight hundred and fifty patients underwent colonoscopy over a period of 12 months by qualified endoscopists. One hundred and two patients were excluded from the study because of familial history of colorectal neoplasia and personal history of familial polyposis. We randomized number, size, localization and endoscopic nature of polyposis.

Results: Out of 748 individuals included, 62 cases of IBD (8.2%) were identified. A total of 14 cases of colorectal polyposis (22.6%) were identified versus 182 cases in general population (26.5%) without statistic differences. There was a slight male predominance in both groups without any statistical significance. Both means of polyp number and size were statistically different with (2.23 ± 2.7 vs. 3.29 ± 2.8; p = 0.01 and 3.83 mm ± 5.8 vs. 6.86 ± 4.4; p = 0,000) respectively. Statistical significance was reported in age of polyp’s detection between both groups with a mean age of 37.9 ± 9.7 years and 54.4 ± 6.4 years in IBD and general population group, respectively.

Conclusion: Our study showed that there are no differences in prevalence between IBD groups and general population. However, number, size and age of detection of polyps were different between the two groups. Prospective controlled studies are necessary to confirm these results.
Prevalence of axial spondyloarthritis associated with inflammatory bowel diseases in a Tunisian cohort

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Introduction: Inflammatory bowel disease (IBD) can be accompanied by a number of extraintestinal manifestations (EIM) in multiple organ systems. Rheumatologic disorders, described in 25–30% of patients, represent the most common EIM of IBD before skin, eye or hepatobiliary disorders. Axial spondyloarthritis is one of the main rheumatological manifestations reported but its frequency is highly variable. The aim of this study is to determine the prevalence, clinical and radiological features of axial spondyloarthritis in patients with IBD and to characterize differences between patients with and without axial spondyloarthritis.

Methods: Patients included in this cross-sectional study were recruited from the Gastroenterology Department, University of Tunisia, over six months. Sixty-four patients with IBD were questioned and examined for axial spondyloarthritis symptoms. Standard pelvic X-rays were performed for all and CT scans and MRI were done for some patients.

Results: Forty-two men (65.6%) and twenty two women (34.4%) with a mean age of 47 ± 22 years were included. Thirty-two patients (50%) had Crohn's disease, thirty-one had ulcerative colitis and one patient has undifferentiated colitis. The disease was confined to the colon among a half of patients with ulcerative colitis. The disease was confined to the colon among a half of patients with ulcerative colitis. Regarding Crohn's disease, all lesions were confined to the ileum and the colon. The mean IBD duration was 6.18 ± 7.2 years. The occurrence of axial spondyloarthritis was 26.5% (The disease was symptomatic in 16 cases). The bowel disease preceded rheumatic manifestations in all cases. Nine patients (14.1%) had isolated sacroiliitis. The patients with and without axial spondyloarthritis had similar sociodemographic, anthropometric characteristics, comorbidities and bowel disease particularities except a higher percentage of corticosteroids use (p = 0.013).

Discussion/Conclusion: More than a quarter of the IBD patients included in this cohort had axial spondyloarthropathy. This high frequency confirms the need for early diagnosis through thorough clinical examination and standard pelvic radiographs.
Anemia in inflammatory bowel disease

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Introduction: Anemia is a frequent pathogenically complex entity associated with inflammatory bowel disease (IBD) which is commonly neglected by clinicians. About one third of IBD patients have hemoglobin levels below 12 g/dl. The aim of this study was to determine the prevalence of anemia in patients treated for IBD, to study the mechanism and factors associated with anemia and its response to treatment.

Methods: Retrospective descriptive study including all IBD patients treated in our Gastroenterology Department from January 2007 to June 2017. Anemia was defined by hemoglobin level < 12 g/dl in women and hemoglobin level < 13 g/dl in men.

Results: One hundred and ninety two IBD patients with a mean age of 39 years old (16–52) were enrolled. One hundred and twelve (58%) had Crohn’s disease (CD) and 80 (42%) had ulcerative colitis (UC). The localization of CD was: ileal in 65 patients (58%), ileocolonic in 16 patients (14%), colonic in 20 patients (18%) and 11 (10%) had upper gastrointestinal CD. UC was distal in 12 patients (15%), left-sided in 30 patients (37.5%) and 38 patients (47.5%) had pancolitis. At the time of diagnosis of IBD, anemia was found in 49 patients with CD (43%) and 30 patients with UC (37.5%). For patients with CD, the mechanisms of anemia were distributed as follows: iron deficiency (55%), inflammation (25%), mixed (10%), vitamin B12 and/or folate deficiency (5%) and drug toxicity (5%). For UC patients, anemia was due to iron deficiency in 60% of cases, inflammatory in 25% of patients, mixed in 10% of patients and drug-induced in 5% of cases.

In CD patients, anemia was significantly more common in young patients (< 40 years) (p = 0.012), with penetrating disease (p = 0.02) or ileal resection > 30 cm (p = 0.03). In UC, anemia was significantly more frequent in women (p = 0.02).

Conclusion: The etiology of anemia in IBD is multifactorial. Iron deficiency was the main cause in our study for both UC and CD. It is important to determine the mechanism of anemia in order to propose the appropriate treatment.
Short-term and long-term outcomes of endoscopic dilatation for Crohn’s disease strictures

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Background: Stricturing represents a common complication in Crohn’s disease. Endoscopic balloon dilation is used to treat ileocolic anastomotic and de novo stricture attributed to recurrent Crohn’s disease.

Objective: The purpose of this work was to investigate outcomes after dilation of ileocolic anastomotic and de novo stricture in patients with Crohn’s disease regarding procedural safety.

Design: This was a retrospective study based on chart review of an electronic medical chart system using OPS (5-489.b, 5-469.b3, 5-469.h3, 5-469.j3, 5-489.2, 5-499.0) and ICD-codes (ICD K50.0-K50.9) including 143 dilatations.

Settings: The study was conducted at two large tertiary care centers (Bogenhausen Academic Teaching Hospital, Klinik und Poliklinik für Innere Medizin II, Technical University of Munich).

Patients: All of the eligible patients with ileocolic anastomotic and de novo stricture attributed to recurrent Crohn's disease treated with endoscopic dilation (between January 2008 and November 2017 were evaluated. Patients with multiple hospitalizations were counted only once, and their earliest hospitalization data was chosen as the index hospitalization.

Main outcome measures: The main short term outcome measures were the need for subsequent surgery and complications (bleeding, infection) because of intervention-related complications while the main long-term outcome measures were defined as repeated dilatation and surgery in the further course of the disease.

Results: A total of 58 patients with Crohn's disease (51.7% women; 48.3% men; age 43.4 yrs. (mean), range 19–79 yrs.) underwent endoscopic dilations using mainly through-the-scope balloons with diameters to 20 mm on inflation (in 90%). 30 dilatations were performed in anastomotic strictures, 30 in de novo ileocolonic strictures (Fig. 1). During a mean follow-up of 4 weeks after endoscopic intervention (short-term follow-up), 4 patients (6.9%) developed postprocedural complications (bleeding, infection; perforation requiring subsequent operation in one patient after dilation of colonic de novo stricture). In all other patients, endoscopic dilatation was safe with no side effects. In 23 patients, data evaluating long-term follow up could be obtained (mean 54 months; range 4–118 months). Of those, operation was performed in 56.5% while repeated dilatation was necessary in 69.6%.
Limitations: The study was limited by its retrospective design.

Conclusions: Endoscopic dilation is a valid option for ileocolonic anastomotic and colonic strictures in Crohn’s disease. However, the cumulative rate of surgery and necessity of repeated dilatation was high.

Fig. 1: All patients (Bogenhausen Academic Teaching Hospital and Klinik und Poliklinik für Innere Medizin II, Technical University of Munich, Munich, Germany)
Correlation between endoscopic lesions and cyclosporine response in steroid-refractory ulcerative colitis

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Introduction: Cyclosporine (CSA) is an effective rescue therapy in steroid-refractory ulcerative colitis (UC) and may avoid immediate colectomy. Approximately 20% of patients fail to respond to intravenous CSA. The aim of this study was to determine the role of endoscopic findings in predicting of response to CSA in steroid-refractory UC.

Methods: We conducted a retrospective study of all patients admitted for acute severe corticosteroid refractory UC and treated with intravenous CSA between January 2007 and December 2016. UC severity was determined according to the modified clinical index by Truelove-Witts or presence of severe colonic lesions (SCL). The patients were divided into two groups by the presence or the absence of SCL. CSA response was compared between the two groups. A probability (p) value of less than 0.05 was considered statistically significant.

Results: Our study included 57 cases. Twenty-two were males and thirty-five were females with a mean age of 33 years (14–73 years). Median follow-up was 34.66 months (6 months–120 months). Thirty-three patients (57, 9%) were known to have UC, while 24 patients (42, 1%) were experiencing the first attack of UC. All patients received intravenous CSA therapy at an initial dose of 2 mg/kg/day. Initial response to CSA was observed in 41 cases (72%). However, 16 patients failed to respond and required colectomy. Thirty-three patients (58%) had SCL: 21 responders (63, 63%) and 12 non-responders (36, 36%) to CSA. Among 24 patients without SCL, 18 patients (75%) were responders, while CSA failure was observed in a quarter of our cases. The difference of CSA response between the groups was statistically significant (p = 0.036).

Conclusion: Our study shows that presence of SCL is correlated with CSA failure in steroid-refractory UC. In these cases other therapeutic alternatives have to be considered. However, a prospective study with large number of patients is necessary to confirm our findings and research others predictors.
Predictive factors of colectomy in patients with steroid-refractory acute severe ulcerative colitis

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Introduction: Approximately 15–20% of patients with ulcerative colitis (UC) will experience a severe attack. Intensive intravenous treatment with corticosteroids is successful in these acute attacks, however, at least 30% of these patients fail to make an adequate response to intravenous corticosteroids and face surgical treatment. The aim of the study is to determine the predictive factors of colectomy in patients with steroid-refractory acute severe colitis.

Methods: We conducted a retrospective study from January 2007 to December 2016. All cases satisfied the Truelove and Witts’ criteria for acute severe UC were included. Patients with Crohn’s disease or inconclusive histology, or presented with complications (bowel perforation, toxic megacolon) were excluded from the study. All statistical analyses were performed using SPSS 21.0. A probability (p) value of less than 0.05 was considered statistically significant.

Results: Our study included 57 cases. Twenty-two were males and thirty-five were females with a mean age of 33 years (14–73 years). Median follow-up was 34, 66 months (6 months–120 months). Thirty-three patients (57, 9%) were known to have UC, while 24 patients (42, 1%) were experiencing the first attack of UC. Colectomy rate was 45, 61% (26 patients). Of these, 70% (18 of 26 patients) underwent surgery as a consequence of failed cyclosporine therapy while 30% of patients required colectomy, following a new severe attack of UC during follow-up, with median time to colectomy of 9.6 months (2–22 months). Predictors of colectomy in the multivariate analysis were previous severe UC (p = 0.039), previous treatment with thiopurines (p = 0.043) and serum albumin < 30 g/l (p = 0.026).

Conclusion: Our study suggested three predictors of colectomy in patient with acute severe UC refractory to corticosteroids: previous severe UC, maintenance therapy with thiopurines and hypoalbuminemia (< 30 g/l). The Knowledge of these factors may facilitate earlier making decision in the treatment of severe refractory UC.
Cyclosporine in acute severe steroid-refractory ulcerative colitis: Short- and long-term outcomes

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Introduction: Intravenous cyclosporine (CSA) therapy followed by oral cyclosporine therapy has been shown to be effective in steroid-refractory ulcerative colitis (UC) reducing the need for urgent colectomy. However, the long-term benefits of cyclosporine remain questionable. The aim of this study is to evaluate the short and long-term efficacy of CSA in patients with acute severe UC refractory to corticosteroids.

Methods: We conducted a retrospective study including all patients admitted in our department for acute severe UC refractory to corticosteroids, treated with intravenous CSA and then oral CSA between January 2007 and December 2016.

Results: A total of 76 patients with severe steroid-refractory ulcerative colitis were treated with intravenous CSA (2 mg/kg/day), for a mean period of 7.8 days (7–10 days). Forty-six patients (68.7%) responded to intravenous CSA and avoided colectomy during hospitalization. Twenty-one (45, 65%) were males and twenty-five (54, 34%) were females with a mean age of 32, 78 years (14–61) years). Subsequently the patients were started on oral cyclosporine (4 mg/kg/day) and followed for a mean of 37 months (6 months–10 years). All patients received azathioprine (AZA) for maintaining remission after response to CSA therapy. During follow-up, twenty-two patients (47.8%) treated with AZA developed new attacks with a mean time of 15.6 months (2–48 months]. Anti-TNF therapy was prescribed to five relapsing patients, while nine patients (19, 56%) required colectomy for new severe attack of UC. At the end of the follow-up, clinical-remission was maintained in 24 cases (52, 2%).

Conclusion: Our study shows that Cyclosporine therapy is an effective treatment for acute severe steroid-refractory UC in the short term. Although long remission was maintained in more than half of the patients, colectomy rate after response to CSA remain relatively high in the longer term (20% in our study).
Mitochondrial DNA is a pro-inflammatory damage-associated molecular pattern (DAMP) released during active IBD

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Introduction: Due to common evolutionary origins, mitochondrial DNA (mtDNA) shares many similarities with immunogenic bacterial DNA. MtDNA is recognised as a damage-associated molecular pattern (DAMP) that is released during uncontrolled cell death and/or during cellular stress. Given the significant tissue injury burden typically observed in active inflammatory bowel disease (IBD), we hypothesised that such pathogenic release is present where mtDNA serves as a novel pro-inflammatory factor.

Methods: Between 2014–2015 we collected plasma separated within 2 hours of sampling from 97 prospectively recruited IBD patients (67 ulcerative colitis [UC] and 30 Crohn’s disease [CD]), and 40 non-IBD controls. We measured circulating mtDNA using qPCR (amplifying mitochondria COXIII/ND2 genes). In parallel, we also studied plasma mtDNA levels during induction of mouse colitis in vivo using the dextran sulfate-sodium (DSS) model. In human studies, we used mass spectometry approach to detect and measure circulating plasma mitochondrial formylated peptide, a second mitochondrial DAMP. Furthermore, we examined for mitochondrial damage using electron microscopy (EM) and TLR9 expression, the target for mtDNA respectively, in human intestinal IBD mucosa.

Results: Plasma mtDNA levels were increased in UC and CD (both p < 0.0001) compared to non-IBD controls. These levels were significantly correlated to blood (CRP, albumin, white cell count), clinical and endoscopic markers of severity; and disease activity. In active UC, we identified 5 mitochondrial formylated peptides (the most abundant, fMYMYALF with known chemoattractant function) in plasma. We observed mitochondrial damage in inflamed UC mucosa and significantly higher fecal MtDNA levels (vs. non-IBD controls [p < 0.0001]), which support gut mucosal mitochondrial DAMP release as primary source. In parallel, plasma mtDNA levels increased during induction of acute DSS colitis and were associated with more severe colitis (p < 0.05). In active IBD, TLR9+ lamina propria inflammatory cells were significantly higher in UC and CD compared to controls (p < 0.05).

Discussion/Conclusion: We present the first evidence to show that mtDNA is released during active IBD. MtDNA is a potential mechanistic biomarker and our data point to mtDNA-TLR9 as a therapeutic target in IBD.
Validation of the CUCQ questionnaire with stoma extension in patients with acute ulcerative colitis in the CONSTRUCT trial

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Introduction: There are no validated quality of life tools that are suitable for assessing patient quality of life in acute severe ulcerative colitis. The purpose of this work was to develop and concurrently validate a patient reported outcome measure suitable for such patients, within the context of the CONSTRUCT trial.

Methods: We developed and piloted a new questionnaire suitable for patients with severe ulcerative colitis. We developed the questionnaires in three stages: item generation by reviewing the literature of previously validated questionnaires and by consultation with patients and experts; initial development of the questionnaires in the CONSTRUCT cohort sample; and definitive validation of the questionnaires in the CONSTRUCT trial sample. We undertook psychometric analysis to examine the underlying dimensions of the scale, internal consistency and validity.

Results: We developed the Crohn’s and ulcerative colitis questionnaire (CUCQ) for patients who had not undergone surgery; and the CUCQ with stoma extension (CUCQ+) for surgery patients. We had 1240 patients in our development sample and 270 patients in our validation sample. The internal consistency of the CUCQ was excellent (Cronbach’s alpha > 0.8). The data did not exhibit any floor or ceiling effects. Principal components analysis indicated that there were 4 main factors. The CUCQ scores achieved significant correlations with the two generic health-related quality of life scales demonstrating good construct validity.

Discussion/Conclusion: The CUCQ is a useful tool for assessing quality of life in patients with acute severe colitis.
CRP/albumin ratio: Predictive factor of the response to corticosteroids in acute severe colitis

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Introduction: Intravenous corticosteroid therapy is the first-line treatment for acute severe colitis (ASC). However, corticosteroids’ failure occurs in one third of patients. Identifying simple clinical and biological factors correlated with the response to corticosteroid therapy predicts refractory forms and indicates early second-line medical treatment (infliximab or cyclosporin) or colectomy.

Methods: A retrospective study, including patients with ASC occurring on ulcerative colitis (UC) from January 2010 to December 2016. C reactive protein (CRP) level, albumin level and CRP/albumin ratio were noted at admission and at day 3 of evolution. The predictive value of the response to corticosteroid therapy was studied by calculating the area under the curve (ROC) for each of these parameters.

Results: Forty eight patients were included. The mean age was 34.3 years (range 16–72 years). The sex ratio was 0.5 [M/F = 14/28]. Twenty six patients (61.9%) were responders to corticosteroid therapy. Eight patients received second line medical treatment (cyclosporin: n = 6, infliximab: n = 2) and 8 patients (19%) had colectomy within an average period of 8.3 days. In the evaluation of corticosteroid response, the area under the curve (ROC) was 0.90 for CRP/albumin ratio at day 3; 0.75 for the albumin level and 0.6 for the CRP level (p = 0.04).

Discussion/Conclusion: A raised day 3 CRP/albumin ratio is strongly associated with subsequent need for colectomy. Early introduction of infliximab at this stage may be justified to reduce risk of subsequent colectomy in this high risk group.
Co-existence of liver steatosis and inflammatory bowel disease: A retrospective study

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Introduction: Emerging data have suggested the co-existence of non-alcoholic fatty liver disease (NAFLD) and inflammatory bowel disease (IBD), both of which are increasingly prevalent disorders with significant complications. In our study, we evaluated the prevalence of ultrasonographic liver steatosis in patients affected by IBD in a single-center.

Methods: We performed a retrospective monocenter study including patients with a confirmed diagnosis of IBD from January 2007 to March 2017. The diagnosis of liver steatosis was based on abdominal ultrasonography (US). The metabolic syndrome was defined according to the National Cholesterol Education Program’s Adult Treatment Panel III report (ATP III) criteria. Patients with a previous history of liver disease were excluded.

Results: A total of 175 patients were included: 87 ulcerative colitis (UC), 88 Crohn’s disease (CD). The mean age was 40.1 (19–65 years) and the sex ratio 0.96 (M/F = 86/89). US showed steatosis in 20.5% (21.8%; n = 19 in UC; 19.3%, n = 17 in CD). Among patients with liver steatosis, 63.8% (n = 23) had a metabolic syndrome. Elevated liver enzymes was found in 19% of patients (n = 33). About two thirds of them (63.6%, n = 21) had liver steatosis.

Discussion/Conclusion: In our study, the prevalence of steatosis in IBD patients was 20.5%, which confirms the presence of a direct correlation between metabolic syndrome and IBD. On the other hand, one third of patients with confirmed steatosis didn’t have a metabolic syndrome, which suggests that IBD related factors such as disease activity may have a role in the development of NAFLD.
Ulcerative colitis: Role of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in predicting disease severity

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Introduction: Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte-ratio (PLR) are effective markers of inflammation that have been linked with several inflammatory and neoplastic diseases. The aim of our study was to determine the value of NLR- and PLR-ratios in predicting disease severity in patients with ulcerative colitis (UC).

Methods: We performed a retrospective study including patients with confirmed diagnosis of UC between January 2007 and March 2017. PLR or NLR was measured without demonstrable infection. Two groups were compared:
- Group 1: Patients with endoscopic active UC
- Group 2: Patients with UC in clinical and endoscopic remission

Results: A total of 87 patients were included. The mean age was 40 years (range 19–65 years). The sex-ratio was 0.84. (38 males, 45 females). The PLR-ratio was higher in group 1 than in group 2 (mean 111 vs. 77.1, p = 0.052). Similarly, activity disease was associated with a high NLR (mean 6.2 in group 1 vs. 2.8 in group 2, p = 0.042). In univariate analysis, the presence of endoscopic lesions was significantly correlated with a C reactive protein (CRP) level > 10 mg/dl and an albumin level ≤ 28 g/l.

Discussion/Conclusion: Our results show that either high NLR or PLR levels can predict active endoscopic disease. This could be useful in stratifying patients and determining individual treatment plan, particularly when these parameters are used in combination with other inflammatory markers (CRP, fecal calprotectin).
Ikaros family transcription factors associate with inflammatory switched-Tregs that are elevated in the bowels of IBD patients

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Introduction: Regulatory T-cells (Treg) are non-redundant for peripheral tolerance and Treg deficiency or functional impairment is observed in many inflammatory conditions. We previously reported increased frequencies of Tregs that co-expressed cytokines and transcription factors associated with inflammatory Th1, Th2 and Th17 cells in the colons of IBD patients. Moreover, these ‘cross-over’ Tregs correlated with disease severity suggesting their involvement in IBD pathology and the need to understand factors governing Treg plasticity in these diseases. GWAS data imply a role for Ikaros family transcription factors: Ikaros, Helios, Aiolos and Eos in IBD and studies in mice support their involvement in T-cell differentiation and contribution to autoimmunity. Our aim was to understand their expression in human T cells and potential relevance in IBD.

Methods: Peripheral blood mononuclear cells were obtained from haemochromatosis blood bags. Protein co-expression was measured by thirteen-colour flow cytometry and gene expression by qPCR in flow-sorted subsets. PBMCs were stimulated with cytostim and sorted T cells with antiCD3/CD28 beads.

Results: Helios was expressed exclusively in CD25+CD127- Tregs whilst Aiolos was present in Tregs and non-Tregs but most abundant in CD25-CD45RA-CCR7+ central memory cells. Aiolos+ Tregs were enriched in the Helios-Tigit- subset. They had reduced CD25 and FoxP3 but higher levels of activation-induced CTLA-4, ICOS and IFNγ-associated CD226. Stimulation increased Aiolos in Treg and non-Tregs and Th17-associated IL-17, RORγ and CCR6 were increased on Aiolos+ cells. IL-17, IFNγ and IL-10-expressing Tregs were most enriched in the Helios- fraction and included FoxP3+ and FoxP3- cells. Eos mRNA was only detected in Tregs in the absence of stimulation but stimulation modestly induced Eos in non-Tregs.

