Symposium 213

Tailored Therapies for IBD: A Look into the Future

October 5–6, 2018
Milan Marriott Hotel
Milan, Italy

Abstracts/Poster Abstracts Symposium 213

Abstracts
Poster Abstracts

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Symposium 213

TAILORED THERAPIES FOR IBD: A LOOK INTO THE FUTURE

Milan, Italy
October 5 – 6, 2018

Scientific Organization:
Prof. Dr. S. Danese, Rozzano (Italy)

Scientific Co-Organization:
A. Armuzzi, Rome (Italy)
A. Dignass, Frankfurt (Germany)
P. Gionchetti, Bologna (Italy)
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A. Sturm, Berlin

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2.* Inflammatory bowel disease in the UK: Is care improving?

3. Clinicians' knowledge about the ionizing radiation of the common investigations used in inflammatory bowel disease
L. Alrubaiy, A. Rikaby, S. Al-Rubaye, C.L. Ch’ng (Swansea, London, GB)

4. Conservative treatment of patients after excision of chronic anal fissure
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7. Disease phenotype and features for natural history of paediatric-onset ulcerative colitis
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8.* Anti-tumour necrosis factor drug cessation in IBD – A source of anxiety?
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9. Comparison of long-standing pediatric-onset and adult-onset inflammatory bowel disease

10. An association between anti-Saccharomyces cerevisiae antibodies (ASCA) and recurrent ileitis following total colectomy: A case series

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14. Possible complications during treatment of patients with M. Crohn – Case report  
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16. Changing patterns of frequency of ulcerative colitis in Lima, Peru  
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   S. Chadokufa, S. Sider, R. Buckingham, B. Huggett, F. Kiparissi (London, GB)  

19. Skin manifestations in monoclonal therapy of paediatric inflammatory bowel disease (PIBD)  
   L. Cococcioni, O. Ogunmoye, S. Sider, R. Buckingham, S. Chadokufa,  
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20. Clinical relevance of probiotic on long-term maintenance therapy outcomes  
   I. Copaci, G. Constantinescu, L. Micu, A. Franculescu-Bertea (Bucharest, RO)  

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   A. Cunningham, R. Kokelaar, M. Jitsumura, D. Harris (Swansea, GB)  

22. Corticosteroid therapy in patient with synchronous Crohn’s ileitis and non-Hodgkin lymphoma type DLBCL  
   I. Curlin, I. Romic (Dubrovnik, HR)  

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25.* Intestinal microbiota changes in urban and rural patients with inflammatory bowel diseases
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26. The role of microbiological research in the treatment of patients with severe attack of ulcerative colitis
   O. Davydova, P. Andreev (Samara, RU)

27. Assessment of quality of life in patients with inflammatory bowel diseases
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30. Osteo-articular manifestations in inflammatory bowel diseases – Diagnosis and treatment
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31. The incidence of extradigestive manifestations in intestinal inflammatory diseases
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32. Adverse effects of infliximab therapy in inflammatory bowel diseases
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33. Efficacy and safety of hepatitis C treatment with direct antiviral agents (DAAs) and ribavirin in patients with ulcerative colitis (UC) with stable disease under treatment
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34.* Vedolizumab: Effects on liver function in an IBD and IBD/PSC cohort
35. Peach pit as a cause of small bowel obstruction in patient with Crohn's disease
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36.* Tuberculosis infection in inflammatory bowel disease patients on anti-TNF therapy: Experience from an endemic country
N. Elleuch, W. Dahmani, H. Jaziri, A. Ben Slama, A. Hammami, A. Brahem,
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37. Phenotype and clinical outcomes of older-onset Crohn’s disease
H. Elloumi, M. Ben Hmida, A. Belkhamsa, S. Ben Hmida, S. Bouaziz, I. Cheikh
(Bizerte, TN)

38. Gender-related differences in clinical course of Crohn’s disease: A Tunisian retrospective study
H. Elloumi, M. Ben Hmida, S. Bouaziz, A. Belkhamsa, S. Ben Hmida, I. Cheikh
(Bizerte, TN)

39. The spectrum of pathological changes in patients with Crohn’s disease under long-term mesalamine treatment

40. Predicting good or bad prognosis in IBD: The role of disorders of the rheological properties of erythrocytes
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(Nizhny Novgorod, RU)

41. Morphological criteria for prediction of the cause of ulcerative colitis in children
E. Fedulova (Nizhny Novgorod, RU)

42. Acceptance and commitment therapy improves body image in inflammatory bowel disease patients
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K. Hartery, B. Dooley, H. Mulcahy (Dublin, IE)

43. Long-term follow-up in children with inflammatory bowel disease at different age of onset
(Buenos Aires, AR)

44. Epidemiological profile of perianal Crohn’s disease in Tunisian population
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(Sfax, TN)

45. The short-term immunosuppressive therapy for induction of remission of the steroid-refractory ulcerative colitis in elderly patients
A.-V. Genunche-Dumitrescu, D. Badea, M. Badea, P. Mitrut, C.I. Deliu,
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46. The study of the mechanism of the development of Crohn's disease in women with endometriosis
D. Gordienko (Rostov-on-Don, RU)

47. Molecular mechanisms of sensorineural hearing loss as the extraintestinal manifestation of inflammatory bowel diseases
E. Gordienko (St. Petersburg, RU)

48. Study on clinical remission and mucosal healing in subtypes of Crohn's disease patients by short-term combination therapy
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49. A patient with Crohn's disease during remission by biological agent treatment, then developed active pulmonary tuberculosis: Determining the eating habits
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50. Vitamin D status and polymorphisms of its receptor gene during Crohn's disease: Results of a prospective comparative study
D. Habiba, M. Serguini, D. Saadouli, J. Boubaker (Tunis, TN)

51. Fatal cerebro-meningeal haemorrhage complicating a Crohn's disease
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52. Choledochoduodenal fistula complicating a Crohn's disease: A case report
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53. Prolonged azathioprine treatment reduces the need for surgery in early Crohn's disease
L. Hamzaoui, A. Ben Mohamed, M. Medhioub, M. Mahmoudi, A. Khsiba, M.M. Azouz (Nabeul, TN)

54. Validation of the CUCQ questionnaire with stoma extension in patients with acute ulcerative colitis in the CONSTRUCT trial
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55. Hematological status of Crohn's disease patients who underwent the same type of surgery
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56. T regulatory, T helper 17 and T effector cell profile in patients with ulcerative colitis on anti-TNFα therapy
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58. Efficacy and safety of azathioprine and methotrexate for maintaining remission in microscopic colitis: Outcomes from a district general hospital  
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59. The imbalance of the homeostasis serine proteases inhibitors in inflammatory bowel disease naive patients: A horizon for new perspectives therapies?  
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60. The prevalence of extraintestinal manifestations in patients with IBD  
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63. How effective are treatments in prevention of hypercoagulability and thromboembolic events in ulcerative colitis patients?