Discussion/Conclusion: Our data support a role for Ikaros family transcription factors in the regulation of human T-cell function and identify Aiolos as a marker of activated, inflammatory-switched Tregs, characteristic of those enriched in the bowels of IBD patients.
The vitamin D status and level of fecal calprotectin in inflammatory bowel disease in children

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Introduction: Vitamin D deficiency is associated with numerous autoimmune disease but its status in children and adolescents with inflammatory bowel disease (IBD) is not well known. Fecal calprotectin is often used to identify children who most likely have IBD but it is still little know about its power to distinguish between ulcerative colitis (UC) and Crohn’s disease (CD). The aim of our study was to investigate the serum levels of 25-hydroxyvitamin D (25(OH)D) and fecal calprotectin in children with IBD.

Results: Retrospective study of children with IBD was conducted at the University Hospital Split, Croatia. Serum levels of 25(OH)D was analyzed in 19 children (aged 11–18 years) and vitamin D insufficiency (25(OH)D < 51 nmol/l) was found in 84%. Mean levels of 25(OH)D in children with CD was 38.8 nmol/L and in children with UC 22.8 nmol/l. Fecal calprotectin level was analyzed in 26 children; 10 with CD and 16 with UC (aged 1–18 years). Approximately 60% of subjects were inflamed (C-reactive protein > 5 mg/l). All patients had calprotectin level more than 50 µg/g. Fecal calprotectin more than 1500 µg/g was found in 50% children with CD and in 69% children with UC.

Conclusion: Our results suggest that concentrations of 25(OH)D < 51 nmol/l are common in children with IBD and that fecal calprotectin level is more often higher in children with UC than CD. Further research is needed to clarify this results.
An association study of long non-coding RNAs in the pathogenesis of inflammatory bowel diseases

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Background: Several genome-wide association studies have provided hundreds of single nucleotide polymorphisms (SNPs) which are related to inflammatory bowel diseases (IBDs). IBDs mainly consist of Crohn’s disease (CD) and ulcerative colitis (UC). However, as the aetiology of these chronic inflammatory diseases is still unknown, the understanding of pathogenetic mechanisms is problematic. Moreover, 90% of IBD-related SNPs are located in non-coding DNA regions and about 10% of these in long non-coding RNAs (lncRNAs). They seem to regulate the expression levels of lncRNAs by altering splicing or affecting their secondary structure.

Aim: This study is trying to elucidate the association between lncRNA SNPs and the pathogenesis of IBDs in Greek population.

Materials and methods: We conducted a genotype analysis in 242 CD patients, 185 UC patients and 220 healthy controls for the SNPs rs3757247 and rs1476514 in order to assess whether the prevalence of the alleles are significantly related with the presence of IBDs.

Results: As far as rs3757247 is concerned, it was shown, that the G-allele is more common in healthy subjects than in UC patients. On the contrary there is no such significant difference in CD patients. About the rs1476514, it was obvious that the A-allele was dominant in healthy controls.

Conclusion: The presence of rs3757247A and rs1476514G alleles in IBD patients is possible to affect the likelihood of IBD in the Greek population. Further studies including sizeable and diverse populations are required in order to confirm these results.
Crohn’s disease clinical phenotypes have distinct gut microbial signatures: An in silico approach

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Introduction: Crohn’s disease (CD) is thought to be associated with microbial dysbiosis in either the development or exacerbation stage. CD is classified according to the Montreal classification in the behavioral phenotypes, B1 non-stricturing non-penetrating, B2 stricturing and B3 penetrating. Our study examines the possible correlation of the gut microbiome with these specific behavioral phenotypes.

Methods: A metagenomic in silico pipeline, consisting of diversity, taxonomic, biomarker and microbial metabolomic analyses was implemented using the QIIME, Calypso, LEfSe, PICRUSt and STAMP tools. The pipeline was mainly focused on detecting changes in microbial 16s rRNA sequencing within the 3 behavioral phenotypes of CD versus healthy patient samples. Our data were obtained via published and publicly available datasets from the QIITA open source microbial study management platform.

Results: The initial identification of microbial populations, taxonomic and diversity analyses via QIIME and Calypso revealed the known loss of α-diversity within all CD samples. In addition, B2 and B3 sample were significantly reduced compared to B1 groups, while no statistical significance between the B2 and B3 samples was detected. β-diversity analysis pointed to microbial compositions similar in the B2 and B3 samples, but statistically different from both B1 and controls. Analysis of the abundance of genera has also highlighted populations that were reduced or increased in CD, but additionally changes of both B2 and B3 were statistically different compared to B1 samples. Finally, similar pattern was detected in our microbial metabolic analysis, where certain metabolic pathway abundancies were reduced or increased in CD versus controls, but both B2 and B3 samples had significant changes versus the B1 group. These analyses revealed differential microbial signatures of both B2 and B3 groups compared to B1.

Discussion/Conclusion: Our findings indicate a distinct signature of microbiome’s behavior in CD phenotypes and suggest further investigation of CD from a different perspective.
Cytokine receptor profiling in human colonic subepithelial myofibroblasts: A differential effect of Th polarization associated cytokines in intestinal fibrosis

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Introduction: Crohn’s disease (CD) often leads to debilitating intestinal strictures. Colonic subepithelial myofibroblasts (cSEMFs) have a pivotal role in the pathophysiology of fibrosis. In the present study, we demonstrate a complete expression mapping of all known cytokine receptors in cSEMFs and how pro-inflammatory cytokines regulate their expression. Furthermore, we show the effect of all Th-associated interleukin combinations on cSEMFs, by measuring pro-fibrotic mediators and through the wound healing assay.

Methods: cSEMFs were isolated from colonic biopsies from healthy individuals. They were cultured under IL-1α and/or TNF-α and cytokine receptor mRNA and protein expression was assessed at 6h and 24h using reverse transcription quantitative (RT-q) PCR and immunofluorescence, respectively. Next, cSEMFs were stimulated for 6 h, 24 h and 48 h with TNF-α/IFN-γ (Th1), IL-4/IL-13 (Th2), IL-17/IL-22/IL-23 (Th17) and IL-10/TGF-β1 (Treg). Their effect on collagen and fibronectin mRNA and protein expression was tested at 6h by RT-qPCR and at 48 h by protein assays, respectively. Effects on wound healing capacity of cSEMFs were assayed with scratch test.

Results: cSEMFs exhibited basal expression levels for most cytokine receptors and their expression was influenced by IL-1-α and TNF-α. Th1-related cytokines upregulated collagen and fibronectin protein expression and downregulated wound healing rate. Th2-related cytokines upregulated collagen mRNA expression and wound healing rate and downregulated fibronectin protein expression. Th17-related cytokines had a mixed effect in cSEMFs; IL-17 and IL-23 upregulated fibronectin, while IL-22 suppressed its expression and IL-17 and IL-22 decreased wound healing rate, while IL-23 increased it. TGF-β was the most potent pro-fibrotic agent, as it upregulated all studied fibrotic factors and increased cSEMFs migratory capacity.

Discussion/Conclusion: These results suggest that cSEMFs may be a dynamic crosslink between inflammation and fibrosis, as they exhibit a rich expression panel of Th-related cytokine receptors, making them responsive to cytokines, abundant in the inflamed mucosa of CD patients.
Risk factors for poor postoperative outcome in patients with Crohn’s disease undergoing ileocecal resection

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Background: The postoperative outcome of intestinal resection in Crohn’s disease (CD) patients may be affected by multiple perioperative factors. The objective of this study was to identify risk factors of 30-day postoperative complications in CD disease patients who underwent ileocecal resection.

Methods: An observational retrospective monocentric study including CD patients who underwent ileocecal resection between January, 1st 2008 and September, 30th 2017 was conducted. Epidemiologic, clinical, biologic and therapeutic characteristics were abstracted from medical records.

Results: We have collected 89 patients of mean age of 32.8 years old. Indications for ileocecal resection was stricturing disease (n = 52; 57.8%) and penetrating complications (n = 38; 42.2%). Preoperative medical therapy included steroids (n = 14; 15.6%), immunosuppressants (n = 13; 14.4%), and biologics (n = 4; 4.4%). Laparoscopic ileocecal resection was performed in 55 (61.1%) patients, while 34 (37.8%) patients underwent an open ileocecal resection. Postoperative complications have been observed in 7 patients (7.8%) after a median period of 11.7 days (5–21). The rates of intra-abdominal abscess, anastomotic leak and enteric fistula were 4.4%, 1.1% and 2.2%, respectively. Postoperative complications were associated with no preoperative blood transfusions (p = 0.016) and a low preoperative cholesterol level (< 1 g/l) (p = 0.016). Intra-abdominal abscess discovered during surgery (p = 0.018) and laparotomy surgery (p = 0.03) were correlated with longer postoperative stay in hospital. Other potential risk factors, such as age, gender, low preoperative hemoglobin or albumin levels, and the use of steroids or biologics were not associated with the occurrence of postoperative complications in our patients.

Conclusions: In CD patients undergoing ileocecal resection, no blood transfusion and low preoperative cholesterol level were associated with unfavorable postoperative outcome. Intra-abdominal abscess discovered during surgery and laparotomy were correlated with longer postoperative stay in hospital.
Long-term outcome of Crohn’s disease patients treated with methotrexate: A retrospective monocenter study

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Introduction: Despite its proven efficiency, methotrexate is rarely prescribe in Crohn’s disease patients. The aim of our study was to report indications and modalities of treatment and long-term outcome of Crohn’s disease patients treated with methotrexate.

Patients and methods: We conducted a retrospective study including Crohn’s disease patients treated with methotrexate from 2007 and 2014. Epidemiologic, clinical and evolutionary characteristics were determined for each patients.

Results: We collected 10 patients (4 males and 6 females). Mean age at disease diagnosis was 32.1 years (8–43 years old). Disease location was: ileal (n = 5), colonic (n = 4) and ileo-colonic (n = 1). No perineal involvement was noted. Upper gastrointestinal involvement was noted in 1 patient. Disease phenotype was non stricturing non-penetration (n = 8), stricturing (n = 1) and penetrating (n = 1). Methotrexate was introduced after a mean time from diagnosis of 53 months (6–156 months). Indications of methotrexate were: refractory rheumatologic manifestation in 2 patients, cortico-dependence in 3 patients, corticoresistance in 2 patients, as maintenance therapy after severe acute colitis in 2 patients, and failure or intolerance to thiopurines in 2 patients. Methotrexate dosage was 15 to 25 mg/week. It was administered intramuscularly (n = 9) or orally (n = 1). Mean duration of treatment was 19.5 months (2–60 months). After a mean follow-up of 31.22 months (10–60 months), clinical remission was obtained in 6 patients (60%) and clinical response in 2 patients (20%). Failure of treatment was noted in 2 patients (20%) of whom one patient had rheumatologic manifestation that required anti-TNF treatment. Adverse events such as precocious hepatic cytolysis were noted in one patient leading to treatment withdrawal.

Conclusion: Methotrexate is trivial and efficient to maintain clinical remission in Crohn’s disease patients. This treatment should be considered in Crohn’s disease patients, namely after failure or intolerance to thiopurines.
The role of the Tec kinase ITK and the transcription factor NFATc1 in disease pathogenesis of inflammatory bowel disease

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Introduction: ITK, a member of the Tec family kinases, is expressed in T cells and involved in Th2-type mediated immune responses. Colitis patients can be successfully treated with CsA but CD patients not. Therefore, we started to investigate the role of ITK (interleukin-2-inducible T cell kinase) and the linked transcription factor NFATc1 in experimental colitis model.

Methods: Oxazolone colitis was induced in ITK deficient mice, conditional NFATc1-delta-CD4-KO mice and controls. Disease activity was measured by means of body weight, histological and endoscopic score of inflammation activity. Lamina propria mononuclear cells (LPMC) and spleen cells were isolated from these mice. The rate of apoptosis induction after treatment with CsA was assessed via flow cytometric analysis of AnnexinV/7AAD staining. Cytokine concentration (IL-6, IL-13, IL-17A, IL-17F, TNF-α) was assessed using ELISA. Immunofluorescence staining for ITK and Caspase 3 of spleen and colonic tissue was performed.

Results: In the oxazolone induced colitis model, ITK-KO mice are protected against the development of intestinal inflammation compared to control mice. Upon administration of CsA there is a significant induction of apoptosis in LPMCs from control mice. Histochemical immunostainings of colonic tissue revealed that ITK-KO mice show less expression of IL-6. Conditional NFATc1-delta-CD4-KO mice show no protection against oxazolone induced colitis compared to control mice. Interestingly, administration of CsA could not prevent inflammation in these mice.

Discussion/Conclusion: Our results indicate that in the oxazolone induced colitis model, CsA induces enhanced apoptosis in LPMCs of control mice whereas ITK-KO mice show no apoptotic phenotype. NFATc1 doesn’t seem to play a pivotal role in the development of intestinal inflammation since its knockout doesn’t lead to protection against the induced colitis even after administration of CsA. Therefore, we suggest ITK to be a possible target for the therapy of colitis ulcerosa.
Vedolizumab levels and endoscopic and clinical remission in patients with Crohn’s disease and ulcerative colitis on vedolizumab therapy

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Introduction: Vedolizumab is a humanized monoclonal antibody blocking the interaction of α4β7 integrin with MAdCAM-1, used for the effective treatment of active ulcerative colitis (UC) or Crohn’s disease (CD) where the conventional anti-TNF-α therapy is ineffective. High vedolizumab levels are associated with deep remission in IBD patients; however the ideal drug levels to maintain clinical and endoscopic remission remain unclear. This study aims to assess correlation between vedolizumab levels with the clinical and endoscopic remission in CD and UC patients.

Methods: 13 IBD patients (6 CD and 7 UC) were treated with vedolizumab, 11 on maintenance dosing and 2 on induction dosing. C-reactive protein (CRP), Harvey Bradshaw index and Simple endoscopic score-CD (SES-CD) (HBI) in CD, Partial Mayo Score and Mayo endoscopic score (MES) (PMS) in UC were identified. Primary outcome was remission (normal CRP and SES-CD ≤ 2 in CD – MES ≤ 1 in UC) and clinical remission (HBI < 4 in CD/PMS < 2 in UC). Vedolizumab levels were measured using LISA TRACKER – vedoluzimab (Theradiag) ELISA kit.

Results: 5 patients (38.5%) had undergone anti-TNF therapy whereas 8 were naive. 6 patients were in both clinical and endoscopic remission and exhibited significantly higher levels of vedolizumab when compared to those who did not achieve these outcomes (55.4 ± 41.2 vs. 16.9 ± 27.6 μg/ml [p = 0.03]). 2 patients had increased vedolizumab levels (25.75 ± 3.41 μg/ml) without clinical or endoscopic remission but those patients were under their second induction dose (week 2) which may explain those relatively high levels. In our cases seems that patients with vedolizumab levels ≥ 12.22 ± 4.04 μg/ml were more likely to be in remission.

Discussion/Conclusion: It seems that there is an association between vedolizumab drug levels and vedolizumab efficacy. Results from larger ongoing cohorts will be enlightening.
What is hidden beneath chronic bloody diarrhea in two-year-old girl?

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Introduction: Ulcerative colitis (UC) is a chronic relapsing inflammatory disease of the colon. The incidence of pediatric-onset UC ranges between 1 to 4 on 100,000 per year and the disease is increasing among young children (< 5 y). Definitive etiology of pediatric inflammatory bowel disease (IBD) is not entirely understood, but environmental, immunologic, infectious and genetic factors are postulated to increase the risk for developing IBD. The main symptoms of UC are bloody diarrhea, tenesmus, abdominal pain and in cases of severe clinical course, weight loss, fatigue and vomiting. Fecal calprotectin (FC) is a useful biomarker for noninvasive diagnosing and monitoring of disease activity in pediatric IBD patients but the final diagnosis is based on an endoscopic and pathohistological findings.

Case report: A 2-year-old girl presented with chronic bloody diarrhea lasting for 2 months. She was well-nourished and had no other symptoms. Performed blood tests were normal (CBC, CRP, serum iron, fT3, fT4, TSH). The stool samples were negative for infectious diseases, in exception of Blastocystis hominis. Antibiotic plus probiotic therapy was conducted but diarrhea persisted. Elimination of cow’s milk protein from child’s diet showed no clinical improvement. Knowing that her mum has been suffering from UC, FC was analyzed and it was high (8170 mg/kg). After 6 weeks, repeated FC was still high (2053 mg/kg). Finally, colonoscopy with biopsies was performed and diagnosis of UC was confirmed. As the girl was in a good condition and getting on weight, we decided to start with mesalamine therapy with excellent response. The remission was achieved in 4 weeks period. Stools became normal and FC levels have fallen significantly (200 mg/kg).

Discussion/Conclusion: With this case report we wanted to show early onset of ulcerative colitis and the importance of fecal calprotectin as a noninvasive biomarker of pediatric IBD.
Cell death independent physiological cell shedding in the absence of GGTase-mediated prenylation in intestinal epithelium

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Introduction: In our last study we identified prenylation as a key player in epithelial cell biology, maintenance of intestinal epithelial barrier function and permeability (López-Posadas et al. JCI. 2016). Cytoskeleton rearrangement and subsequent epithelial cell shedding alterations led to destruction of epithelial architecture, and severe gut pathology. Based on these observations, we aim at the identification of physiological and/or pathological cell shedding alterations upon inhibition of prenylation.

Methods: Taking advantage of inducible intestinal epithelial cell specific GGTase-Iβ knock-out mice, we performed a kinetic study in order to define molecular events leading to altered cell shedding within GGTase-deficient intestinal epithelium.

Results: Inhibition of prenylation due to deletion of pggt1b, the gene encoding for GGTase-Iβ, does not lead to increased cell death activation in small intestinal tissue (TUNEL-Caspase-3 immunostaining and western blot). This data indicates that caspase-activated pathological cell shedding is not activated in GGTase-deficient epithelium. However, intravital microscopy studies revealed early accumulation of so-called “permeable epithelial cells”, which are able to uptake rhodamine dextran into the cytoplasm. This goes along with upregulated gene expression of tight junction proteins (ZO-1, Claudin-2 and Occludin-1) and early accumulation of epithelial cells within the tissue (Villin expression in gut tissue, and number of epithelial cells/length of the epithelial layer). Interestingly, our preliminary data support the hypothesis that overcrowding might occur due to cytoskeleton rearrangement and uncompleted physiological cell shedding.

Discussion/Conclusion: Our data indicate that cell death-independent cell shedding alterations upon inhibition of prenylation within intestinal epithelial cells might be due to defects in physiological cell shedding due to cytoskeleton rearrangement.
The clinical course of Hermanski-Pudlak syndrome associated with granulomatous colitis: Relations with genotype in patients from western Ukraine

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Introduction: Hermansky-Pudlak syndrome (HPS) is a rare autosomal recessive disorder consisting of systemic complications associated with accumulation of ceroid lipofuscin. HPS-4 type is often associated with gastrointestinal complications related to granulomatous colitis that is pathologically and phenotypically indistinguishable from Crohn’s disease (CD).

Aim: To study the relationship between the genotype and the phenotype in the patients with HPS associated with granulomatous colitis; to monitor clinical course of the disease for adequate treatment and genetic counseling.

Methods: The diagnosis of HPS is established by physical examination, chest X-ray, CT, endoscopic examination with biopsy, and laboratory tests, including histology. Molecular genetic testing for HPS gene mutations, R702W, G908R, L1007fs and P268S mutations in NOD2 gene, and TaqI variant of the VDR gene were carried out.

Results: We report 2 cases of HPS from unrelated families. Both were complicated by IBD with pathologic features of CD refractory to antibiotics and corticosteroids. One patient (family 1) with Ashkenazi Jewish ancestry had pathogenic variant of the HPS-4 gene in exon 8, mutation P268S of NOD2 genes and TaqI variant of the VDR gene. Another patient (family 2) carried two different mutations of NOD2 gene. No consistent success with the standard medical therapy, used for treating granulomatous colitis, associated with HPS, in presented cases was achieved. Patients needed surgical interventions at a young age and a long-term surveillance of the probable development of complications. Azathioprine and Salofalk® were used with positive effect for prevention of CD postoperative recurrence.

Discussion/Conclusion: The occurrence of perianal lesions, the histopathological findings and the mutations of NOD2 gene suggest that HPS was truly associated with CD variant with early onset and severe course.
Clinical characteristics and L1007fs mutation of NOD2 gene in patients with Crohn’s disease from Western Ukraine, associated with colorectal cancer and without cancer

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Introduction: IBD clearly predisposes to colorectal cancer (CRC) development although the risk differs in different parts of the world. CRC accounts for approximately 10–15% of all deaths among IBD patients.

Aim: To compare the clinical characteristics of Crohn’s disease (CD) and CD-associated CRC in patients of different age, gender, disease severity, spectrum of surgical interventions, and occurrence of L1007fs mutation in the NOD2 gene.

Methods: A comparison of clinical characteristics and the results of surgical treatment of 98 patients with CD and 16 patients with CD-associated CRC were carried out. The diagnosis of CD and CRC is established by physical examination, CT, endoscopic examination, laboratory tests. Molecular genetic testing for mutation L1007fs in the NOD2 gene was carried out in 83 individuals (40 patients with CD, 10 patients with CD-associated CRC and 33 healthy controls).

Results: The median age of CD onset in the patients without CRC was 35.0 ± 1.4 years and appeared significantly lower comparing to the patients with CD-associated CRC (52.1 ± 3.7 years). The age of the disease onset in female mutation carriers with CD was significantly less than in the females without mutation. Colonic localization (L2) and non-stricturing non-penetrating behavior of the disease (B1) dominated in patients with CD. L1007fs mutation was highly associated with penetrating CD and ileal disease localization (p = 0.01). Generally, 67.5% of CD patients needed surgical interventions. The most frequent operation in patients with CD complicated by CRC was left-sided hemicolectomy performed mostly in males of the A3 age group. Females of the A2 age group with colonic localization of the CD prevailed among the patients that underwent total colectomy without presence of CRC.

Discussion/Conclusion: The mutation p.Leu1007fs was not found in patients with CD-associated CRC. Early detection of patients with CD from the CRC risk group leads to timely adequate treatment, achievement of long remissions, and prevention of life-threatening complications.
Evaluation of CD40 and CD80 receptors in the colonic mucous membrane of children with Crohn’s disease

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Introduction: CD40, a 45–50 kDa molecule, is a component of the CD40/CD40L pathway. It is classified as the type I transmembrane protein, which belongs to the TNF receptor superfamily. CD80 is a membrane receptor activated upon binding of CD28 or CTLA-4, i.e. co-receptors present on the surface of CD4-positive and CD8-positive lymphocytes.

The aim of the study is the evaluation of CD40 and CD80 molecules in biopsy specimen of the large intestine mucosa in children with Crohn’s disease.

Methods: The study included 10 patients with Crohn’s disease (CD) aged 3–17 years of age, with the mean age of 12.30 (± 2.83), and 10 children as the control group with the mean age of 10.28 (± 4.07). The mucosal specimens were the target of CD40 and CD80 evaluation. The specimens underwent appropriate procedures and were incubated with mouse antiCD40 monoclonal antibody (R & D Systems) and with rabbit antiCD80 monoclonal antibody (Abcam). The number of cells with CD40 and CD80 expression per all the inflammatory cells in the field of vision in the stroma, was counted on four fields of vision (400 x). The STATISTICA 2010 package was used for the mathematical analysis of the results.

Results: In the assessment of differences between the group of patients with CD and the control group it was shown that the number of CD40-positive cells in the sigmoid colon mucosa and caecal mucosa was higher in the group of patients with CD (median 40.0% and 70.0%, respectively) than in children from the control group (median 10.0% each), (sigmoid p = 0.05, and caecal p = 0.76, respectively). The number of CD80-positive cells in the colon mucosa was higher in all three segments evaluated in patients with CD (median: sigmoid 80.0; caecum 42.5; rectum 60.0, respectively) than in the control group (median 20.0% each), however, only in the caecum it was statistically significantly higher (p = 0.0004) (rectum p = 0.37; sigmoid p = 0.06).

Conclusion:
1. The number of CD40- and CD80-positive cells in the mucous membrane of the large intestine in children with Crohn’s disease is significantly higher than in the controls.
2. The highest number of CD40+ and CD80+ cells is observed in the caecal mucous membrane in patients with Crohn’s disease.
Whipple’s disease – Clinical case

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Introduction: Whipple’s disease is a chronic systemic bacterial infection, characterized as a gastrointestinal disorder for the first time in 1907 by Dr. George Hoyt Whipple. Its rare occurrence is reported mostly in Europe and North America. The disease involves various body parts especially the central nervous system, joints, and heart and vascular system. Patients suffer from non-specific complaints such as weight loss, hypotension, peripheral lymphadenopathy, low-grade fever, and anemia. It is possible to diagnose Whipple’s disease on the basis of an intestinal biopsy. Unfortunately, the results often yield false negatives, due to the fact, that many patients are administered antibiotics before the biopsy.

Methods: Our poster discusses the etiopathogenesis, diagnosis, and treatment of Whipple’s disease based on a case of a 51-year-old man in the University Hospital in Bialystok. Predominant symptoms in the clinical picture included: marked lymphadenopathy as well as persistent diarrhea with accompanying weight loss for three months. In addition, laboratory tests revealed that the patient suffered from microcytic anemia. A diagnosis of Whipple's disease was given based on laboratory tests and a histopathological examination obtained during a gastrointestinal endoscopy. Obtained histopathological studies showed intestinal inflammation and villus obstruction. PAS-positive macrophages in the lamina propria were significantly increased.

Results: Improvement of the patient’s general condition and relief of pain were observed after a 14-day course of intravenous antibiotic (ceftriaxone) therapy and with additional treatment with trimethoprim for one year. Currently the patient is in a good
general condition and with regular visits to a gastroenterologist. A control gastroscopy after one year showed significant clinical improvement which allowed for the cessation of treatment.

**Discussion:** Diversity of symptoms and an atypical course of this disease make obtaining a correct diagnosis quite difficult. Comprehensive and thorough examinations are very important in the diagnostic process due to the risk of resulting disability and even death associated with long-term and untreated Whipple’s disease.
Different histological indexes for the assessment of ulcerative colitis activity


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Background and aims: Histopathological analyses have become an important part of ulcerative colitis (UC) assessment both in clinical practice and in research trials. Our work is focused on three histological indices that have been at least partially validated: Geboes score (GS), Nancy index (NI) and Robarts histopathology index (RHI). It aims to evaluate the agreement between these three histological classification systems and to relate these scoring systems with the patients’ endoscopic outcomes and inflammation burden. Moreover, intends to disclose which (if any) histological features could be predicted from fecal calprotectin (FC) levels.

Methods: Biopsy samples from 377 UC patients were blindly evaluated using GS, NI and RHI. The results were compared with the patients’ Mayo endoscopic score and FC levels.

Results: The concordance between GS, NI and RHI, evaluated in terms of histological remission/activity, was considerably high. In fact, using the GS with a 3.1 cutoff as the reference, 87 and 71% of the patients with histological activity and 89 and 100% of the patients in histological remission, were correctly identified by the NI and RHI, respectively. Regarding endoscopic outcomes, the sensitivity is higher when 1 is used as the Mayo endoscopic score cutoff (96 to 100% of all patients with macroscopic lesions have histological inflammation), and the specificity is higher when 0 is used as the Mayo endoscopic score cutoff (56 to 93% of all patients considered to be in mucosal
remission have no histological activity). Patients that have an FC level below 150 ug/g are in histological remission according to NI, RHI and GS (with a negative predictive value (NPV) of 81, 93 and 88%, respectively). Moreover, the presence of neutrophils in the lamina propria did not associate with FC levels. Conversely, higher FC levels were statistically associated with the presence of neutrophils in the epithelium, as well as with ulceration or erosion of the intestinal mucosa.

**Conclusion:** The classical GS is accurate concerning the newly-developed and formally-validated NI and RHI scores. Our results suggest that one can spare a patient from an endoscopic examination based solely on the non-invasive and cheaper FC test. Additionally, FC levels are increased when neutrophils are present in the epithelium and the intestinal mucosa has erosions or ulcers.
The role of gamma-secretase subunit PSEN1 in intestinal inflammation

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Introduction: Notch signalling is an important molecular pathway that controls and regulates cell differentiation and proliferation in the intestine. The pathway is active and is known to play a major role during chronic inflammatory intestinal disorders like Crohn's and ulcerative colitis (UC). The cleavage of Notch receptor-ligand complex by gamma-secretase subunit which consists of Presenilins (PSEN1) functions as an important checkpoint in the regulation of Notch signalling. Although previous studies have demonstrated the role of Notch receptors in chronic colitis models, the precise involvement of Presenilins during the development and resolution of intestinal inflammation still remains unknown.

Methods: We generated a transgenic mouse where PSEN1 is specifically deleted in intestinal epithelial cells (PSEN1ΔIEC). To study the role of PSEN1 during inflammation, the PSEN1ΔIEC mice were subjected to an experimental model of UC, by administration of DSS in drinking water for 7 days. The effect of PSEN1 was determined using immunohistochemical, immunoblot and real-time PCR analysis.

Results: Our data for the first time demonstrates that the absence of PSEN1 in intestinal epithelial cells leads to a higher susceptibility during DSS induced colitis. Although the PSEN1ΔIEC mice showed an increased number of secretory cells (Paneth, goblet, etc) at steady state condition, this did not protect the PSEN1ΔIEC mice from developing a severe epithelial erosion, increased immune cell infiltration and inflammation as compared to floxed littermate controls. Moreover, in vitro developed organoids from PSEN1ΔIEC mice exhibited arrested budding and atypical morphology as compared to controls indicating that PSEN1 plays an important role in cell differentiation.

Conclusions: Our data shows a novel mechanism of PSEN1 in notch signalling and in chronic intestinal inflammation. Therefore, understanding the regulation of gamma-secretase subunits may lead to the development of new therapies for UC.
The serotonin role in the intestine motor function violation in patients with ulcerative colitis

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A serotonin plays a significant role in the regulation of the gastrointestinal tract (GIT) motility, first of all the intestine motility. In addition, the serotonin is involved in the immune response modulation, regulates the processes of leukocyte migration, phagocytosis, secretion of cytokines. The pathogenetic significance of the serotonin is not sufficiently studied in the development of clinical symptomatology of ulcerative colitis (UC) exacerbation.

**Aim:** To investigate the pathogenetic role of serotonin in the development of UC clinical symptoms.

**Materials and methods:** We examined 41 patients with UC in the period of exacerbation, of which 18 women, 23 men, 21–55 years old. The endoscopic examination of the large intestine, a full-scale Mayo count, and the serum serotonin level test (normal values 80–400 $\mu$g/l) were done. The group of practically healthy persons included 24 persons (11 women and 13 men), 18–25 years of age without gastrointestinal diseases.

**Results:** According to the fibrocolonoscopy, distal UC was detected in 14 (34.2%) patients, the left side UC – in 12 (29.2%), total colitis – in 15 (36.6%) patients. The endoscopic activity index was grade I in 4 (28.6%) patients, grade II – in 8 (57.1%), grade III – in 2 (14.2%) patients with distal UC. In patients with left-sided UC, the endoscopic activity index was grade I in 2 (16.7%) patients, grade II – in 7 (58.3%), grade III – in 2 (25%) patients. The endoscopic activity index of grade I was in 2 (13.3%) patients with total UC, grade II – in 8 (53.4%), grade III – in 5 (33.3%) patients of this group. According to the results of Mayo’s full scale, taking into account the frequency of defecations, rectal bleeding, endoscopic index, and evaluation of the UC activity by the physician, 9 (21.9%) patients had mild activity, 27 (65.8%) – moderate activity and 5 (12.2%) patients – severe UC activity (11–12 points).

The serum serotonin level of patients on the background of UC exacerbation exceeded the rates of practically healthy subjects in 2.2 times (324.8 ± 68.1 versus 145.65 ± 40.6 $\mu$g/L, $p < 0.05$). In addition, maximum serotonin values were noticed in patients with severe Mayo full scale activity, and ranged from 346 to 392 $\mu$g/l.

**Conclusion:** Clinical exacerbation of UC is characterized by II and III grades of endoscopic activity. The statistically significant increase in serum serotonin level with a clear dependence of its level on the severity of UC activity according to the Mayo full scale was noted on the background of UC exacerbation.
Diagnostic accuracy of tissue transglutaminase antibodies for detecting persistent villous atrophy among adult patients on a gluten-free diet

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Introduction: Tissue transglutaminase (tTG) and endomysial IgA antibodies are hallmarks of CD diagnosis. The aim of our study was to assess whether serum IgA-tTG tests are useful to detect villous atrophy in patients with CD treated with gluten free diet (GFD).

Material and methods: We performed a prospective study using the information entered into a structured database including adult patients diagnosed with CD hospitalized at the Institute of Gastroenterology and Hepatology, adherent to GFD for at least 12 months after diagnosis. Data from adult patients with CD (diagnosed between January 10, 2010 through December 10, 2015) with biopsy, and serological tests (IgA/IgG-tTG antibodies) were retrieved from a computerized database. Results of non-invasive tests were compared with the persistence of villous atrophy on follow-up biopsy.

Results: The study group included 81 adult patients with a female: male ratio of 3:1, mean age 40.02 ± 12.14 years. When assessing the serological parameters, IgA-tTG levels (61.45 ± 76.458 u/ml vs. 162.02 ± 106.179 u/ml, P = 0.001) correlated with intestinal villous atrophy (Marsh 1–2 vs. Marsh 3 a–c) in CD patients, with a sensitivity of 82.56% and a specificity of 91.78% for mucosal atrophy upon diagnosis (AUC = 0.909; IC95%: 0.86–0.95). Follow-up biopsy and serology testing were available for 47 (74.6%) treated patients. Twenty-one patients had variable degrees of villous atrophy, and IgA-tTG assay was 51% sensitive and 67.3% specific in identifying Marsh 3 lesions among patients allegedly adherent to a GFD with normal IgA-tTG levels.

Discussion/Conclusion: Increased IgA-tTG levels in the treated population may reflect quantity and frequency of gluten exposure. The diagnostic accuracy of IgA-tTG antibodies for detecting persistent villous atrophy on a GFD is limited, showing relatively high specificity, but low sensitivity. Consequently, the majority of patients with villous atrophy on a GFD had normal levels of IgA-tTG.
Named patient supply programs allow earlier access to treatments for complex patients: UK multicentre ustekinumab experience

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Introduction: Before UK regulators granted funding approval for ustekinumab use in Crohn’s disease (CD) in April 2017, it was available via a named patient supply (NPS) scheme. Here, we describe disease phenotype of patients who accessed the scheme and the ‘real-world’ effect of ustekinumab from baseline through to the 3rd dose (Median 29 [24–36]).

Methods: Data was provided from 5 UK tertiary centres for 17 patients. Disease activity was assessed at baseline and before the first 3 doses using Harvey Bradshaw Index (HBI), IBD- Control PROM, and physician’s assessment of activity with bloods taken as routine care.

Results: Subjects had mean disease duration of 16.7 years (9–33) and 12/17 had undergone previous surgery. All but 1 (contraindicated) had failed 1 anti-TNFα, 14/17 failed 2 and 2/17 failed 3 - most commonly due to loss of response (LOR). 15/17 had failed vedolizumab, 8 for primary non-response (PNR). 11/17 had penetrating or stricturing disease and more 3 perianal involvement. All patients tolerated ustekinumab for the duration of the follow-up, with 1 being stopped as disease was considered fibrotic. In those with HBI collected to dose 3, Clinical response (defined by a fall in HBI ≥ 3) was seen in 6/12 (50%), clinical remission (HBI < 3) 5/12 (42%); Median HBI falling from 8 at baseline to 5 at dose 3 (p 0.020).

Discussion/Conclusion: NPS schemes offer patients with complex and treatment-resistant CD early access to therapies and a chance of better disease control earlier than if regulatory approval was awaited. Although small numbers, this “real-world” data complements the findings of the UNITI-2 trial in a complex CD cohort.
Association between inflammatory bowel disease and celiac disease: About 4 cases

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Introduction: The association between inflammatory bowel disease (IBD) and celiac disease is rare. This association poses a diagnostic problem as these two conditions are often revealed by diarrhea.

Methods: We report four cases of patients with IBD and celiac disease who are followed in the gastroenterology department of Nabeul. For each patient, epidemiological, clinical and endoscopic data were specified.

Results: There were 4 patients: 2 men and 2 women. No patient had a family history of celiac disease or IBD. Three patients had Crohn's disease and only one patient had ulcerative colitis (UC). The average age of patients at the diagnosis of the initial pathology was 35 years (13–47 years). The diagnosis of IBD preceded that of celiac disease in 3 cases. For the 4th patient, the diagnosis of celiac disease preceded that of Crohn's disease of 2 years, the latter was revealed by subocclusive syndromes. The diagnosis of celiac disease was made on the endoscopic aspect of the FOGD and duodenal biopsy data showing total villous atrophy in all cases. The reason for performing the FOGD was: epigastralgia in 2 cases and anemia in one case. The serology of celiac disease was positive in 3 patients. The gluten-free diet was well followed by 3 patients with a good evolution. Crohn's disease was ileocolic for 2 patients and ileal for one patient. The profile was stenosing in two cases. UC was pancolitic complicated by severe relapses and treated with colectomy.

Discussion/Conclusion: The association of IBD and celiac disease is rare. The diagnosis can be difficult because of the intricacy of clinical and biological signs.
Active disease prevention in inflammatory bowel disease through exercise

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Introduction: Our goal was to study the utility of physical exercise in the prevention of inflammatory bowel disease (IBD) exacerbations.

Methods: Our study included 100 patients with Crohn’s disease (CD) and 100 patients with ulcerative colitis (UC). All patients were chosen to be in remission. We measured the exercise status of each patient at the beginning of the study, using the validated Godin leisure-time activity index. The study follow-up, conducted after 6 months, assessed active disease status among all patients. We used bivariate and multivariate analyses to describe the independent association between exercise and risk of active disease.

Results: 18 patients with CD and 25 patients with UC developed active disease after 6 months. Higher exercise level was associated with decreased risk of active disease for CD (adjusted risk ratio: 0.70, 95% confidence interval: 0.52–0.89) and UC (adjusted risk ratio: 0.81, 95% confidence interval: 0.56–1.08).

Discussion/Conclusion: IBD patients in remission with higher exercise levels were less likely to develop active disease at 6 months.
Acne vulgaris related to ulcerative colitis treated with infliximab standard therapy

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Introduction: Anti-TNF agents are generally well tolerated, even if they are not free of side effects. Almost 25% of patients undergoing anti-TNF therapy have dermatological reactions. Skin lesions were not associated with IBD activity, but were more frequent among females and occurred with any type of anti-TNF-α agent (infliximab, adalimumab or certolizumab). Usually topical therapy with corticosteroids, keratolytics (salicylic acid, urea), emollients, vitamin D analogues and ultraviolet (UV) therapy (UVA or narrow band UVB) resulted in partial or total remission in almost 50% of patients, the treatment is mainly based on expert opinion (ECCO guidelines).

Case report: This is a prospective observational review of a 27 years old female who had been diagnosed with left-sided ulcerative colitis (UC) (Mayo 6) since 2008. In June 2016 the patient was admitted to Pauls Stradins Clinical University Hospital Division of Gastroenterology, Hepatology and Nutrition with an exacerbation of UC (Mayo 10). She was receiving standard UC treatment with mesalazine and azathioprine, but from 2015 following with exacerbations three times per year. Biologic therapy with infliximab was initiated in August 2016. After 1.5 months induction therapy severe acne vulgaris with purulent content presented on her face. Patient was consulted with a dermatologist, positive culture of coagulase-negative Staphylococci was determined and per oral treatment with sulfamethoxazole-trimethoprim 960 mg twice a day and local cream methylprednisolone aceponate was prescribed. Due to unsuccessful treatment results therapy was changed on per oral doxycycline 100 mg once a day for 15 days. Infusion of infliximab was delayed for 2 weeks and azathioprine was cancelled.

After positive treatment effect biologic therapy was continued with infliximab. Six months after control colonoscopy was performed and showed proctitis (Mayo 1).

Conclusion: Case report presented a rare skin reaction acne vulgaris after infliximab therapy started. Our data showed a successful treatment outcome with topical corticosteroids and systemic antibiotic therapy without discontinuing or switching the anti-TNF agent.
Are lower levels of fecal calprotectin reassuring in Crohn’s disease patients?

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Introduction: Fecal calprotectin (FC) is a non-invasive marker of intestinal inflammation. Predicting relapse in Crohn’s disease (CD) patients could allow earlier changes in therapy. The aim of this study was to evaluate the role of FC to predict relapse in CD patients in clinical remission at 6 months follow-up.

Methods: CD patients in clinical remission at least ≥ 3 months were included. The first FC sample in the remission period was evaluated and was used as baseline value. The serum C reactive protein (CRP) value in the same period was also evaluated. Relapse was defined as an unexpected escalation in therapy, hospitalization or surgery for active CD. Demographic, clinical variables and time of relapse after FC baseline were evaluated. The accuracy and optimal cut-off FC for predicting clinical relapse at 6 months was assessed by the area under the ROC curve (AUC).

Results: One hundred forty-four patients were evaluated, with mean age of 38.4 years, 54.2% were female. Of those patients, 13 (9%) relapsed during follow-up, mean time of relapse of 115 ± 47.2 days after FC sample. There was no significant difference of mean CRP values between patients who relapsed from those who did not relapse by 6 months, 7.02 mg/l vs. 4.8 mg/l, p = 0.2. The mean FC was lower for non-relapsers, 203.2 μg/g, than for relapsers, 871.3 μg/g (p < 0.001). The AUC for predict relapse for FC was 0.924. The optimal cut-off of FC value to predict relapse was 327 μg/g with a sensitivity, specificity, negative predictive value and positive predictive value of 92.3%, 82.4%, 99.1% and 34.3%, respectively.

Discussion/Conclusion: FC is a more useful tool to predict remission maintenance than relapse in CD patients in clinical remission. FC ≤ 327 μg/g can exclude relapse at least in 6 months follow-up.
C-reactive protein/albumin ratio is a good predictor of response to intravenous corticosteroids in acute severe ulcerative colitis

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Introduction: Patients with acute severe ulcerative colitis (ASUC) have a high risk of rescue medical therapy or colectomy. The aim of the study was to evaluate the accuracy of CRP/albumin ratio on admission, to predict response to intravenous corticosteroids in patients with ASUC.

Methods: Retrospective assessment of systematically hospitalized patients with first episode of ASUC, who required intravenous corticosteroids. Demographic, clinical, laboratory and endoscopic variables were evaluated on admission. The response to intravenous corticosteroids on day 3 was based on Oxford criteria. In unresponsive patients, rescue medical therapy with infliximab or cyclosporine has been instituted. The accuracy of CRP/albumin ratio in predicting non-response to intravenous corticosteroids was assessed by the area under the ROC curve (AUC).

Results: 51 patients were included, 30 (58.8%) of them female, with a mean age 34.3 ± 14.5 years. Twelve patients (23.5%) required medical rescue therapy. No patient underwent colectomy. The presence of deep ulcers and a shorter evolution of the disease were associated with a lack of response to intravenous corticosteroids, p < 0.001 and p = 0.008, respectively. Patients with no response to intravenous corticosteroids had higher CRP admission values and lower albumin values, compared to patients with response, 111 vs. 67.5 (mg/L), p = 0.028, 2.8 vs. 3.5 (g/dl), p = 0.005, respectively. The CRP/albumin ratio was also higher in unresponsive patients 40.06 vs. 22.14, p = 0.022, showing a good accuracy for predicting no response to intravenous corticosteroids with an AUC of 0.746, p = 0.01.

Discussion/Conclusion: A high value of CRP/albumin ratio was significantly associated with the absence of response to intravenous corticosteroids, at the 3rd day of treatment. This index may allow a better risk stratification on admission, of patients with acute severe ulcerative colitis.
Surgical aspects of Crohn’s disease

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Introduction: Surgical treatment is indicated for disabling and/or complicated Crohn’s disease (CD). However, surgery is not curative and most patients develop post-operative recurrence (POR). Our purpose was to study the characteristics of operated patients and determine predictive factors of POR.

Methods: We collected all patients operated for CD during the period between January 2012 and August 2017. We have determined their epidemiological, clinical, evolutionary features and predictive factors of POR.

Results: Our study included 50 patients. The average age at the time of surgery was 32.6 years (19–69). The sex ratio was 1.8 (32 men and 18 women). Twenty-three patients (46%) were smokers. The location of CD was ileal in 28 cases, Ileocolic in 20 cases and colic in 2 cases. Extraintestinal manifestations were found in 18 patients (36%). The indications of surgery were: symptomatic stenosis in 43 cases (86%), severe acute colitis in 4 cases and intra-abdominal abscess in 3 cases. Surgical interventions performed were ileocecal resection in 40 patients (80%), right hemicolectomy in 6 patients and subtotal colectomy in the 4 patients with severe acute colitis. Operative follow-up was simple in most patients, 3 patients had postoperative peritonitis by anastomotic lacing and a patient who died after a pulmonary embolism. After an average follow-up period of 31 months (6–84), 18 patients (36%) presented POR. Sixteen patients progressed well under medical treatment and two patients required a second intestinal resection. The factors significantly associated with POR were the absence of Azathioprine as preventive treatment of POR (p = 0.04) and the presence of extra-intestinal manifestations (p = 0.02).

Discussion/Conclusion: In our series, the POR rate was 36%. Predictors of this recurrence were the absence of azathioprine as preventive treatment of POR and the presence of extra-intestinal manifestations.
Appendiceal Crohn’s disease presenting as acute appendicitis

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Introduction: Crohn’s disease limited to the appendix was described for the first time in 1953 by Meyerding and Bertram. Since then, fewer than 180 cases have been reported in the literature.

Methods: We report a new observation of appendiceal Crohn’s disease presenting as acute appendicitis.

Results: This is a 47-year-old patient with no particular history presenting with abdominal pain evolving for 3 days without fever or transit disorder. On clinical examination, the patient was in good general condition, subfebrile at 37.7°C with a defense of the right lower quadrant. There was leukocytosis at 12000 elements/mm³ and an increased C-reactive protein. The abdominal ultrasound showed an acute appendicitis complicated by abscesses. The patient was operated on Mac Burney’s right iliac tract. The intraoperative examination revealed the presence of swollen appendix. The ileum and colon were normal. Appendectomy was performed. Anatomopathological examination of the operative specimen revealed a fibroinflammatory and granulomatous remodeling of the appendiceal wall with a fistular pathway bordered on both sides by a granulation tissue and a sclerolipomatosis in the subserosa leading to the diagnosis of appendiceal Crohn’s disease. The patient remained asymptomatic with a follow-up of one year.

Discussion/Conclusion: Crohn’s appendix is more indolent than Crohn’s disease of the ileum or colon. Appendectomy alone is curative in the majority of cases.
Surgical treatment in Crohn’s disease

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Introduction: Despite considerable advances of medical treatment in Crohn’s disease (CD), surgery continues to be necessary for the majority of patients. The aim of our study was to determine the main factors predictive of surgery in CD.

Methods: We conducted a retrospective study collecting all CD patients admitted in our department between January 2012 and June 2017. We have determined their epidemiological, clinical and therapeutic characteristics in order to identify predictive factors of surgery.

Results: Our study included 37 patients. Their mean age was 33 years (16-70) and the sex ratio was 1.17 (20 men and 17 women). Eighteen patients (48.6%) were smokers. The localization of the CD was ileocolic in 15 cases (40.5%), colic in 14 cases (37.8%) and ileal in 8 patients (21.6%). Anoperineal lesions were associated in 4 cases. Extraintestinal manifestations were found in 10 patients (27%). CD was stenosing in 10 patients, fistulizing in 4 patients and stenosing and fistulizing in 6 cases. Maintenance treatment was mesalazine in 8 patients, azathioprine in 23 patients and/or Anti-TNF in 6 patients. Surgery was performed in 15 patients (40%) with a mean delay of 38.1 months between the diagnosis of CD and surgery. The main surgical indications were: symptomatic stenosis in 12 cases (80%), severe acute colitis in two cases and intra-abdominal abscess in one case. Surgical treatment was significantly associated with young age at diagnosis of CD (< 30 years) (p = 0.04), ileocolic localization (p = 0.027), stenosing (p = 0.02) and fistulizing phenotype of CD (p = 0.001).

Discussion/Conclusion: In our study, Surgery was performed in 40% of patients. Predictive factors of surgery were young age at diagnosis of CD, ileocolic localization, stenosing and fistulizing phenotype.
Appendectomy in Crohn’s disease: Is it a risk factor or a mis-diagnosis?

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Introduction: The relationship between appendectomy and Crohn’s disease (CD) is still debated. Increased incidence of CD after an appendectomy may result from a diagnostic problem. Also, involvement of appendix is followed by subsequent involvement of other intestinal segments. The aim of our study was to determine the epidemiological clinical and morphological characteristics of patients operated for acute appendicitis (AA) and presenting histologic signs of CD.

Methods: This is a retrospective study collecting all patients operated for AA between January 2014 and September 2017 and showing signs of CD in histopathologic examination of the resected specimens.

Results: Among 900 appendectomies performed, 18 patients (2%) had histological signs of CD. They were 10 men and 8 women with average age of 39 years. All patients presented with acute pain of the right lower quadrant evolving between 1 and 3 days without transit problems. Fever was present in 5 patients (28%). Twelve patients had a biological inflammatory syndrome. Uncomplicated AA was confirmed by imaging in 13 cases showing a swollen appendix. In the other 5 cases, an appendiceal abscess was suspected. Intraoperative examination showed a phlegmous appendix in 8 cases and an appendiceal abscess in 2 cases. The appendix was macroscopically normal in 8 cases, however, terminal ileum was abnormal with inflammatory aspect in 2 patients. These patients had an ileocecal resection. An appendectomy was performed in all the other patients. Histological examination of the appendectomy specimen found sclero-lipomatosis in 11 cases, chronic inflammatory infiltrate of the appendicular wall in 4 cases and appendiceal Crohn’s disease in 1 case. The diagnosis of ileocecal CD has been retained on the two ileocecal resections.

Discussion/Conclusion: Although typical clinical presentation of acute appendicitis, histological findings may be atypical. CD is the main differential diagnosis.
Is transabdominal ultrasonography as effective as CDAI and MR enterography in Crohn’s disease?

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Introduction: Transabdominal ultrasound is useful both in diagnosing Crohn’s disease (initial diagnosis) and follow up of the disease course and treatment by evaluating bowel wall thickness and extent and localization of involved bowel segments. It also detects the extraluminal complications such as ileus, fistula, and abscesses. In this study we have aimed to find out if transabdominal ultrasound is as effective as MR enterography in determining the course of the disease.

Methods: Twenty five patients with ileocolonic Crohn’s disease receiving immuno-modulator treatment or biologics were investigated by transabdominal ultrasonography simultaneously with MR enterography on the same day. Crohn’s Disease Activity Index (CDAI) was calculated on the same day as well.

Results: We have found that wall thickness was significantly higher in active disease with CDAI > 150 compared (5.8 ± 2.7 mm) to inactive disease (4 ± 2.2 mm) (p < 0.001). By comparing the results of MR enterography the sensitivity and specificity for detecting fistulas were 70% and 95%, for detecting abscesses were 85% and 100%.

Discussion/Conclusion: Transabdominal ultrasonography is a reasonably cheap and effective technique with good concordance with clinical symptoms and MR enterography.
First experiences with vedolizumab therapy in a Croatian tertiary center

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Introduction: Vedolizumab is a monoclonal antibody against α4β7 heterodimer on leukocyte surface that selectively inhibits gut leukocyte homing. It is an effective therapeutic option in patients with ulcerative colitis and Crohn’s disease, with a good safety profile. Aim of this study is to present our first data on vedolizumab therapy in our IBD patients.

Methods: We retrospectively collected data of patients who received vedolizumab at the Department of Gastroenterology and Hepatology of Clinical Hospital Center Osijek from May 2016 till the end of November 2017. Data on diagnosis, disease duration, previous therapy, previous surgical procedures, duration of vedolizumab therapy, response and adverse events were collected.

Results: During observed period, 21 of our patients received vedolizumab, 13 patients with Crohn’s disease and 5 patients treated for ulcerative colitis. Three patients were treated for refractory pouchitis. Six patients (29%) were anti-TNF-naïve and 15 patients (71%) received one or more anti-TNF drugs in prior therapy. Only five patients had disease duration prior to therapy of less than 5 years. Two patients did not respond to the induction therapy and 17 (81%) had clinical remission after the induction period. Sixteen patients (76%) were still in remission at the time of data collection (median follow-up period was 9 months; min. 2, max. 15 months). Of adverse events, two patients had urticaria (after which the drug was stopped) and one patient had CMV colitis.

Discussion/Conclusion: Even in our difficult to treat group of patients (anti-TNF experienced and with long disease duration), vedolizumab showed to be an effective and safe therapeutic option.
Can we predict the adverse reactions in patients with inflammatory bowel disease treated with azathioprine?

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Introduction: Azathioprine (AZA) as an immunosuppressive drug has proven benefit, but adverse reactions (AR’s) such as hepatotoxicity, bone marrow suppression and aphtous ulcers can often limit its use. Thiopurine methyltransferase enzyme (TPMT) metabolize AZA to inactive metabolites which are responsible for the drug related toxicity.

The aim of this study was to investigate the correlation between TPMT enzyme activity and registered AR’s in patients with IBD treated with AZA.

Methods: Seventy-one patients with IBD, treated with AZA were included. A blood sample (3 ml) of all patients was taken to determine TPMT enzyme activity using ELISA method. TPMT enzyme was classified as low enzyme activity (< 5.0 U/ml Er), intermediate (5.0–13.7 U/ml Er) and high enzyme activity (> 13.8 U/ml). Possible AR’s were registered.

Results: Analyzing the TPMT enzyme activity and patients where AR’s were registered, the results have shown that patients with AR’s had significantly lower mean value of TPMT enzyme when compared with patients without AR’s [13.96 U/ml Er ± 8.69 U/mL Er (min. 3.72 U/ml Er, max. 24.56 U/ml er) vs. 18.43 U/ml Er ± 7.22 U/ml Er (min. 5.26 U/ml, max. 35.82 U/ml)] (p = 0.0001). Most of the patients with AR’s belonged to the group of low TPMT enzyme activity (50%), following the group with intermediate activity (18.38%) and the group with high enzyme activity (15.38%).

Discussion/Conclusion: Our results suggests that reduced TPMT activity brings a greater risk of AZA related AR’s. Screening of TPMT enzyme activity should be considered before AZA administration, so the dose of AZA can be adjusted and the AR’s can be avoided.
Clinical aspects of microscopic colitis

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Introduction: It may sometimes be difficult to diagnose microscopic colitis because of the sparseness and lack of specificity of its symptoms and because of the need to carefully detect histological alterations. At times, until a correct diagnosis is achieved, the clinical modifications may be conducive to a different diagnosis. Depending on the symptoms’ severity and persistence, the treatment requires adjustments which may increase the quality of the patient’s life.

Aim: In 5 patients diagnosed with microscopic colitis, we have analyzed the potential causes of the emergence of the disease, the coexistence of autoimmune diseases and the response to treatment.

Results: Out of the 5 patients, 4 (80%) were female and 1 (20%) was male. The mean age of the disease emergence was 63 years. Clinically, in 3 patients, the symptoms consisted of diarrheic stools (> 3/day) and intermittent abdominal pain. In the other 2 patients, the symptoms were minimal and inconclusive. The histopathological diagnosis revealed lymphocytic colitis in 3 patients, collagenous colitis in 1 patient, while in the case of 1 patient, microscopic colitis was unclassifiable. 2 patients had used NSAIDs for more than 6 months. In the case of 4 patients the pre-existing diagnosis had been of irritable bowel syndrome. No associated autoimmune disease was identified.

The mild or average forms only required anti-diarrheic, anti-spastic treatment, the interruption of the treatment with NSAIDs and the interdiction to use medication prone to cause microscopic colitis.

Conclusions: Histological modifications are crucial in diagnosing the various types of microscopic colitis, given the fact that the symptomatology is non-specific and the potential causes are difficult to identify or to assess. The irritable bowel syndrome may hide or precede the development of certain forms of microscopic colitis. The average forms of the disease only benefit from the standard treatment and from the cessation of the use of medication potentially inductive of this disease.
Challenges in patients with ulcerative colitis and primary sclerosing cholangitis

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Introduction: The association between primary sclerosing cholangitis (PSC) and the inflammatory bowel diseases is well-known. PSC occurs more frequently in cases of patients with ulcerative colitis than in the case of patients with Crohn’s disease. The comorbidity between primary sclerosing cholangitis and ulcerative colitis increases the risk of digestive cancers.

Material and methods: From September 2007 to September 2017, we followed 37 patients with ulcerative colitis and 17 patients with Crohn’s disease. The characteristic evolutionary features we had in view were the emergence of certain hepatobiliary diseases (mainly PSC) and the potential development of digestive cancer, taking into consideration the fact that both inflammatory bowel diseases and hepatobiliary diseases (PSC) show high risk of malignancy. Characteristics regarding family history and epidemiological and clinical characteristics were analyzed in patients who showed an association of an inflammatory bowel disease and PSC.

Results: Out of the 37 patients with ulcerative colitis, 3 (8.1%) were also diagnosed with PSC during the follow-up period. Two of these were male and one was female. No patient with Crohn’s disease was diagnosed with primary sclerosing cholangitis disease during this decade. In the case of one patient with ulcerative colitis, the biliary disease appeared almost at the same time as the inflammatory bowel disease, and in the case of the other two patients, PSC appeared within 3 and 5 years, respectively, since the onset of the inflammatory bowel disease. We found no evidence of family history in those patients with ulcerative colitis who were afterwards diagnosed with PSC.

We found clinical similarities in the three patients with ulcerative colitis and PSC: the colonic affection was more obvious on the right side, with backwash ileitis, and the clinical evolution of the inflammatory bowel disease was mild.

In the case of only one patient, who was older and had a longer evolution of the hepatobiliary disease, a cholangiocarcinoma appeared, while to date the evolution of the other patients has shown neither malignancy, nor hepatobiliary or colonic complications. The evolution of ulcerative colitis in the patient who developed cholangiocarcinoma was not altered and did not require a change of medication when the intestinal bowel disease was active. Chemotherapy was inefficient and survival after diagnosing the malignant disease was of for months.

It was only in the case of one male patient with primary sclerosing cholangitis that a severe episode of inflammatory disease activity required treatment with Prednisolone. We avoided resorting to immunosuppressive therapy, which is known to increase the risk of emergence of certain malignancies.

Conclusions: One patient developed malignant complications, but neither did they require a change of treatment nor did they alter the clinical evolution of the inflammatory bowel disease. In the case of the male patient with ulcerative colitis and primary sclerosing cholangitis, a severe episode of inflammatory bowel disease was not treated with immunosuppressants because of the augmented risk of malignancy emergence.
What factors affect the processes of fibrosis in pediatric inflammatory bowel diseases?

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Introduction: Factors of fibrosis: YKL-40/CH3L1 (glycoprotein with a mass 40 kilodaltons) and PIIINP (procollagen III N-terminal propeptide) are predicting the occurrence of fibrosis. The aim of the study was to determine the association of fibrosis with variable factors such as: Pediatric UC Activity Index-PUCAI, Pediatric CD Activity Index-PCDAI, Mayo Endoscopic Score for UC-MES UC, Simple Endoscopic Score for CD-SES CD, range of lesions (Paris classification: ileal – L1, colonic – L2, ileocolonic – L3, perianal-P for CD, left colitis vs. pancolitis) and treatment (5-ASA, steroids, AZT).

Methods: In 66 patients (21 with ulcerative colitis – UC, 45 with Crohn’s disease-CD, median age for UC: 15.7 years, for CD: 13.5 years). Concentrations of YKL 40/CH3L1 and PIIINP were measured at baseline (day 0), after 3 weeks of treatment and after 6–8 weeks of treatment.
YKL40/CH3L1 and PIIINP serum concentration was estimated by ELISA tests (Metra YKL40 by Quidel, PIIINP by USC Wuhan Science Ltd). A statistical analysis of the correlation was carried out.

Results: PIIINP concentrations were significantly higher in children with CD compared with children with UC (baseline results: median concentrations 1013.73 vs. 78.30 ng/ml; p = 0.06 for the Kruskall-Wallis test; results at 6–8 weeks: 1076.48 vs. 53.10 ng/ml, p = 0.01).
Fibrosis was clearly present in patients with CD and its severity increased (reflected by both YKL-40/CH3L1 and PIIINP concentrations) in 6–8 weeks of follow up. In patients with UC the patterns of YKL-40/CH3L1 and PIIINP concentrations were different. The levels were lower and further decreased (median YKL-40/CH3L1 concentration was 39.5 ng/ml at baseline, and 24.7 ng/ml after 6–8 weeks; median PIIINP concentration was 78.3 ng/ml at baseline and 53.1 ng/ml after 6–8 weeks).
At 8 weeks of follow-up, there was no statistically significant correlation between YKL40/CH3L1, PIIINP concentrations and: PUCAI, PCDAI, SES-CD, MES-UC. There were no significant correlations between the concentration of the factors of fibrosis and the location of lesions in the CD (L1, L2, L3, P), the exception for YKL 40/CH3L values measured at week 3 of treatment which differed for CD L2 patients (median: not L2 - 29 ng/ml vs. L2- 69 ng/ml, p = 0.012). There were no significant correlations between the concentration of the fibrosis factors and the range of lesions in UC (pancolitis vs. left side colitis). The exception was the PIIINP concentration measured at week 3 of treatment with significantly higher level in pancolitis (median: 259 ng/ml vs. 24 ng/ml, p = 0.018).
Also treatment (with exclusion of anti-TNF-α and exclusive enteral nutrition patients) during the observation period did not significantly affect the concentration of the fibrosis factors.

**Discussion/Conclusion:** In patients with CD fibrosis was severe and no significant changes in its course were found in the first weeks of treatment. In patients with UC fibrosis seemed to be of low intensity and its severity decreased during several weeks of treatment. Neither clinical manifestations of the disease, nor the severity of endoscopic lesions, or the type of treatment used have been shown to have a significant effect on fibrosis. However, some trends were noted for increased fibrosis in CD with involvement of the colon and CU with pancolitis.
Sleep impairment and inflammatory bowel disease activity

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Introduction: Our aim was to examine the role of sleep impairment on risk of relapse in inflammatory bowel diseases (IBD).

Methods: Our study included 75 patients with Crohn’s disease (CD) and 75 patients with ulcerative colitis (UC) in remission. Sleep quality was measured using the Patient Reported Outcomes Measurement Information Systems sleep disturbance questionnaire. Logistic regression was used to examine the effect of sleep quality at the beginning of the study on risk of active disease at 6 months.

Results: CD patients with impaired sleep had a 2-fold increase in risk of active disease at 6 months (adjusted odds ratio, 2.10; 95% confidence interval, 1.39–2.72); however, no effect was observed in patients with UC (odds ratio, 1.02; 95% confidence interval, 0.71–1.82).

Discussion/Conclusion: Sleep impairment was correlated with an increased risk of disease exacerbations in CD but not UC.
The role of *Helicobacter pylori* eradication on disease activity measures in patients with Crohn’s disease

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**Introduction:** *Helicobacter pylori* (H. pylori) is one of the most successful human pathogens. The virulence of different strains of *H. pylori* is associated with increased local inflammation and severe tissue damage. The aim of our study is to assess the prevalence of *H. pylori* in patients with Crohn’s disease (CD) and to establish the role of eradication on disease activity measures.

**Methods:** We have conducted a single-center clinical retrospective study. 130 patients (male/female: 43/87; mean age: 47.3) with biopsy confirmed CD were included. Demographic, clinical characteristics and laboratory findings were retrieved from medical records. Clinical disease activity index (CDAI), full blood count, C-reactive protein (CRP) and fecal calprotectin (FC) were performed for each patient. *H. pylori* stool antigen test was used for diagnosis and eradication confirmation. Patients infected with *H. pylori* received eradication treatment with sequential therapy. Exclusion criteria were: recent use of antibiotics within the past 2 months, recent use of H₂-receptor antagonists, bismuth or proton pump inhibitor therapy within the past 2 weeks. The role of *H. pylori* eradication on disease activity measures was assessed.

**Results:** Based on our findings, the prevalence of *H. pylori* in CD patients was 21.5% (male/female: 10/18; mean age: 43.6). After 4 weeks of sequential therapy, 100% eradication rate was achieved. 8 weeks after eradication confirmation, there were no statistically significant changes in FC (before: FC = 86 ± 83.5 µg/g; after: FC = 78 ± 73.4 µg/g; p = 0.6), serum levels of CRP (before: CRP = 1.9 ± 0.7 mg/dl; after: CRP = 4.3 ± 3.7 mg/dl; p = 0.05) and CDAI score (before: CDAI = 26.1 ± 24.3; after: CDAI = 30.05 ± 26.8; p = 0.01).

**Discussion/Conclusion:** Our study demonstrates that *H. pylori* infection is rather common in patients with CD. In our patients, eradication therapy had no effect on disease activity measures. Further studies are needed to demonstrate if the *H. pylori* eradication therapy trigger or protect against CD.
**TH1 transcription factor T-bet as a new target for Crohn’s disease therapy**

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**Introduction:** Crohn’s disease (CD) is one severe form of inflammatory bowel disease (IBD). By dysregulation of the effector T cell/regulatory T cell balance with a massive involvement of TH1 and TH17 cells, patients show signs of mucosal inflammation mostly localized in the ileum. T-bet is one of the important transcription factors of highly pathogenic TH1 cells that secrete a wealth of inflammatory cytokines like IFN-γ and TNF-α.

**Methods:** To test the contribution of T-bet in the development of CD we analyzed samples of CD patients and healthy controls for T-bet expression. To test T-bet involvement in the experimental colitis model we used conditional T-bet CD4 KO mice and wildtype (WT) littermates and performed a TNBS-induced colitis which simulates CD-like inflammation in mice. The inflammation level was documented via miniendoscopic analyses. The colon was taken out for histological sections and gene expression analyses. Mesenteric lymph node cells were isolated for FACS analyses. Furthermore we tested a tbx21 specific DNAzyme, a catalytically active synthetic DNA antisense molecule, as a therapeutic approach during the TNBS-colitis model.

**Results:** We saw a highly upregulated T-bet expression level in human samples of CD patients compared to samples of healthy controls. Furthermore we detected significantly decreased colonic inflammation in the conditional T-bet CD4 KO mice compared to WT animals during experimental colitis. Mice that received the tbx21 specific DNAzyme also showed decreased susceptibility to TNBS colitis compared to control mice that received either nothing or a control compound.

**Discussion/Conclusion:** Taking these results together T-bet arises as a potential target for a new therapeutic treatment of Crohn’s disease.
Simultaneous presentation of Crohn’s disease in siblings: Genes or environment?

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The aim of the study is to describe simultaneous presentation of Crohn’s disease in two pairs of siblings: two brothers and monozygotic twin sisters. These children developed symptoms in the same time with similar localization and activity of the diseases as well as similar endoscopy findings.

Case 1: Monozygotic twin sisters. At the age of 14 years at the same time following symptoms occurred in both of them: abdominal pain, loss of appetite, weight loss, 2–5 unformed stools containing mucus per day. Laboratory tests showed elevated levels of inflammatory parameters (CRP, OB, platelet count).
Colonoscopy revealed: inflammatory skip lesions in the right colon with many aphthae and linear, deep ulcerations, a change by inflammation and distorted ileocecal valve as well as inflammatory changes in the terminal ileum on a stretch of several centimeters. Histological investigation showed inflammatory changes with forming of epithelial-cell granulomas. Based on the whole clinical picture Crohn’s disease was diagnosed – Paris classification A1b, L1, B1G0.
Disease activity assessed by PCDAI – 52 points. Treatment with budesonide 9 mg/day was started, remission was subsequently sustained with azathioprine (2 mg/kg/day). The girls were qualified for anti-TNF therapy, what allowed to obtain remission.

Case 2: In both boys, at the age of 9 and 12, at the same time abdominal pain, hypochromic anemia and syderopenia occurred. Additionally in both of them elevated inflammatory parameters (CRP, OB, platelet count) as well as positive results of FOBT were found.
Colonoscopy of the older brother revealed an extensive circular ulceration covered with a fibrinous layer and contact bleeding at the entrance to the cecum that constricted the lumen of the bowel. There were signs of edema and many flat aphthae with a fibrinous layer at the mucus membrane in the terminal ileum.
In the younger boy a slightly deformed cecum with a swollen ileocecal valve was revealed that could not be passed. In the ascending colon there were several disseminated ulcerations. Histological findings correspond to ileitis chronica activa erosiva.
Disease activity (PCDAI) was 15 points in the older and 17.5 points in the younger boy. Treatment with budesonide and ASA were introduced. Patients obtained a long-term clinical and biochemical remission. Both are presently treated with azathioprine (2 mg/kg/d).
Approximately half a year after the disease was diagnosed in the brothers, Crohn’s disease was diagnosed in their father.
The results of the newfound Department of Gastroenterology with Endoscopy Unit of Prijedor Hospital

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Introduction: It is estimated that in Bosnia and Herzegovina around 1600 patients suffer from inflammatory bowel disease while in Republic of Srpska around 600 patients suffer from this disease. In April 2017, the Department of Gastroenterology was opened in Prijedor Hospital, for availability of tertiary-level health care for the patients of Prijedor region. The aim of this paper was to analyze the people, at our center, suffering from ulcerative colitis (UC) according to disease extensiveness, age, sex, and determine the correlation of clinical and endoscopic indices of disease activity.

Methods: We have conducted a retrospective study at the Department of Gastroenterology with Endoscopy of Prijedor Hospital. The study included 20 patients, 10 of which were males and 10 were females, the average age was 58.4 and the patients were diagnosed with UC in the period from April to October 2017. All patients had clinical and endoscopic activity index. Truelove & Witt’s severity index was used for the clinical degree of activity, and Baron index was used for the endoscopic degree of activity.

Results: The average age of newly diagnosed patients was 55.6 whereas 45.6 for men and 63.5 for women. 10 patients (50%) were diagnosed with left-sided colitis, 8 patients (40%) had pancolitis, while the disease affected the rectum in 2 patients (10%). The comparison between endoscopic and clinical indices demonstrated no significant differences in illness activity. Endoscopic and clinical disease activity was associated with higher inflammatory parameters (CRP, SE, Le) and lower parameters of hemoglobin (Hb).

Discussion/Conclusion: Patients were most often treated for medium-severe left side colitis, with significantly lower average age in newly discovered males. Our research has established a good correlation between clinical and endoscopic index of disease activity in the UC in inflammation. Clinical indices can be used for monitoring inflammation.
Correlation of fecal calprotectin with endoscopically defined activity index and localization in IBD patients

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Aim: Fecal biomarkers such as calprotectin emerged as a non-invasive diagnostic tool owing to their ability to identify patients with inflammatory bowel disease (IBD), assess disease activity and predict relapse. The objective was to evaluate the diagnostic accuracy of fecal calprotectin (FC) for the assessment of endoscopically defined disease activity and localization in IBD patients.

Methods: Stool samples were collected and assessed for FC levels by CALPRO Calprotectin ELISA test. SES CD for Crohn’s disease (CD) and Mayo endoscopic subscore (MES) for ulcerative colitis (UC) were used for the assessment of endoscopic activity. A total of 39 patients were included, 14 patients with Crohn’s disease and 25 with ulcerative colitis. Correlation analysis was done with Spearman’s rank correlation statistics. For qualitative variables we used chi-square test of independency.

Results: Median (IQR) for FC in UC was 932 (18–2368), and 1074 (100–1933) for CD. We used FC cut-off value 100 µg/g to distinguish active from inactive disease. CD patients had L1, L2 and L3 14.30%, 35.70% and 50% disease localization, respectively. UC patients had disease localization E1, E2 and E3 24%, 60% and 16% respectively. CD endoscopic disease activity was recorded as mild (SES CD 3–6), moderate (SES CD 7–15) and severe (SES CD > 15) at 21.4%, 57.1%, 21.4% patients, respectively. UC disease activity was assessed as mild (MES 1), moderate (MES 2) and severe (MES 3) at 12%, 68% and 20% patients, respectively. There was no significant correlation between SES CD and FC ($\rho$ = 0.175, $p$ = 0.549). Correlation was significant between MES and FC ($\rho$ = 0.443, $p$ = 0.465). For relation between FC and disease localization in CD patients, $\chi^2$ test statistic was 2.333 ($p$ = 0.311 > 0.05), which was not significant, while in UC patients, $\chi^2$ test statistic was 11.611 ($p$ = 0.020 < 0.05), which was significant.

Conclusion: FC correlated significantly with disease localization and endoscopic activity in UC patients, while no significant correlation was found in CD patients. FC could be useful as a non-invasive marker for disease assessment in UC. However, further evaluation of the utility of FC in CD patients is needed.
The selectivity of the neutrophils infiltration in ulcerative colitis may be dependent on the claudin-4 expression

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Introduction: Claudin-4 protein is one of the claudins family member that play the main role in tight junction (TJ). Claudins are present on epithelial membranes of endothelial cells. By limiting the exchange of lipids between the main and basal membranes of endothelial epithelial cells, TJs determine the polarity of the membrane, ensure continuous intercellular seal and regulate paracellular transport of water, solutes as well as immune cells. In patients with inflammatory bowel disease, many cytokines are involved in the regulation of TJ. In these patients the permeability of TJ in the intestinal epithelium for inflammatory cells is increased. Among others, incorrect expression and post-translational modifications of claudins in the intestinal epithelium may play a role in the pathogenesis of inflammatory bowel diseases. Therefore the aim of our study was to evaluate the expression of claudin-4 in correlation with inflammatory cells in ulcerative colitis.

Materials and Method: The study consisted of 22 patients with ulcerative colitis (UC). Endoscopic materials were taken from archival paraffin-embedded tissue. Sections were stained with H & E and subjected to routine histological evaluation. The expression of claudin-4 protein in tissue sections was assessed by immunohistochemical methods. The color reaction was observed in cytoplasmic membrane and cytoplasm of the surface epithelium in villi and of the glandular epithelium of glands. The staining reaction was assessed as % of positive cells with normal cytoplasmic membrane reaction. To visualize inflammatory cells two antibodies was used: CD45 for all leukocytes and CD15 for neutrophils.

Results: Statistical analysis didn’t show a correlation between claudin-4 expression in glandular epithelium in ulcerative colitis and the degree of leukocytes infiltration (CD45+). However, lower cytoplasmic membrane expression of claudin-4 protein in surface epithelium in villi and of the glandular epithelium of glands was occurred in patients with higher neutrophils infiltration in mucosa (p < 0.001 and p < 0.005, respectively).

Conclusion: The tightjunction-mediated paracellular route can be used by inflammatory cells to migrate through biomembranes. The selectivity of the neutrophils infiltration in ulcerative colitis may be dependent on the claudin-4 expression.
Irritable bowel syndrome may be associated with elevated hepatic enzyme and metabolic syndrome

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Aim: Recent studies have revealed close relationships between hepatic injury, metabolic pathways, and gut microbiota. The microorganisms in the intestine also cause irritable bowel syndrome (IBS). The aim of this study was to examine whether IBS was associated with elevated hepatic enzyme (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), gamma-glutamyl transferase (γ-GT) levels, and metabolic syndrome (MS).

Materials and Methods: This was a retrospective, cross-sectional, case-control study. The case and control groups comprised subjects who visited our health promotion center for general check-ups from June 2014 to June 2016. Of the 1127 initially screened subjects, 83 had IBS according to the Rome III criteria. The control group consists of 260 age- and sex-matched subjects without IBS who visited our health promotion center during the same period.

Result: Compared to control subjects, patients with IBS showed significantly higher values of anthropometric parameters (body mass index, waist circumference), liver enzymes, γ-GT, and lipid levels. The prevalences of elevated ALT (16.9% vs. 7.7%; \( p = 0.015 \)) and γ-GT (24.1% vs. 11.5%; \( p = 0.037 \)) levels were significantly higher in patients with IBS than in control subjects. A statistically significant difference was observed in the prevalence of MS between controls and IBS patients (12.7% vs. 32.5%; \( p < 0.001 \)). The relationships between elevated ALT levels, MS, and IBS remained statistically significant after controlling for potential confounding factors.

Conclusion: On the basis of our study results, IBS may be an important condition in certain patients with elevated ALT levels and MS.

Keywords: Irritable bowel syndrome, liver enzymes, metabolic syndrome
Can the inflammatory bowel disease biologics registry lead to improved quality of care?

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Introduction: A registry is a systematic collection of data about a disease or diseases. For some years there has been a desire amongst the gastroenterology community to develop a comprehensive registry of patients with inflammatory bowel disease (IBD). However, there has been no coordinated national approach. In this study, we will review the grounds behind setting an IBD registry; suggest a methodological approach, and the ways to maintain its continuity.

Methods: We searched the PubMed, Embase and PsycINFO databases for articles describing the development and/or evaluation of one or more of the registries in IBD. We assessed these registries using a standardized checklist.

Results: There have been several registries of biological therapy in Crohn’s disease like TREAT registry for Infliximab®, Registry study for Adalimumab®, the Rotherham IBD management software, and the Inflammatory Bowel Disease Information System (IBDIS). The British Society of Paediatric Gastroenterology Hepatology and Nutrition (BSPGHN) has established a registry of paediatric IBD in late 1990s but it was only maintained for a few years. Recently the UK IBD registry was established following the second round of the UK IBD audit, and the launch in Feb 2009 of the National IBD Service Standards.

Discussion/Conclusion: In summary, having a successful IBD registry will ensure efficient patients monitoring and follow up. It will also support data collection for audit and research purposes. However, any registry should be tailored for individual users’ needs to ensure their engagement and participation. A few difficulties associated with setting a wide IBD registry may include lack of clinicians’ participation or interest, costs related to setting and maintaining the registry, providing enough time to use the registry and data quality assurance.
Systematic review of the clinical disease severity indices for inflammatory bowel disease

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Introduction: Clinical disease severity indices are increasingly being used in choosing treatment and monitoring response of patients with inflammatory bowel disease (IBD). Our aim is to systematically review the clinical disease severity indices in IBD and to appraise their measurement properties and methodological quality.

Methods: We searched the PubMed, Embase and PsycINFO databases for original articles describing the development and/or evaluation of one or more of the measurement properties of clinical disease severity used in IBD. We assessed these properties (e.g., internal consistency, reliability, validity, responsiveness) using a standardized checklist.

Results: We examined the full text of 142 articles that we deemed potentially eligible and identified 22 clinical disease severity indices in IBD. No clinical disease index has met all the required measurement properties. All of the validation studies were not descriptive enough to allow assessment of their methodology.

Discussion/Conclusion: Although commonly used in multiple clinical trials, none of the clinical disease severity indices in IBD had all the required measurement properties. Further validation studies are required.
Paradoxical reaction to anti-tuberculosis therapy in a patient with disseminated tuberculosis under infliximab

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Introduction: The increased risk of Mycobacterium tuberculosis infection in patients exposed to inhibitors of tumor necrosis factor alpha (anti-TNF-α) is known. Discontinuation of these drugs in active tuberculosis may be associated with paradoxical worsening of symptoms as result of an inflammatory immune reconstitution syndrome.

Clinical case: We present a case of a 26-year-old man with Crohn’s disease diagnosed in 2009, under azathioprine since January/2010 and infliximab since July 2012. Latent tuberculosis screening was negative before starting each treatment. In December 2012, went to emergency department for fever, productive cough and hyperhidrosis. Pancytopenia and CRP 123 mg/l. Normal chest radiograph. He was diagnosed with respiratory infection and discharged with azathioprine suspension and levofloxacin. In January 2013, days after infliximab perfusion, developed headache, neck pain, fever, vomiting and weight loss. Lymphopenia and CRP 6 mg/l. Normal cranioencephalic CT. Lumbar puncture suggestive of meningitis with mononuclear pleocytosis. Thoraco-abdominopelvic CT with mediastinal and retroperitoneal adenopathies, lungs with diffuse reticulo-nodular interstitial pattern, spleen with heterogeneous nodular mass and hepatomegaly with micronodules. Cerebrospinal fluid (CSF) immunophenotyping not suggestive of lymphoproliferative disease. Began empirical antibiotic, antiviral and anti-tuberculosis therapy. Later M. tuberculosis was detected in Ziehl-Neelsen and in cultures of bronchoalveolar lavage and CSF. Clinical worsening with hydrocephalus and infectious vasculitis of the CNS treated with corticosteroid therapy for 7 months. Months later, new thoracoabdominal adenopathies and epididymal nodule were detected. Histology revealed bacillary granulomas, however with negative cultures. Due to clinical improvement and negative cultures for M. tuberculosis, these changes were assumed to be an immune reconstitution syndrome due to the discontinuation of infliximab. He resumed steroid therapy with a favorable response.

Discussion/Conclusion: The present case illustrates an uncommon complication of anti-TNF-α therapy: disseminated tuberculosis with meningeal-encephalic, pulmonary, hepatic, splenic, lymph node and genital involvement. Rarer is the paradoxical reaction associated with anti-TNF-α suspension, expressed by inflammatory resurgence despite microbiological improvement.
A non-treated Crohn’s disease flare during pregnancy: The impact of perianal disease

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Women admitted with a primary Crohn-related diagnosis during pregnancy have a quite unpredictable and poor outcome. Associated perianal disease may be an even bigger approach challenge.

Authors report case of a 23 year-old pregnant (20-week) woman with ileocolic non-treated Crohn’s disease (CD; diagnosis in Poland, 2016). Being a resident in Portugal for 5 months, patient was referred to IBD outpatient clinic for abdominal pain, up-to 30 bowel movements/day and significant weigh loss (5 kg in 1 month). Objectively there was pale skin, right-quadrant abdominal tenderness (10 cm plastron), 2 perianal abscesses. Blood tests showed low iron anaemia, low albumin and elevated inflammatory markers. Enteral magnetic resonance without gadolinium was performed showing an ileocolic extension and a fistulizing perianal complex disease with a perianal abscess. At the ward, clinical remission therapy was attempted with double antibiotic therapy (Cefuroxime and metronidazole), exclusive enteral nutrition and abscess surgical drainage and in situ seton placement. Clinical and analytical response was quick and evident and patients weigh was recovered. Obstetrician repeated evaluations were also favorable which was extremely important to deal with patient’s anxiety. In the meanwhile, an anergic tuberculin test was documented and patient was started on anti-TNF at the 14th ward day and was discharged the day after (being 22-week pregnant) kept on antibiotic monotherapy (metronidazole) and enteral nutrition only.

This case’s interest is twofold: Points out the therapeutic challenge of a perianal disease presentation in a foreign pregnant woman with a never-treated ileocolic CD; highlights the need for a multidisciplinary (Gastroenterology, Radiology, General Surgery, Nutrition, Obstetrics) approach for adequate treatment and disease coping.
Sustained deep remission with intermittent low-dose rifaximin schema for antibiotic-dependent pouchitis – A 2-year open-label study data

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The recommended probiotic mixture for chronic/antibiotic-dependent pouchitis (PouchitisAB) maintenance therapy was off Portuguese market. This led to alternative therapies searches.

**Aims:** To verify compliance, safety and efficacy of Rifaximin schema for maintenance therapy in pouchitisAB.

**Methods:** Observational interceptive (2015–2017) study of pouchitisAB patients (PDAI-baseline > 7). Induction therapy was first performed with antibiotic monotherapy (ciprofloxacin 500 mg bid or metronidazole 500 mg 3id) and patients were then started on rifaximin schema for maintenance therapy (200 mg 2id, 1 week; 200 mg/day, 1 week; 200 mg eod, 2 weeks; 200 mg 2 times/week, 4 weeks; 4-week pause (optional); retake on 200 mg 2 times/week, 4 weeks; 4-week pause, and so on). Demographical and clinical patient characterization and outcome evaluation: Compliance, safety concerns and efficacy [clinical remission (PDAI < 7 or PDAI-baseline decrease in 3 points), endoscopic (PDAI-baseline endoscopic subscore decrease in 2 points) and histological (PDAI-baseline histological subscore decrease in 2 points)] at week 6–8, 24–26 and 50–52. Fecal calprotectin measurement was also performed at the same timepoints. Statistics: T-student test.

**Results:** 4 patients were studied (3 men; mean age 53 ± 21.9 years old) on Rifaximin schema for maintenance therapy for a mean follow-up time of 23 months (14–29). 100% compliance was verified and 2 cases of perianal dermatitis were reported. Every patient fulfilled clinical and endoscopic remission criteria at the timepoints. A statistically significant variation was checked for the initial and final histological PDAI subscore (p = 0.002 < 0.05; 95% CI: 3.23–6.27) and histological remission was checked for all patients. The mean fecal Calprotectin measure was significantly superior during the active pouchitis episode compared to the maintenance therapy period (5154 vs. 235 vs. 213 vs. 149: p = 0.002).

**Conclusion:** Rifaximin appears as a safe, workable and effective option for pouchitisAB maintenance therapy. Histological remission ensures the therapy’s deep remission outcome. Non-invasive monitoring with fecal calprotectin during the maintenance therapy period may be a strategy.
Extraintestinal manifestations of Crohn’s disease and its clinical features among patients in Split-Dalmatia County, Croatia

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Introduction: Patients with Crohn’s disease (CD) frequently express clinical symptoms resulting intestinal and extraintestinal manifestations (EIMs). The EIMs can involve almost every organ system, particularly the skin, joints and eyes. EIMs tend to follow the clinical course of CD. The aim of this study was to investigate the EIMs appearance and clinical features (gender, localization, phenotype and activity of disease) in patients with CD.

Methods: All CD patients were assessed, regarding afore-mentioned characteristics. We had firstly defined portion of CD patients expressing EIMs, then we compared EIMs expressing group to non-EIMs expressing group of patients according to gender, disease localization, phenotype and disease activity.

Results: There were 216 patients diagnosed with CD in Split-Dalmatia County, 37 among them with EIMs. There were 50% more women in EIMs group then in non-EIMs group (X² = 5.1, p = 0.023). Odds for expressing EIMs were 2.4 times higher in women than in men (95% CI: 1.2–5.1; p = 0.016). As for disease localization, there was no significant correlation between EIMs expression and small intestine localization (X² = 0.200; p = 0.655) nor ileocolonic (X² = 2.4; p = 0.119). Portion of patients with colonic disease localization was 1.7 times higher in EIMs group (X² = 6.6; p = 0.010). Odds for expressing EIMs were 2.7 higher with colonic disease localization (95% CI: 1.3–5.6; p = 0.07). Disease activity and phenotype were not significantly correlated with EIMs expression.

Discussion/Conclusion: Female gender and colonic localization of the disease appear to be predictors of development of EIMs in CD patients.
The severity of endoscopic lesions in ulcerative colitis: Between the assessment of endoscopist and the Ulcerative Colitis Endoscopic Index of Severity score

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Introduction: There is a huge variability in the description of lesions and in the assessment of their endoscopic severity during relapses of ulcerative colitis (UC). The Ulcerative Colitis Endoscopic Index of Severity (UCEIS) has recently been validated to homogenize the description of lesions in a reproducible way, allowing the standardization of endoscopic reports and consequently to codify the management. The aim of our study is to evaluate the interindividual variation in the evaluation of the severity of lesions and to compare it with the UCEIS score.

Patients and methods: A retrospective study including patients treated for UC and had a lower gastrointestinal endoscopy in the Department of Gastroenterology of Sahloul between January 2016 and August 2017. The UCEIS score was calculated, assigning values of 0 to 8 corresponding to lesions of increasing severity, then compared to the evaluation of the endoscopist.

Results: Eighty-three lower gastrointestinal endoscopies were performed for 63 patients. The mean age was 42.5 years with a sex ratio of 0.89. The indication of exploration was dominated by a relapse in 63.9% of cases. Of the 63 examinations with an UCEIS score ≥ 6, 65.1% were judged by the endoscopist as a moderate activity disease, 15.9% severe and severe acute colitis in 6.3% of cases. In addition, for a maximum score of 8, in the presence of different operators, this activity was considered moderate in half of the cases, severe and severe acute colitis in 25% of cases respectively.

Conclusion: In our study, the endoscopist’s evaluation underestimated the severity of lesions in 77.8% of cases and overestimated it in 6% of cases. This prompts us to adopt the UCEIS score, which is a reproducible tool for endoscopic assessment of UC and has the advantage of giving objective results that can be compared with those obtained during subsequent endoscopies.
Correlation between Crohn’s Disease Activity Index and the severity of disease flare-up

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Introduction: Several clinico-biological indices have been advanced to evaluate the severity of Crohn’s disease (CD) flare-up, but only the Crohn’s Disease Activity Index (CDAI) has been validated. This study aims to evaluate the contribution of the CDAI in assessing the severity of the flare of CD.

Methods: We report a retrospective comparative study from January 1998 to December 2012, including 151 patients suffering from CD. The patients were divided into four groups (Gpes): Gpe 1 (CDAI < 150: n = 54), Gpe 2 (CDAI between 150–350: n = 84), Gpe 3 (CDAI between 350 and 450: n = 10), Gpe 4 (CDAI > 450: n = 3).

Results: In univariate analysis, a statistically significant difference between groups was found in the necessity of oral corticosteroid to induce remission (Gpe 1: 22%; Gpe 2: 85%; Gpe 3: 90%; Gpe 4: 0%) (p = 0.000) and the use of intravenous corticotherapy (Gpe 1: 3.7%; Gpe 2: 59%; Gpe 3: 80%; Gpe 4: 100%) (p = 0.000). No statistically significant difference was found between groups with respect the indication of surgery for a complicated CD or a severe flare-up with medical therapies failure (Gpe 1: 29.62%; Gpe 2: 36%; Gpe 3: 50% and Gpe 4: 66%).

Conclusion: In the group of patients with quiescent or mild-to-moderate disease according to CDAI, the necessity of corticosteroid therapy and surgery was common. This highlights that this index may underestimate disease activity.
Azathioprine and Crohn’s disease: Efficacy and tolerance

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Introduction: Immunosuppressive agents, and especially azathioprine, are indicated for chronic active, steroid-dependent or steroid-refractory Crohn’s disease (CD), following a severe relapse and for the prevention of postoperative recurrence in moderate to high-risk patients.

Purpose: To describe and analyze the different indications, efficacy and tolerability of azathioprine treatment during CD.

Patients and methods: A 12-year retrospective study including all patients taking azathioprine at a dose of 2 to 2.5 mg/kg/day.

Results: Fifty-two patients were included, divided into 26 men and 26 women, with a mean age of 30.29 years (9–93). Azathioprine was indicated for steroid-dependence (n = 11 [21.2%]), steroid-refractory CD (n = 1 [1.9%]), chronic active disease (n = 10 [19.6%]), for prevention of postoperative recurrence (n = 16 [30.8%]) and after a severe relapse (n = 14 [26.5%]). Remission was observed in 75% of cases. For medium-term outcomes, relapse under azathioprine was noted in 25% of patients initially put in remission, with an actuarial relapse rate of 13.5% at 1 year, 7.7% at 5 years, 1.9% at 10 years and 1.9% after 10 years. The use of systemic corticosteroid was necessary in 7.69% of cases, anti-TNF (indicated for intolerance or failure) in 25% and surgery in 11.5%. Most of patients tolerated well the treatment (78.8%), and 11.15% had presented with complications dominated by acute pancreatitis (n = 7), acute hepatitis (n = 1), hepatic cholestasis (n = 1) and digestive intolerance (n = 2).

Conclusion: Our study highlights that azathioprine is effective and relatively well tolerated in maintenance therapy for Crohn’s disease. This molecule represents a real therapeutic arsenal.
Predictive factors for a severe clinical course in ulcerative colitis

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Introduction: The evolutionary course of ulcerative colitis (UC) is variable and can be difficult to predict, with symptoms ranging from mild to severe. There is no generally accepted definition of severe UC, and no single outcome is sufficient to classify a disease course as severe.
We have attempted to determine the predictive factors of a severe evolution of UC, which is defined by requiring immunosuppressive drugs, biotherapy or colectomy.

Methods: We studied retrospectively a cohort of 105 patients who were diagnosed with UC and admitted to our clinic over a period of 17 years (January 1998–January 2015). Sex, age at diagnosis, disease extent, extraintestinal clinical manifestations, the severity of the first flare, C-reactive protein (CRP) rates, steroid-dependence or steroid-resistance as well as smoking habit were studied as predictive factors of severe evolution of UC.

Results: Out of the 105 patients (aged 19–83), 45 (42.9%) had a severe evolution of the disease: thirty three patients were treated by azathioprine, 6 patients required anti-TNF therapy and 12 patients underwent surgery. Proportion of females, smokers and disease duration were 53.3%, 15.2% and 96 months. The analysis showed a significantly higher risk of severe clinical course in UC for patients who were steroid dependent (p < 0.01) or steroid refractory (p < 0.01), and for patients with a severe first flare (p < 0.01), and for young age < 30 years (p = 0.02) or a high CRP level > 40 (p = 0.01) at diagnosis.

Conclusion: Age at diagnosis, severity of the first flare, CRP levels, and steroid dependent or steroid refractory UC were all significantly associated with UC prognosis. These results may clarify the relative influences of these and other prognostic factors in the natural course of the disease and therefore help improve the management approach, thus improving the follow-up of patients.
Predictive factors of recurrence of Crohn’s disease after ileocecal resection

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Introduction: Recurrence after ileocolectomy for Crohn’s disease (CD) is common and occurs in up to 80% of patients. Such recurrence can result in repeated surgical interventions, an increased need for medical treatment and, frequently, an impaired quality of life. This study aims to evaluate the factors associated with disease recurrence after ileocolectomy for CD.

Methods: We report a retrospective study from January 1998 to December 2012, including all patients who underwent ileocecal resection (ICR). We had been interested to the risk factors of surgical recurrence of Crohn’s disease.

Results: Twenty three patients were included in this study. Endoscopic and/or clinical recurrence was observed in 43.5% of our patients after an average follow-up of 24.5 months [6–110]. Predictors of postoperative recurrence in univariate analysis were young age at diagnosis of CD (p = 0.002), ICR in the first year of diagnosis of CD (p = 0.041), the length of the resected small bowel (p = 0.001), penetrating disease pattern (p = 0.031) and tobacco (p = 0.036). Two other factors analyzed were not associated with a high risk of postoperative recurrence of CD: a family history of CD (p = 0.382) and disease extent (p = 0.4).

Discussion/Conclusion: After ICR for CD, recurrence is relatively frequent and its incidence increases with tobacco, after extensive resection, at young age and according to the phenotype of the disease (penetrating disease).
**Which ulcerative colitis patients are at risk of having proximally extending disease?**

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**Introduction:** In the recent years, it has been shown that around 20% of distal ulcerative colitis (UC) patients, colonic involvement proceeds proximally by time. We have investigated retrospectively which patients had the risk of extending of their disease.

**Methods:** One hundred ulcerative colitis patients were randomly selected and some parameters were investigated retrospectively. The patients were divided into two groups: extending group (n = 18; 18%) and stable group (control, n = 82; 82%). Bivariate analysis, logistic regression (chi square test) and Student’s t-test.

**Results:** Median age was 46 and 53% were males. Fifteen UC patients (15%) had familial inflammatory bowel disease history. Forty five patients (45%) ex-smokers, 4% patients had extraintestinal symptoms and findings. During the diagnosis 35% had distal colitis, 65% had left-sided colitis, 31% required steroids. During the disease course, 20% needed immunosuppressive drugs and 10% were given biologic agents. Predictive factors for anatomic extension during the disease course identified by logistic regression analysis were: having proctitis during the diagnosis (OR = 3.04, CI: 2–4.6, p < 0.0001), extraintestinal symptoms and findings (OR = 2.21, CI: 0.99–4.91, p = 0.05), having moderate/severe relapses (OR = 2.98, CI: 1.56–5.68, p = 0.001) and frequent number of relapses (OR = 1.1, CI: 1.05–1.15, p = 0.0001). Biologic agents and immunomodulators were mostly used in the research group (OR 3.39, CI: 2.11–5.44; p = 0.0001 for immunomodulators; OR = 2.75, CI: 1.48–5.09; p = 0.001 for biologics).

**Discussion/Conclusion:** We found that having proctitis, extra-intestinal symptoms and findings during the diagnosis, frequent moderate/severe relapses during the course are risk factors for extending disease.
The prevalence of Clostridium difficile infection in patients with inflammatory bowel disease – A study in a tertiary care center in Romania

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**Introduction:** Clostridium difficile infection (CDI) represents a serious public health concern due to its high prevalence and life threatening complications. Patients with inflammatory bowel disease (IBD), have increased CDI rates and higher morbidity and mortality compared to CDI patients without IBD. The aim of this study was to determine the prevalence of CDI in a group of patients with IBD from a tertiary center in North Eastern Romania.

**Methods:** We conducted a single-center retrospective study over a period of 2 years (September 2015–September 2017). 68 patients (38 UC/30 CD) with diagnosed IBD were included. All patients included provided stool sample and toxins A and B of Clostridium difficile were detected with ELISA immunoassay.

**Results:** 68 IBD patients were enrolled in our study (male/female: 40/28). The mean age at diagnosis of CDI in IBD patients was 40.3 years. The overall prevalence of CDI was 17%, with no statistic significant difference between CD and UC patients. CDI patients were more frequently treated with antibiotics (p < 0.001) and with steroids (p < 0.001). Only 12 patients were actively on a biologic at the time of CDI diagnosis. IBD patients with CDI had a higher rate of extraintestinal manifestations (p < 0.001). The extraintestinal manifestations included peripheral arthritis, spondilytis, osteo-porosis, pyoderma gangrenosum and uveitis.

**Discussion/Conclusion:** Our study shows that CDI infection is more common in young patients with IBD. There is no difference in the frequency of CDI between CD and UC patients. IBD patients with CDI have greater rates of extraintestinal manifestations.
The correlation between fecal calprotectin and disease location in patients with Crohn’s disease

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Introduction: Fecal calprotectin is a non-invasive marker of inflammation used for diagnosis and disease monitoring in patients with inflammatory bowel disease (IBD). The aim of this study was to evaluate the correlation between fecal calprotectin (FC) and disease location in a group of patients with Crohn’s disease (CD).

Methods: We conducted a retrospective study between June 2015 and June 2017 in a tertiary center from North Eastern Romania. The study included 50 patients with diagnosed CD. Clinical disease activity index (CDAI), full blood count, C-reactive protein (CRP), fecal calprotectin, serum albumin, sex, age, age at disease onset, disease extent, disease duration and smoking status were examined.

Results: A total number of 50 adult CD patients were included. Of these, 18% had ileitis, 46% ileocolitis and 36% colitis. Median age at diagnosis was 31 ± 1 years and median duration of disease was 10 ± 4 years. From the total number of patients, 76% had FC > 200 mcg/g (cut-off value for disease activity in our laboratory). Patients with ileal CD had significantly lower calprotectin levels than those with colonic and ileo-colonic CD (p < 0.001). The FC levels were significantly correlated with the disease activity (UCDAI score > 150) (p < 0.001), C-reactive protein (p < 0.001) and serum albumin (p < 0.001). No association was found with sex, current age, age at disease onset and smoking status.

Discussion/Conclusion: An accurate assessment of mucosal inflammation is important for an effective management of patients with inflammatory bowel disease. Our study demonstrates that measuring fecal calprotectin could help predict disease location in patients with CD.
Patient perception and approval of fecal microbiota transplantation (FMT) as an alternative treatment option for ulcerative colitis

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Introduction: Fecal microbiota transplantation (FMT) represents a treatment option for recurring Clostridium difficile-associated colitis. However, there is also evidence that FMT can be effective in treating ulcerative colitis. This study examined the approval and willingness of affected patients to undergo FMT.

Methods: A standardized questionnaire containing 27 both polar and open questions was dispatched to a cohort of 262 patients suffering from UC. It included questions aiming at the process of FMT itself, donors as well as possible concerns. Additionally aspects of social background and disease activity were dealt with.

Results: The response rate amounted to 31.3% (n = 82). 58.5% of patients were already aware of FMT. 56.8% were willing to undergo FMT given a respective indication. The effectiveness of the procedure (40.2%) followed by failure of all other therapies (17.1%) formed the principal motivation. The transmission of possible infectious agents (26.8%) and the potential contamination of the stool graft leading to a deterioration of clinical symptoms raised the most concerns. (20.7%).

The preferred delivery system of FMT were capsules (67.1%) followed by coloscopic application (47.6%). The patients were in favor of a donor proposed by the physician (52.4%). Willingness to undergo FMT did not differ significantly between sexes (56.4% with women vs. 57.1% with men). Smokers (88.9%), patient who did not watch television at all (77.8%) and those with a private health insurance especially showed a high willingness to undergo FMT.

Conclusion: For the majority of the UC patients surveyed FMT represents a feasible, already high profile treatment option. Approximately half of the questionees would consider FMT as an alternative treatment option, even in spite of a satisfactory disease response to current standard therapies. Unsurprisingly there are concerns in regard to the transmission of possible infectious agents as well as to the hygienic implementation of FMT itself.
The efficacy of 5-ASA and infliximab therapy in patients with Crohn’s disease

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Introduction: We have evaluated the treatment options for Crohn’s disease (CD) retrospectively in a single-center in Turkey.

Methods:
A total of 180 patients with CD who presented at the Ankara University Internal Medicine Departments of Gastroenterology outpatient clinics between 2009 and 2015 were recruited in this study. Crohn’s Disease Activity Index (CDAI) is used to describe disease severity and according to this method CDAI < 150 is considered as asymptomatic remission while CDAI 150–220 as mild to moderate CD, CDAI 220–450 as moderate to severe CD and CDAI > 450 as severe to fulminant CD.

Results: In this population, 84% of patients have small bowel involvement while 56% have ileocolitis, 24% have diseases limited to colon and 7% have predominant involvement of gastroduodenal area. %10 of them were already in remission at the admission. 69% of patients determined as mild to moderate CD at the admission and 63% of them entered remission only by 5-ASA treatment. 44% of patients diagnosed as moderate to severe CD which includes 21% at the time of diagnosis and 23% during the follow-up. These patients used 5-ASA, azathioprine, methylprednisolone and budesonide combinations and 78% of these patients have seen in remission during the follow-up. The patients who are refractory for these agents (10% of total population) admitted to infliximab therapy and 89% of them have seen in remission with infliximab at the end of the follow-up.

Discussion/Conclusion: 5-ASA is a common drug for mild to moderate CD treatment and we have seen nearly 2/3 of these patients in remission by 5-ASA drug monotherapy. Infliximab is a very effective agent against CD patients who show resistance to 5-ASA, steroid and azathioprine combinations and at the end of follow-up nearly 90% of these patients entered remission by infliximab therapy.
Role of laboratory markers in pediatric inflammatory bowel disease

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Introduction: Non-invasive methods for objective assessment of disease activity are particularly valuable in pediatric patients with inflammatory bowel disease (IBD). The aim of this study was to evaluate the utility of 6 blood tests - white blood cell (WBC) and platelet (PLT) counts, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fibrinogen and albumin, and 2 fecal markers: fecal alpha-1-antitrypsin (fA1AT) and fecal calprotectin (FC) to distinguish patients with endoscopic inflammation despite having no symptoms from patients in deep remission.

Methods: 31 children with ulcerative colitis (UC) and 22 children with Crohn’s disease (CD) in clinical remission provided blood and fecal samples for evaluation of WBC, PLT, ESR, CRP, fibrinogen, albumin, fA1AT and FC. Endoscopic disease activity was assessed according to the Mayo endoscopic subscore (MES) and Simple Endoscopic Score for Crohn’s Disease (SES-CD) in UC and CD patients, respectively.

Results: In UC children only FC and fA1AT were able to distinguish between patients with intestinal inflammation and endoscopic remission. Median levels for intestinal inflammation versus endoscopic remission were (1000 µg/g vs. 100 µg/g, p < 0.001) for FC and (560 µg/g vs. 480 µg/g, p = 0.032) for fA1AT.
In CD children only FC and fibrinogen were able to distinguish between patients with intestinal inflammation and endoscopic remission. Median levels for intestinal inflammation versus endoscopic remission were (808 µg/g vs. 97 µg/g, p < 0.001) for FC and (435 mg/dl vs. 327 mg/dl, p = 0.032) for fibrinogen.

Discussion/Conclusion: FC is a useful non-invasive marker of intestinal inflammation that may assist the follow-up of pediatric IBD patients.
A rare cause of retroperitoneal fibrosis

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Introduction: A 69 year old gentleman presented with a five week history of abdominal distension. He has a past history of diabetes and myocardial infarction, is an ex-smoker with no significant history of alcohol intake. Examination demonstrated a distended non tender abdomen with shifting dullness, no organomegaly and no signs of chronic liver disease.

Methods: Investigations included ultrasound scan of abdomen, ascitic tap, CT abdomen/pelvis and CT guided biopsy.

Results: Ascitic tap revealed chylous ascites with high SAAG (serum ascites-albumin gradient) of > 1.1 g/dl indicating a nonperitoneal cause of ascites. Cytology revealed no evidence of malignancy. CT abdomen revealed a mildly enhancing soft tissue mass encasing the mesenteric and renal vessels and the upper abdominal aorta and also the left peritoneal space; appearances were suggestive of lympho-proliferative disorder. CT guided biopsy showed reactive changes consistent with retroperitoneal fibrosis.

Immunohistochemistry done at University College of London showed no evidence of Ig4 disease. Patient was commenced on Prednisolone and Azathioprine. He failed to tolerate Azathioprine which was then stopped. Treatment with Prednisolone failed to slow the rate of reaccumulation of the ascites, and he continued to require frequent abdominal paracentesis.

Discussion/Conclusion: Chylous ascites has rarely been reported as a presenting feature of retroperitoneal fibrosis. [1] Retroperitoneal fibrosis may be an idiopathic in 70% of cases or secondary condition. The incidence of idiopathic form is 0.1 per 100,000 person-years with a prevalence of 1.4 per 100,000 population. [2] The primary modality used for diagnosis of retroperitoneal fibrosis is CT imaging, biopsies are performed in cases of unusual presentation and to exclude malignancy and IgG 4 related pathology. Treatment of retroperitoneal fibrosis in most cases depends on whether it is idiopathic or secondary. The mainstay of treatment is corticosteroids and if no response, immunosuppressive therapy can be used. Case series data is present which has shown that high dose corticosteroids like prednisolone are effective in reducing the chronic inflammatory response caused by retroperitoneal fibrosis; however there is a high rate of recurrence once the steroids are withdrawn. Mycophenolate mofetil in addition to corticosteroids has shown reduced duration of steroid use without affecting the efficacy and reduces disease recurrence rate.
Violations of the intestinal microbiocenosis on the background of non-specific ulcerative colitis exacerbation

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In recent decades, the attention of clinicians focused on the research of non-specific ulcerative colitis (UC) etiological factors and the mechanisms that lead to the next exacerbation development.

Aim: To investigate the nature of changes in the intestinal microbiocenosis in patients with UC exacerbation.

Materials and methods: We examined 41 patients with UC in the period of exacerbation, of which 18 women, 23 men, 21–55 years old. The clinical data and endoscopic activity index according to the Mayo scale were evaluated. The hydrogen breath test (HBT) with lactulose was performed, the concentration of hydrogen in the air, which was exhaled by the patient, was measured before and at 15, 30, 60, 90 and 120 minutes after taking the drug. In parallel, feces were analyzed for dysbiosis.

Research results: According to the fibrocolonoscopy, distal UC was detected in 14 (34.2%) patients, the left side UC – in 12 (29.2%), total colitis – in 15 (36.6%) patients. The endoscopic activity index was grade I in 8 (19.5%) patients, grade II – in 23 (56.1%), grade III – in 10 (24.4%) patients. According to the results of Mayo’s full scale, 9 (21.9%) patients had mild activity (up to 5 points inclusive), 27 (65.8%) – moderate activity (6–10 points) and 5 (12.2%) patients – severe UC activity (11–12 points). According to the HBT data in patients with UC in the exacerbation stage, the presence of two peaks were detected: at 15 and 30 minutes with a concentration of hydrogen 44.26 ± 4.08 ppm and 48.92 ± 3.94 ppm, respectively. At 60 minutes, a decrease of the hydrogen level to 16.47 ± 2.9 ppm was noticed, with its increase at 90 and 120 minutes up to 41.05 ± 4.12 ppm and 40.86 ± 3.1 ppm, respectively. The microbiocenosis violations on the background of UC exacerbation was characterized by a decreased content of bifidobacteria in feces in 30 (73.1%) patients and increased content of Klebsiella and Staphylococcus in 14 (34.14%) patients.

Conclusion: In patients with exacerbation of UC, the Mayo scale of activity is largely influenced by the endoscopic grade of activity, which leads to increase in the frequency of excretions and intensification of rectal bleeding. The development of the bacterial overgrowth syndrome with an increase in the propulsion activity of the intestine has been reported on the background of UC exacerbation, according to the HBT. The microbiocenosis violation against the backdrop of UC exacerbation was characterized by a significant decrease in the content of normal anaerobic microflora, which should be taken into account during concomitant therapy in this category of patients.
Clinical and psychological features of patients with different variants of non-specific ulcerative colitis

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Non-specific ulcerative colitis (UC) significantly impairs the quality of patients' life due to its severity and leads to the psycho-emotional changes. This in turn affects the nature of the clinical course of the disease. It is known that in remission phase in patients with UC may occur IBS-like syndrome, which causes changes in mental and emotional status.

Aim: To assess the role of clinical and socio-demographic factors in UC patients and determine their impact on the psychological status and life quality.

A total of 35 UC patients aged 18 to 68 years were examined, the ratio of men 20 (57.1%) and women 15 (42.9%), the average duration of the disease was 8.3 ± 4.9 years. A special questionnaire was used to determine the quality of life of patients with inflammatory bowel disease (IBDQ) (Guyatt G., 1989) and a non-specific questionnaire for determining the life quality SF-36 with the identification of physical and mental health components.

It was found that the quality of life in patients with UC was reduced on all parameters (intestinal, systemic, emotional and social), which amounted to 50.4 ± 11; 23.7 ± 5.1; 53.4 ± 10.5 and 25.5 ± 6.5 compared with the maximum possible 70, 35, 84 and 35 points, respectively.

The exacerbation of UC was characterized by intestinal dysfunction (p = 0.005), which was significantly associated with the duration of the disease (p < 0.01) and endoscopic activity index (p < 0.05).

On the background of ongoing therapy, basing on the results of repeated questionnaire after 2 months, a significant improvement in the life quality of the intestinal factor and the overall result (p < 0.05) was noticed. There was a tendency to increase the quality of life according to the rest parameters.

Patients' diaries allowed to establish the efficacy of 5-aminosalicylic acid (mesalazine) in the mild form of UC with a short history of the disease (p = 0.0006) and a low activity index (p < 0.05).

A statistically significant improvement in the life quality of patients with moderate and severe forms of UC was found in case of treatment with biological medications (vedolizumab, adalimumab) versus glucocorticoid therapy (methylprednisolone, budesonide) (p < 0.05).

In addition, prolonged use of high therapeutic doses of systemic glucocorticoids caused pronounced changes in psychoemotional status (p < 0.05), insomnia, which significantly worsened the quality of life.

Conclusion: Quality of life of the patients with ulcerative colitis in the dynamics of observation is an important component of their managing, which allows individualizing the approach to the patient’s treatment.
Correlation between endoscopic and histological activity in IBD with level of the FCP

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Background: Colonoscopy is a standard procedure in assessment of UC activity. Histological remission confirms existence of mucosal healing. Using these methods in everyday practice is expensive and cause great discomfort to patients. Using biomarker FCP can be a suitable surrogate.

The aim of this study is to explore the correlation of FCP with histological and endoscopic activity in IBD.

Methods: Study covers 40 patients with UC. Endoscopic activity is evaluated by Mayo endoscopic subscore and histological activity by Geboes score. Biohuman rapid test is used to determine FCP.

Results:
42% (23/40) of patients were in an endoscopic activity.

40% (16/40) of patients were in a histological activity.

Reciprocal relationship of patients with histological and endoscopic activity (Table 1 and Table 2).
Positive correlation is found between histological activity/Geboes score and level of FCP (p-value < 0.01, Rho = 0.961 a Spearman correlation) (Table 3).

<table>
<thead>
<tr>
<th>N</th>
<th>Median</th>
<th>Min</th>
<th>Maximum</th>
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<tbody>
<tr>
<td>Geboes &lt; 3.1</td>
<td>23</td>
<td>1.6</td>
<td>0.2</td>
</tr>
<tr>
<td>Geboes ≥ 3.1</td>
<td>17</td>
<td>5.6</td>
<td>3.9</td>
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</tbody>
</table>

**Table 1:** The ratio of patients with easier and more severe histological activity of the disease

<table>
<thead>
<tr>
<th>N</th>
<th>Median</th>
<th>Min</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCP ≤ 200</td>
<td>22</td>
<td>110.5</td>
<td>50</td>
</tr>
<tr>
<td>FCP &gt; 200</td>
<td>18</td>
<td>681.1</td>
<td>250</td>
</tr>
</tbody>
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**Table 2:** The ratio of patients with normal and elevated level of FCP

<table>
<thead>
<tr>
<th>Spearman correlation</th>
<th>FCP</th>
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<tbody>
<tr>
<td>Geboes score</td>
<td>Rho 0.961</td>
</tr>
<tr>
<td></td>
<td>p-value &lt; 0.01</td>
</tr>
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**Table 3**

**Conclusion:** FCP can be a useful marker in monitoring histological activity in UC.
Treatment of patients with ulcerative colitis and arthritis

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Introduction: Arthritis is the most common complication of ulcerative colitis. More of twenty-five percent of patients with ulcerative colitis suffer from it, and it is often found in young patients. In addition to joint pain, arthritis also causes swelling and stiffness. Ulcerative colitis with arthritis can manifest itself in two different forms: Peripheral arthritis and spondyloarthritis. Treatment of patients with ulcerative colitis and arthritis very problematic.

Methods: We study used for treatment of patients with ulcerative colitis and arthritis in tree groups. In first group application prednisolone and mesalazine (Salofalk®), second group application mesalazine (Salofalk®) with non-steroidal anti-inflammatory drugs (NSAIDs) and tree group application of initial dose of infliximab (Remicade®).

Results: In most cases, the symptoms of peripheral arthritis decrease with the disappearance of inflammation in the large intestine. After a course of drugs such as prednisolone and mesalazine (Salofalk®), joint pain usually disappears. The use of infliximab (Remicade®) for the treatment effectively reduces inflammation and swelling of the joints. Unlike peripheral arthritis, unfortunately, in spondyloarthritis there is no such clear relationship between the disappearance of signs of inflammation in the intestine and the disappearance of joint symptoms. In such patients, non-steroidal anti-inflammatory drugs (NSAIDs) are used to relieve pain and swelling of the joints.

Discussion/Conclusion: However, these drugs should be used under the supervision of a doctor, as they can provoke an exacerbation, since they irritate the intestinal mucosa. To prevent a decrease in the volume of movement in the joints it is very important to engage in exercise therapy.
Ulcerative colitis and adenocarcinoma – Case report at 24-year-old pregnant with long-lasting IBD

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Introduction: Inflammatory bowel disease (IBD) patients are at an increased risk of developing colorectal cancer (CRC). We report case of young pregnant women with long-standing IBD and a family history of genetic defect.

Case report: The patient was hospitalized at the Gynecology clinic for abdominal pain and frequent diarrhea stools with fresh blood. Since it was a patient who was in the seventh month of pregnancy, it was regularly monitored by a gynecologist. The initial laboratory tests showed high levels of white blood cells, iron deficiency anemia, increased inflammatory markers, hypoproteinemia. Initially involved 5-ASA and probiotic therapy. During hospitalization, the problems are intensified, worsening of the general condition. The general condition of the patient is extremely bad with the increase in inflammatory parameters. Imagine diagnostics, ultrasound abdominal examination and computerized tomography are performed and focal changes in the liver are visualized in the sense of metastatic disease. It was performed rectosigmoidoscopy with biopsy and it revealed inflammatory lesions in a various stage and at 15 cm from the anocortic line seen tumor, stenosing forms. The histopathological examination was suggestive ulcerative colitis and adenocarcinoma. A medical committee decided to initial surgical therapy-laparoscopic restorative proctocolectomy.

Discussion/Conclusion: It was a patient who had ulcerative colitis with the presence of fresh blood in the back of the year and had been diagnosed with ulcerative colitis since early diagnosis but did not appear to have been under regular control over the past 10 years. Anamnestic and information about a brother with a genetic disorder which increase tendency of adenocarcinoma gastrointestinal system. All of this has led to the development of metastatic disease with a very bad prognostic factor. It is necessary to regularly monitor patients, perform endoscopic examination. This is the most severe case ulcerative colitis and adenocarcinoma under 25 years old reported in our hospital.
Eosinophilic esophagitis, clinical practice: Case report and literature review

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Eosinophilic esophagitis (EoE) is a chronic and abnormal Th2 type immunological response characterized by intense eosinophilic inflammation localized within the esophagus. This leads to esophageal dysfunction and remodeling accompanied by subepithelial fibrosis. Recently, EoE has been recognized as one of the major causes of dysphagia. EoE should be differentiated from secondary esophageal eosinophilia (EE) in gastroesophageal reflux disease (GERD) and eosinophilic gastroenteritis, involving the entire gastrointestinal tract. Male gender is a strong risk factor for EoE both in children and adults. Because inflammatory changes in EoE are frequently patchy and may not be present in all biopsies, it is recommended that at least 6 biopsies should be obtained from at least two different locations in the esophagus, typically in the distal and proximal halves of the esophagus. Currently, the histologic diagnosis of EoE relies on a peak count \( \geq 15 \) eos/hpf assessed within the epithelial stratum. However, other histologic features that can be assessed in HE-stained slides include eosinophil abscesses, basal zone hyperplasia, dilated intercellular spaces, eosinophil surface layering, and papillary elongation of the squamous epithelium. Several endoscopic findings have been associated with EoE, either affecting the mucosal surface (edema or decreased vascularity (also referred as loss of vascular pattern), longitudinal furrowing, rings (also called trachealization), white plaques (also referred as spots or exudates), and fragile (or crêpe paper) mucosa or the esophageal caliber, strictures and narrow caliber esophagus.

Case report: M.S., 37-years-old, with symptom EoE, refractory with all therapy and all complications underlying disease. EoE may have a profound effect on the quality of life and psychosocial adjustment of affected children and their families, including social difficulties, anxiety, sleeping difficulties, depression. In steroids responsive patients, long-term therapy with topical corticosteroids is effective in maintaining remission in a proportion of patients.
Gene expression profile of endoscopically active and inactive ulcerative colitis: Preliminary data

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Introduction: Multiple cytokines and chemokines related to immune response, apoptosis and inflammation have been identified as molecules implicated in Ulcerative colitis (UC) pathogenesis. The aim of this study was to identify the differences at gene expression level of a panel of candidate genes in mucosa from patients with active UC (UCA), patients in remission (UCR) and normal controls.

Methods: Eleven individuals were enrolled in the study: eight UC patients (four with active lesions, four with mucosal healing) and 3 controls without inflammatory bowel disease (IBD) seen on endoscopy. All the individuals underwent mucosal biopsy during colonoscopy. Gene expression profile was evaluated by PCR array. Investigating eighty-four genes implicated in apoptosis, inflammation, immune response, cellular adhesion, tissue remodelling and mucous secretion.

Results: Seventeen and three genes out of 84 were found significantly differentially expressed in UCA and UCR respectively, compared to controls. In particular REG1A, and CHI3L1 genes reported an up-regulation in UCA with a fold difference above 200. In UCR, among the three significant genes, only ISG15 seemed to be specifically associated to the remission state.

Discussion/Conclusion: These preliminary data represent a starting point for defining the gene profile of UC in different stages in Romanian population. Identification of genes implicated in UC pathogenesis could be useful to select new therapeutic targets.
The importance of an early proactive anti-TNF therapy monitoring in patients with ulcerative colitis

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Introduction: Therapeutic drug monitoring when using anti-TNF therapy in clinical practice may help tailoring treatment by maintaining effective drug concentrations over time. Thus, measurement of serum antibodies to infliximab has been proposed to monitor for the formation of anti-drug antibodies which may cause some patients to become non-responders.

Methods: We studied 75 patients (33 males, 43.5% and 42 females, 56.5%), mean age: 46.76 (± 15.62) years, with UC admitted in 3 private hospitals from Timisoara, Romania for a 3 years period.

Results: Mean UCDAI score was 7.4 ± 2.9 points. Patients were classified as follows: 30 patients (39.8%) with mild disease, 31 (40.4%) moderate disease and 14 (19.8%) severe disease (UCDAI score: 4.7 ± 2.1, 8.3 ± 1.8 and 10.3 ± 2.0, respectively). A number of 24 (32%) patients underwent infliximab therapy. We studied 75 patients (33 males, 43.5% and 42 females, 56.5%), mean age: 46.76 (± 15.62) years, with UC admitted in 3 private hospitals from Timisoara, Romania for a 3 years period (UCDAI score 9.1 ± 2) -5 mg/kg every 4 weeks. In these patients median serum TNF-alfa levels were 6.5 (IQR 2.5–18.7) pg/ml and the median IFX trough level was 4.5 (IQR 2.8–5) μg/ml. In 16 patients (75%) IFX levels were concentrations ≥ 12 microg/mL. 6 (25%) patients presented ATIs (845 microg/ml (IQR 250–3250), and clinical and endoscopic loss of response, requiring switch to another biological agent. ATIs positivity correlated significantly with low trough levels of IFX (2.5 microg/ml vs. 4.96 microg/mL, p = 0.012). 3 (12%) patients presented low therapeutic serum TNF-α levels, with undetectable ATIs (in 2–8% of these patients dose escalation was necessary and in 1 patient the dose was doubled).

Discussion/Conclusion: In patients with UC treated with infliximab, a detectable trough serum infliximab and IFX levels ≥ 12 μg/ml predicts clinical and endoscopic remission. The presence of ATIs requires switching to another biologic agent. Thus, it is important that the management decisions in these patients are taking by drug concentration monitoring.
Elements influencing health-related quality of life in patients with collagenous colitis

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Introduction: Collagenous colitis (CC) is a common cause of watery diarrhea, abdominal pain, and nausea. The aim of the study was to examine the quality of life (QOL) in patients with CC and to determine the effect of treatment with budesonide 9 mg for a 6 weeks period, using SF-36 (a generic questionnaire for the assessment of health status with 36 questions), grouped in eight scales: physical functioning (PF), role physical functioning (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional functioning (RE) and mental health (MH).

Methods: We studied 19 patients with CC assessed by colonic biopsy (5 male – 27% and 14 – 73% female), from a private Gastroenterology Department. Data before and after 6 weeks of treatment were obtained by face-to-face interview.

Results: At baseline, QOL was low in patients with CC. Mean value of SF-36 was 62.5. Scores for physical functioning, role physical functioning, bodily pain, general health, vitality, social functioning, role emotional functioning, and mental health were as follows: 68.7, 75.1, 87.6, 75.7, 64.4, 63.6, 79.4, and 76.9. When compared to the general population (values of mean SF-36 scores published by The National Institute of Statistics), all domains of health-related quality of life were reduced in CC, mainly for PF (p = 0.08), SF (p = 0.005) and RE (p = 0.004). After 6 weeks of treatment with budesonide 9 mg, all the eight scales of the SF-36 II questionnaire significantly increased (ANOVA < 0.0001).

Discussion/Conclusion: Patients with CC presented an impaired QOL which was more important in the emotional than in the physical and the mental component. In our study, diarrhea and pain were the clinical elements that impaired all 8 domain of SF-36.
Is postoperative course of rescue colectomy in severe acute ulcerative colitis affected by preoperative biologic treatment?

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Introduction: Medical treatment of severe acute colitis is given in order to avoid surgery, most of the patients require colectomy even after biologic agent treatment. We aimed to investigate the effect of biologic or steroid treatment on postoperative course after rescue colectomy.

Methods: All the patients who underwent rescue colectomy for severe acute ulcerative colitis were included and divided into two groups. First group having postoperative early complications and the other group which is without postoperative morbidity. Preoperative physical, endoscopic and radiological data, and medical treatment were compared between groups.

Results: Twenty patients (11 males) operated for severe acute ulcerative colitis were included from 2013 to 2017. Postoperative morbidity occurred in 7 patients (35%) including wound infection, anastomotic leakage, ileus, bleeding and intra-abdominal abscess (n = 5). There was no mortality. Receiving preoperative biologic agent did not reveal any difference in the postoperative course (60 versus 40%, p = 1).

Discussion/Conclusion: Postoperative complication rates after colectomy for severe acute colitis are not elevated in the biologic agent receiving ulcerative colitis patients compared to the non-receiving group.
The expression of MMP-7 dependent of CD45-positive cells in lamina propria of inflammatory bowel disease

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Introduction: The proteins belonging to the MMPs is matrix metalloproteinase 7 (MMP-7) whose over expression was observed in inflammatory and neoplastic processes. The aim of this study was to analyze the expression of MMP-7 matrilysin in inflammatory bowel disease dependent of inflammation cells CD45 in lamina propria.

Methods: The study group consisted of 41 patients diagnosed with ulcerative colitis and 10 with Crohn’s disease. The biopsy slices were used as the study material in which the expression of MMP-7 and CD45 protein was determined by immunohistochemical method with the use of monoclonal antibodies and standard immunoperoxidase technique. The staining reaction in a 4-point scale was assessed as absent, weak, medium and strong.

Results: The expression of MMP-7 protein in normal epithelial cells and inflammatory cells was observed. In patients with ulcerative colitis in epithelial cells, the reaction was absent in 54.9%, weak in 29% and medium in 16.1% of cases, while in patients with Crohn’s disease the expression was defined as weak in 50%, medium in 40% and strong in 10% of cases. The expression of MMP-7 was higher in CD45 inflammatory cells than in epithelial cells of patients with ulcerative colitis that was shown as absent in 6.4% of cases, weak in 35.5%, medium in 32.3%, and strong in 25.8% of cases. In the cases of Crohn’s disease it was weak at 20%, medium in 20% and strong in 60%. Statistical analysis showed that increased expression of MMP-7 protein in epithelial cells in patients with ulcerative colitis was associated also with its growth in CD45 inflammatory cells (p < 0.000). Moreover, the overexpression of MMP-7 in epithelial cells in patients with Crohn’s disease was found to correlate with the location of the disease in the rectum (p < 0.000).

Discussion/Conclusion: The increased expression of MMP-7 protein appears to be an important factor in the pathogenesis of non-specific inflammatory bowel diseases and is strongly correlated with expression of CD45-positive cells.
Epidemiology, complication, extraintestinal manifestation and treatment of inflammatory bowel disease in Sanliurfa region of Turkey

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Objective: The epidemiological, clinical and therapeutic features of inflammatory bowel disease (IBD) cases, followed up in our department, were investigated.

Materials and methods: The data of 173 IBD cases, followed between January 2012 and December 2017, were evaluated retrospectively.

Results: 90 (52%) of the patients were female, mean age was 36.32 ± 13.59 (16–75) years and body mass index was 23.9 ± 3.7 (16–33) kg/m². Of the patients, 124 (73.4%) were ulcerative colitis (UC), 43 (25.4%) were Crohn’s disease (CH) and 2 (1.2%) were indeterminate colitis. Median disease age was 9 months (1–120) months. 16 patients (9%) developed severe complications; 6 fistulizing CH, severe bleeding in 4 patients, intestinal resection in 3 patients, toxic megacolon in 1 patient, short bowel syndrome due to 1 bowel resection and 1 fistulizing CH sepsis using infliximab. Extraintestinal manifestation was detected in 8 patients (4%), including 6 ankylosing spondylitis and the other peripheral arthritis, 1 polymyalgia rheumatica and 1 cholelithiasis. At the time of application, 55% of patients had mild-severe activation. 66% of the patients were treated with 5-aminosalicylic acid (5-ASA), 28% with 5-ASA and immunosuppressive, and 4% with immunosuppressive therapy alone. The most commonly used immunosuppressive drug was azathioprin (AZA) and used approximately 25% of the patients. Approximately 40% of patients used cortisone or budesonide. Twelve of the patients (7%) were used infliximab or adalimumab.

Conclusion: Our cases of inflammatory bowel disease were in the third decade and three quarters were ulcerative colitis. About one in ten of the patients, one mortal, developed complications. The frequency of extraintestinal manifestation was found to be low according to the literature and the most frequent involvement was ankylosing spondylitis. Four-thirds of patients use 5-ASA, four use 5-ASA and/or immunosuppressive drugs (most commonly, AZA) in the treatment of admission.

Key words: inflammatory bowel disease, epidemiology, complication, treatment
Hyperbaric oxygen therapy in the treatment of ulcerative colitis

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Hyperbaric oxygen therapy is up-to-date for the treatment in IBD. The curative effect of hyperbaric oxygen therapy is very important to tissue's hypoxia and compensates organ's reaction.

There were examined 64 patients with exacerbation's ulcerative colitis in our clinic. All patients were treated by Salofalk® 4 x 500 mg, curative enemas by Salofalk® susp. and hyperbaric oxygen therapy.

The other group of patients with ulcerative colitis – (18) we treated with hyperbaric oxygen therapy only. For hyperbaric oxygen therapy we have used Dragger chambers 1000–1200 for 60–75 min -10–12 sittings. We've found good effect after 5th–6th of treatment. We have made approval after endoscopical examination.

We have made clinical retrace for number of defecation, blood in feces etc.

We have found endoscopical and clinical remission after treatment with Salofalk®, curative enemas and addition hyperbaric oxygen therapy in 81% of patients. Hyperbaric oxygen therapy is useful as a part of treatment of ulcerative colitis in 81% of patients with ulcerative colitis, but hyperbaric oxygen therapy as single therapy is useful in 60% of patients.
Efficacy of vedolizumab in inflammatory bowel disease refractory to anti-TNF-α

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Introduction: Vedolizumab, a monoclonal antibody used for the treatment of ulcerative colitis (UC) and Crohn’s disease (CD), blocks the α4β7 integrin, resulting in gut-selective anti-inflammatory activity. In our study we aimed to assess the clinical response, at week 14, of induction vedolizumab therapy in inflammatory bowel disease (IBD) patients refractory to the administration of anti-TNF-α agents.

Methods: Patients with UC or CD who have shown primary non response or responded initially and subsequently lost response to infliximab, adalimumab or golimumab were scheduled to receive vedolizumab 300 mg at weeks 0, 2, 6 and 14. Clinical response at week 14 was defined for CD as a decrease in Harvey-Bradshaw index ≥ 3 and for UC as a decrease in the total Mayo score of at least 3 points and at least 30% percent from baseline.

Results: From September 2015 till July 2017, 10 UC (E1 = 1, E2 = 5, E3 = 4) and 8 CD (A1L1B1 = 2, A1L2B1 = 2, A1L3B1 = 2, A2L1B1 = 2) patients (Female = 10, Male = 8) with a mean age of 41 ± 14.9 years, and a mean disease duration of 11.9 ± 9.2 years have been included in the study. Ten patients received vedolizumab because they have shown primary non response (n = 2) or responded initially and subsequently lost response (n = 8) to one biologic (infliximab = 7, adalimumab = 2, golimumab = 1), while 8 patients received vedolizumab because they have shown primary non response (n = 1) or responded initially and subsequently lost response (n = 7) to two biologics (adalimumab + infliximab = 6, golimumab + infliximab = 2). Clinical response was seen in 6 patients with UC (60.0%) and 3 patients with CD (37.5%) at week 14. No serious adverse events were noted in the patients included.

Discussion/Conclusion: Our results indicate that vedolizumab is well tolerated and is efficacious in IBD patients, even more so in those with UC, who have failed or lost response to anti-TNF-α agents.
The diagnostic yield of small bowel capsule endoscopy in postsurgical Crohn’s disease

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Introduction: Postoperative endoscopic recurrence (POER) of Crohn’s disease (CD) is frequent and unpredictable. In clinical practice, colonoscopy is recommended 6–12 months after surgery, in order to detect early POER and guide management. The aim of our study was to determine the diagnostic yield of small bowel capsule endoscopy (SBCE) in this setting.

Methods: We reviewed the records of 5471 patients subjected to SBCE in our department from March 2003 to March 2017 (males/females: 2693/2778, mean age ± SD: 50.8 ± 28.4 years). Among these patients, we identified 677 with known CD, of whom 41 had undergone SBCE 6–12 months following ileocolonic resection. Any lesions detected in the proximal small bowel were also recorded. All these patients had also undergone ileocolonoscopy at the same time to assess for POER using the Rutgeerts score. The findings of the two tests were compared to examine whether SBCE can detect more proximal lesions in patients who did not exhibit POER (that is a Rutgeerts score ≤ 1) during ileocolonoscopy.

Results: POER was detected in 16/41 (39%) patients by ileocolonoscopy. SBCE detected lesions in the neoterminal ileum in 15 of these 16 patients (overall rate 36.6%) as in one patient the capsule did not reach the neo-terminal ileum during the battery’s life span. Concurrent lesions in the neo-terminal ileum and more proximally were detected by SBCE in 9/15 patients; however, two patients with an ileocolonoscopic Rutgeerts score of 0 had more proximal lesions during SBCE.

Discussion/Conclusion: SBCE is not cost-effective and cannot be recommended as an adjuvant to ileocolonoscopy to identify more proximal lesions postoperatively in CD patients. However, it may substitute for ileocolonoscopy considering local cost, disease characteristics and patient preferences.
Switching from subcutaneous anti-TNF to intravenous anti-TNF in ulcerative colitis: A multicenter study

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Introduction: Infliximab (IFX) and s.c adalimumab (ADA) or golimumab (GOL) are approved for moderate to severe ulcerative colitis (UC) and only switch from IFX to ADA has been investigated. The aim of our study was to investigate disease outcome after switch from s.c to i.v anti-TNF.

Methods: In this retrospective multicenter study, we analyzed the charts of UC patients unresponsive/intolerant or with loss of response (LOR) to ADA or GOL who have been switched to IFX. We collected data concerning patients’ characteristics and data related to the disease and treatment. We evaluated clinical response, remission and adverse events (AE) at 3, 6 and 12 months of follow-up.

Results: The study included 67 patients (male 47, mean age 46 yrs ± 16). Mean age at diagnosis and at start of first anti-TNF was respectively 34 yrs ± 13 and 43 yrs ± 20. Thirty-eight (50%) patients started ADA and 38 (50%) GOL for a mean therapy duration of 6 ± 6 months. Indications for switch were AE in 2 patient (2%), primary failure in 61 (80%), and LOR in 14 (18%). At 3, 6 and 12 months clinical response was reached in 50 (65%), 37 (48%) and 28 (36%) patients and clinical remission was reached in 26 (36%), 24 (34%), and 26 (30%) patients respectively. Data from 50 patients were available at 12 months. Sixteen patients did not complete follow-up for primary failure or LOR. In 27 patients (35%) IFX was optimized increasing dose or reducing interval and 15 patients were in combo therapy with IMM. Twelve AE were recorded leading to 6 treatment interruption. Endoscopy was performed in 63 patients and mucosal healing was achieved by 13 patients (20%).

Discussion/Conclusion: S.c. anti-TNF agents are infrequently used in UC as first-line approach, but in case of switch to i.v. anti-TNF, our data show a superior response/remission rate compared to i.v – s.c switch reported in literature.
**TrueColours Ulcerative Colitis (TCUC): Will patients with UC complete digital questionnaires in real-time?**

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**Introduction:** TCUC is a real-time web-based programme housed on the NHS server. It monitors parameters via electronic questionnaires. Medications are entered and personalised treatment guidance formulated. This information, graphically displayed, is available to the patient and clinical team (https://ouh.truecolours.nhs.uk/ibd/en/). The objectives were to assess feasibility, usability and adherence of TCUC.

**Methods:** A 6-month pilot study recruited patients from the Oxford Inflammatory Bowel Disease service. Recruitment and retention rates were calculated. Questionnaires were scheduled either daily (simple clinical colitis activity index, SCCAI), fortnightly (QoL: IBD-Control-8, CUCQ-8 and EQ5D-5L), or once only (outcomes, www.ichom.org). Patients received email prompts linked to scheduled questionnaires. Monthly home faecal calprotectin measurements were incorporated, monthly blood tests collected and flexible sigmoidoscopy performed at entry and after 6 months. Usability was assessed via the System Usability Scale (SUS) (n = 59) as well as qualitative interviews (n = 28).

**Results:** Recruitment rate was 66/240 (28%). Retention rate was 57/66 (86%). Of 66 patients, 29 (44%) were male, median age 41 yrs (IQR 17.0), median duration of disease 5.6 years (IQR 10.7), distribution of disease (E1 18%, E2 38%, E3 33%, unknown 11%), activity of disease at entry (remission 38%, mild 35%, moderate 26%, severe 1%), tertiary education 58%, biologic use 47%. Adherence to daily SCCAI questionnaires: 76%, fortnightly QoL questionnaires: 95%, and ICHOM: 100%. Uptake of faecal calprotectin home testing was 73% (48/66), median tests 4 (IQR 3). Median SUS score was 92.5 (IQR 15). Qualitative interviews confirmed that TCUC was efficient and effective. Improvements suggested included optimisation of the graphical display on smartphones.

**Discussion/Conclusion:** Patients with UC will collect digital data in real-time, with good adherence to symptom, QoL, and outcome questionnaires as well as faecal calprotectin home testing. Usability was classified as ‘superior’ but further improvements are possible. Larger studies are required to determine cost effectiveness.
Transcription factor GATA-3 in ulcerative colitis: Use of specific DNAzymes to inhibit experimental colitis

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Introduction: GATA-3 has been identified as a major transcription factor of Th2-cell differentiation. By the activation of the production of pro-inflammatory cytokines like IL-6 and IL-13 GATA-3 is considered as the pacemaker of Th2-cell mediated ulcerative colitis, one. We investigated GATA-3 in the ulcerative colitis and were able to inhibit inflammation with specific DNAzyme oligo-antisense.

Methods: First, we analysed samples of UC patients and normal tissue for GATA-3 expression by immunofluorescence staining. Additionally, conditional GATA-3-CD4 deficient mice were used in the oxazolone-mediated colitis model. Inflammation level was documented with miniendoscopy. The colon was isolated for histological sections for immunofluorescent staining as well as LPMC’s and splenic cells were isolated for the analysis of inflammatory cytokines. The GATA-3 DNAzyme is catalytically active and act as DNA antisense molecule with cleaving facility specific for the GATA-3 mRNA. We tested the specific DNAzymes as a therapeutic treatment.

Results: We found a higher GATA-3 expression in samples of UC patients. GATA-3-CD4 KO mice showed a protection of inflammation in the colitis model. These results were supported by histological sections. To investigate further the protective effect we analyzed the production of inflammatory cytokines by cell supernatant analysis and immunofluorescent staining. We found a reduced production of inflammatory cytokines like IL-6, IL-9 and IL-13 in the GATA-3-CD4 KO mice. Furthermore, we observed a protective effect of the GATA-3 DNAzyme in the colitis model compared to mice that get a control DNAzyme.

Discussion/Conclusion: In summary, we have targeted expression and function of the transcription factor GATA-3 by genetic ablation strategies and local administration of a GATA-3-specific DNAzyme in experimental colitis. GATA-3 blockade ameliorated colitis activity and was associated with suppression of local production of multiple pro-inflammatory Th2/Th9 cytokines in experimental colitis. GATA-3 specific DNAzyme emerges as a novel approach for therapy in human UC. This concept can be further improved in therapy regarding the oral route of administration.
Clinical and translational outcomes in patients with primary sclerosing cholangitis and inflammatory bowel disease receiving vedolizumab

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Introduction: Primary sclerosing cholangitis (PSC) is commonly associated with inflammatory bowel disease (IBD). Blocking integrin alpha4beta7 with vedolizumab (VDZ) has been shown to be effective in IBD and is postulated to potentially benefit patients with PSC.

Methods: Patients with PSC-IBD commenced on VDZ for IBD were prospectively studied. Clinical, endoscopic and translational parameters were compared pre- and post-VDZ including alkaline phosphatase (ALP), Ulcerative Colitis Endoscopic Index of Severity (UCEIS), and expression of beta7 on mononuclear cells from peripheral (PBMC) and intestinal lamina propria (LPMC).

Results: 11 PSC-IBD patients on VDZ were followed for a mean 288 days (range 95–509). Baseline mean ALP was 170.4 IU/l (± SEM 29.1), day 42 was 198.1 IU/l (± 36.4), and at last follow-up was 249.8 IU/l (± 95.1) (mean increase not statistically significant). Patients with normal baseline ALP followed a relatively stable ALP course, whereas for those whose baseline ALP was above normal, most (5/6, 83%) had ALP initially rise, thereafter following a fairly erratic course (Fig. 1).

VDZ caused a drop in mean UCEIS (4.4 ± 0.5 vs. 2.5 ± 0.8, p = 0.0185). All patients who had a UCEIS drop with VDZ (i.e. improvement) had a reduction in ALP at the last observation timepoint, whereas those who did not have an endoscopic response had a rise in ALP over time (p = 0.0179).

There was a reduction pre- vs. post-VDZ in proportion of CD4+ and CD8+ T-cells which were beta7+ (CD4: 9.3% ± 1.9% vs. 2.8% ± 0.8%, p = 0.004; CD8: 15.7% ± 4.4% vs. 6.5% ± 2.3%, p = 0.004). (Fig 2).

There was a reduction in proportion of CD4+ T-cells which were beta7+ in the colon -9.0% ± 1.1% pre-VDZ vs. 6.0% ± 0.9% post-VDZ, p = 0.009. There was no difference among CD8+ T-cells.

Discussion/Conclusion: This single-centre analysis of PSC-IBD patients receiving VDZ shows a trend towards a ALP rise post-VDZ, and a reduction in beta7+ cells in PBMC and colonic LPMC after VDZ.
Perianal Crohn’s disease – Association with significant inflammatory activity in proximal small bowel segments

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Introduction: Perianal Crohn’s disease prevalence varies according to disease location, being particularly frequent in patients with colonic involvement. We aimed to evaluate small bowel involvement and compare small bowel capsule endoscopy findings and inflammatory activity between patients with and without perianal disease.

Methods: Retrospective single-center study including 71 patients – all patients with perianal Crohn’s disease (17 patients) who performed a small bowel capsule endoscopy were included and non-perianal Crohn’s disease patients were randomly selected (54 patients). Clinical and analytical variables at diagnosis were reviewed. Statistical analysis was performed with SPSS v21.0 and a two-tailed p value < 0.05 was defined as indicating statistical significance.

Results: Patients had a median age of 30 ± 16 years with 52.1% females. Perianal disease was present in 23.9%.

Patients with perianal disease had significantly more relevant findings (94.1% vs. 66.6%, \(p = 0.03\)) and erosions (70.6% vs. 42.6%, \(p = 0.04\)), however no differences were found between the two groups regarding ulcer, villous edema and stenosis detection. Overall, patients with perianal disease had more frequently significant small bowel inflammatory activity, defined as a Lewis Score \(\geq 135\) (94.1% vs. 64.8%, \(p = 0.03\)), and higher Lewis scores in the first and second tertiles (450 ± 1129 vs. 0 ± 169, \(p = 0.02\) and 675 ± 1941 vs. 0 ± 478, \(p = 0.04\), respectively) No differences were found between the two groups regarding third tertile inflammatory activity assessed with the Lewis Score.

Discussion/Conclusion: Patients with perianal Crohn’s disease have significantly higher inflammatory activity in the small bowel, particularly in proximal small bowel segments, when compared with patients without perianal disease.
Stricturing Crohn’s disease – Can we predict need for surgery at first hospitalization?

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Introduction: Patients with stricturing Crohn’s disease (CD) frequently require surgery in the course of the disease. We aimed to assess if there are any predictors of surgical management by the time of the first admission to hospital with obstructed bowel symptoms.

Methods: Retrospective unicentric study. Patients over 18 years old, with structuring ileal or ileocolonic involvement, with at least one hospitalization and a minimum follow up of 1 year were included. Excluded patients with penetrating disease, those who had their first hospitalization before anti-TNF agents became available in our center and those without appropriate records.

Results: Included 43 patients of which 53.5\% underwent surgery to treat structuring disease.

Comparing patients with and without need for surgery, females were more frequently submitted to surgery (73.9\% vs. 30.0\%, \(p = 0.004\)) as well as patients who already had a structuring behavior at diagnosis when compared with those with inflammatory behavior at diagnosis (65.6\% vs. 18.2\%, \(p = 0.006\)).

At the first hospitalization, patients with need for surgery were less frequently under anti-TNF (0.0\% vs. 20.0\%, \(p = 0.039\)), presented with longer-standing obstructed bowel symptoms (3.0 ± 1.5 days vs. 1.0 ± 1.0 days, \(p = 0.010\)), higher leukocytes count (12.0 ± 5.3 x 10\(^3\)/ul vs. 9.2 ± 6.9 x 10\(^3\)/ul, \(p = 0.037\)) and admission computerized tomography (CT) more frequently showed proximal small bowel dilation (86.4\% vs. 40.0\%, \(p = 0.002\)) and longer extent of small bowel involved (8.0 ± 12.0 cm vs. 5.0 ± 7.0 cm, \(p = 0.016\)). Also, patients that were diagnosed by the time of the first hospitalization were more frequently submitted to surgery than those who already had a CD diagnosis (60.9\% vs. 39.1\%, \(p = 0.043\)).

Discussion/Conclusion: Females, patients with structuring behavior from diagnosis and those diagnosed in the first hospitalization were more frequently submitted to surgery. Small bowel dilation and extent of small bowel involved in admission CT were also predictors of need for surgery. Anti-TNF therapy before the first admission seems to reduce need for surgery in this group of patients.
A case of pyoderma gangraenosum associated with ulcerative colitis

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Introduction: Pyoderma gangraenosum (PG) is a rare non-infectious neutrophilic dermatosis. Clinically it starts with sterile pustules that rapidly progress and turn into painful ulcers with variable depth and size. Etiology has not been clearly determined yet. In half of the cases it is associated with an underlying disease: inflammatory bowel disease (IBD), rheumatologic or hematological disorders. Typical skin lesions of PG develop about 5% of patients with ulcerative colitis (UC) and about 1% of patients with Crohn’s disease. The lower extremities are most commonly affected but other parts of the skin and mucous membranes may also be involved.

Methods: We present a case of a 12 year-old-boy with UC who decided to stop taking his medications for several months. He visited our clinic experiencing a relapse of the underlying disease and bilateral leg ulcers (one oval shaped with necrotic surface on the left knee, one smaller on the left shin and one smaller but deeper on the right shin). The skin lesions exhibited the classic appearance of PG.

Results: After restarting the basic immunosuppressive treatment for UC and treating the skin lesions with topical tacrolimus, the patient’s condition was gradually improved and the ulcers started slowly to heal.

Discussion/Conclusion: PG is one of the extraintestinal manifestations of IBD. Successful treatment of the underlying disease usually results in complete remission or dramatic improvement of the skin lesions.
Fecal calprotectin for detection of postoperative endoscopic recurrence in Crohn’s disease: Systematic review and meta-analysis

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Introduction: Anastomotic recurrence is frequent in patients with Crohn’s disease (CD) following ileocecal resection. The degree of endoscopic recurrence, quantified by the Rutgeerts score (RS), correlates with risk of clinical and surgical recurrence. Several studies demonstrate the accuracy of fecal calprotectin (FC) for detection of endoscopic recurrence, however the optimal threshold FC value remains to be established. The aim of our meta-analysis was to evaluate the accuracy of common FC cutoffs for detection of endoscopic recurrence.

Methods: We performed a systematic literature search for studies evaluating postoperative recurrence in CD which reported RS and FC levels. Endoscopic recurrence was defined as RS = 2–4 (or RS ≥ 2). We calculated pooled diagnostic sensitivity, specificity, diagnostic odds ratio (DOR) and constructed summary receiver operating characteristic (SROC) curves for each available FC cutoff value.

Results: A total of 54 studies were retrieved; 9 studies were eligible for analysis. Diagnostic accuracy was calculated for FC values of 50, 100, 150 and 200 µg/g. A significant threshold effect was observed for all FC values. The optimal diagnostic accuracy was obtained for FC value of 150 µg/g, with a pooled sensitivity of 70% (95% CI: 59–81%), specificity 69% (95% CI: 61–77%), and DOR 5.92 (95% CI: 2.61–12.17). The area under the SROC curve was 0.73.

Discussion/Conclusion: FC is an accurate surrogate marker of postoperative endoscopic recurrence in CD patients. The FC cutoff 150 µg/g appears to have the best overall accuracy. Serial FC evaluations may eliminate or defer the need for colonoscopic evaluation in up to 70% of postoperative CD patients.
Entero-MRI in Crohn’s disease: Predictive value of the inflammatory angiogenesis

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Introduction: Crohn’s disease is a long-term condition that causes inflammation of the lining of the digestive system. Angiogenesis is a critical component in inflammatory bowel disease (IBD). Pharmacological inhibition of angiogenesis, therefore, has the potential to be a therapeutic strategy in IBD. Our aim is to assess the effectiveness of treatment with Infliximab, so to differ between active and inactive Crohn’s disease through analysis of intensity/time curves on dynamic contrast-enhanced MRI.

Methods: From January 2014 to March 2016, 47 patients with terminal ileal Crohn’s disease underwent enteric-MRI. Sequences were performed in coronal and axial plan at 0, 25, 55, 65, 75, 100, 125 seconds after intravenous medium contrast injection. Parietal enhancement was evaluated with two ROIs placing on regular wall and on a thickened one. Intensity/time curves were built. The curves of pathological wall were compared with curves of not-pathological morphologically ileal wall. Enhancement values were related with laboratory data, with Crohn’s Activity Index disease and with density of microvessels at biopsy of terminal ileal. Data were statistically analyzed with (Student’s T test and Fischer).

Results: There was statistically significant correlation (t < 0.001) between maximum intensity value (# 400) and disease activity. High-intensity curve with rapid wash-in and slow wash-out corresponded to active disease with calculated probability of 89% (Fisher test). Low intensity curve with slow wash-in and rapid wash-out corresponded to inactive disease or stabilized fibrosis with calculated probability of 93% (Fischer test).

Discussion/Conclusion: Intensity/time curves related to wall enhancement was useful and effective to assess activity disease, and is relate with density of new inflammatory microvessels. In inflammatory conditions, early, rapid, and marked contrast enhancement is related to increased vascularity, while late interstitial accumulation of contrast material is due to increased capillary permeability.
Role of DWI and ADC maps in Crohn’s disease

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Introduction: Magnetic resonance enterography provides information in the study of Crohn’s disease (CD) and requires gadolinium injection. Through the MR images it is possible to identify the main features of the disease. Evaluation of CD through diffusion weighted imaging (DWI) is a more and more growing field. Overall diffusivity reduction as measured by the apparent diffusion coefficient (ADC) in patients with CD has been recently demonstrated. Our purpose was to investigate the role of DWI and ADC in the evaluation of CD comparing ADC values of distal and normal ileal loops at b = 500, 800.

Methods: We reviewed 37 patients (21 females, 16 males; mean age 35 ± 17.16) with CD of terminal ileum who underwent MRE and DWI from January 2016 to July 2017. The MR studies had been performed on two 1.5 Tesla superconducting device (Philips Medical Systems, Shelton, CT). Patients fasted for 6 h before the MRI examination. MR studies were realized with BBFEM2D sequence on the axial plane, T2 SPIR on axial and coronal planes, E-THRIVE before and after contrast medium injection (after 30-75-120 sec) on axial and coronal planes and DWI sequences on the axial plane. ADC values were calculated in the wall of terminal and normal ileum at b 500 and 800.

Results: There was a significant (p < 0.05) restriction of the diffusion in patients with CD in the active phase (mean ADC values for the unharmed loops: 3.07 ± 0.7 x 10^{-3} at b = 500 and 2.32 ± 0.51 x 10^{-3} at b = 800, mean ADC values for pathological loops: 2.67 ± 1.04 x 10^{-3} at b = 500 and 1.97 ± 0.6 x 10^{-3} at b = 800).

Discussion/Conclusion: DWI and ADC values at different b can help identifying inflamed areas of the bowel wall in CD and, if validated in larger studies, their use in daily practice could avoid gadolinium injection.
The evaluation of CD40 and CD80 receptors in the colonic mucosal membrane of children with ulcerative colitis

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Introduction: Abnormal response of the immune system to an unknown antigen causes disturbances in the balance between pro-inflammatory and anti-inflammatory factors in the mucous membrane and all the intestinal wall.

The aim of the study was the evaluation of CD40 and CD80 receptors in the colon mucosal membrane in children with ulcerative colitis.

Methods: The study objective was the group of 18 patients with ulcerative colitis, aged 3–17 years of age (mean age was 11.55 [± 4.07]) and 10 children (the control group); the mean age was 10.28 (± 4.07).

Biopsy specimens were fixed in formalin, embedded in paraffin and cut with a microtome into 4 µm slices. CD40 and CD80 in the specimens of mucous membrane were assessed after appropriate procedures with mouse monoclonal anti-CD40 antibody (R&D Systems) and rabbit monoclonal anti-CD80 antibody (Abcam). In four fields of vision (400x), the number of cells with expression on CD40 per all the inflammatory cells in the field of vision observed in the stroma.

The STATISTICA 2010 package was used for the mathematical analysis of the results.

Results: The number of CD40-positive was statistically significantly higher in the group of patients with ulcerative colitis in relation to individuals from the controls (p = 0.001 in the rectum, p = 0.00009 in the sigmoid, p = 0.04 in the caecum, respectively). The higher number of CD80-positive cells in patients with ulcerative colitis was also noticed (rectum p = 0.009, sigmoid p = 0.001, respectively). The number of CD40-positive cells was statistically significantly higher in the group of patients with ulcerative colitis in relation to the controls (rectum p = 0.001; sigmoid p = 0.00009; caecum p = 0.04, respectively). The higher number of CD80-positive cells were also noticed in patients with ulcerative colitis (rectum p = 0.009; sigmoid p = 0.001, respectively).

Conclusions:
1. The number of CD40- and CD80-positive cells in the mucous membrane of the large intestine in children with ulcerative colitis is significantly higher than in the controls.
2. The highest number of CD40+ and CD80+ cells is observed in the rectum in individuals with ulcerative colitis.
Spleen abscess: Rare complication of Crohn’s disease

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Introduction: Approximately 20–40% of patients with Crohn’s colitis (CD) are developing external or internal fistulas and the most common internal fistulas are ileosigmoid, although colovaginal and colovesicular fistulas are well described [Lichtenstein, 2000]. Colosplenic fistula is an exceedingly rare condition described by few in the literature [Goldberg, 2012]. Splenic abscess is very uncommon and often related with constitutional symptoms: fever, nausea, general malaise and abdominal pain.

Case report: This is a prospective observational review of a 52 years old female who had been diagnosed with fibrostenotic CD (A2L2B2,3) and started on anti-TNF therapy with infliximab in 2015. Due to adverse reaction of rash and myalgia, therapy was changed on adalimumab.

In June 2016 the patient was admitted to Pauls Stradins Clinical University Hospital with exacerbation of CD (CDAI 209). Once the diagnosis of a splenic abscess with sepsis has been made, abscess puncture was performed, drainage and antibacterial therapy with metronidazole started. Due to negative dynamic and unsuccessful abscess drainage the antibacterial therapy was changed for piperacillin/tazobactam and vancomycin.

One month after patient was discharged with clinical response (CDAI 180) and on ultrasonography (US) control there was small cavum 0.8 x 0.5 cm size. On the next day with a febrile temperature and high inflammatory laboratory tests (CRP 42.3 mg/l, procalcitonin 0.11 ng/ml) patient was admitted to hospital. Computer tomography angiography (CTA) of abdomen revealed colon transversum fistula connected with a spleen abscess. Due to unsuccessful conservative therapy, 2 weeks after, laparotomy with left sided hemicolectomy, splenectomy and left part of diaphragm resection was performed. Postoperative period was without complications (CDAI 98) and one month after biologic therapy was resumed.

One year after treatment patient feels well, CDAI 46. Colonoscopy does not show any signs of inflammation.

Conclusions: Case report presented successful treatment outcome of a rare extraintestinal Crohn’s disease complications – spleen abscess and colosplenic fistula treated with TNFα, antibiotics and surgical resection.
Toxic myocarditis as a consequence of change in mesalamine therapy

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Introduction: Cardiac involvement in IBD patients is a rare condition that could be presented as acute pericarditis, myocarditis, myopericarditis, pericardial and pleural effusion, conduction defects, and cardiac tamponade

Methods: We presented female patient, aged 19, that was hospitalized in our center due to fever, liquid bloody stools and abdominal pain. One month before she had the same symptoms, when the rectoscopy was performed and the diagnosis of ulcerative proctitis was set. She got mesalamine (Salofalk® 1.5 g per os per day), and got better for two weeks. Then she got fever, liquid bloody stools and abdominal pain, so she was referred to a hospital. Colonoscopy was performed and the diagnosis of ulcerative pancolitis was set. During hospitalization change in class and dose of mesalamine therapy was presented (Salofalk® to 5-ASA, dose 3 g per os per day). Beside that she was treated with corticosteroids, proton pump inhibitors, antibiotics. During hospitalization she complained at chest pain, with no elevation of cardiac specific enzymes. Also, chest radiography and electrocardiogram did not reveal any abnormalities. During the following two days, the pain did not resolve, so she was referred to cardiologist who performed cardiac ultrasound and the diagnosis of acute myocarditis was set, with heart ejection fraction 40%.

Results: Based on the fact that no other cause of myocarditis could be found except for the use of mesalamine (5-ASA), we decided to interrupt its use. Few days after that patient felt better, had no chest pain and had better cardiac function (EF 65%).

Discussion/Conclusion: Patients with ulcerative colitis should be observed in case of recently occurred chest pain. Cardiac injury in IBD patients could be extraintestinal manifestation of inflammatory bowel disease or could be a secondary effect of drugs containing mainly mesalamine.
Extraintestinal manifestations of pediatric inflammatory bowel disease – Experience from a tertiary center

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Introduction: Inflammatory bowel diseases (IBD) are multisystemic disorders that often involve other organs besides the gastrointestinal tract. One quarter to almost half of pediatric patients with IBD experience at least one extraintestinal manifestation (EIM). EIMs are more common in patients with Crohn’s disease (CD) than in patients with ulcerative colitis (UC). They may occur before, concurrently or after the IBD diagnosis and their resolution is usually associated with the disease management. The aim of our study was to assess the prevalence of EIMs in pediatric patients with IBD and to evaluate the relationship between their appearance and the disease type and course.

Methods: We retrospectively analyzed the data of children with an established diagnosis IBD in our center from March 2011 to November 2017.

Results: Seventy-five patients were enrolled – 46 with UC and 29 with CD. Thirty-three (44%) of study participants experienced at least one EIM. The EIMs were more frequent in CD patients than in UC patients (58.6% vs. 34.8%, p < 0.05). The most prevalent EIMs were: anemia (8/33, 24.2%), growth failure (5/33, 15.2%), arthritis (5/33, 15.2%) and hepatitis (3/33, 9.1%). Most of the EIMs (22 cases) were associated with an active underlying disease. In 8 cases the EIM preceded the IBD diagnosis. In 3 cases the EIM run a clinical course independent of IBD disease activity.

Discussion/Conclusion: EIMs usually parallel the disease activity but sometimes they may run an independent course.
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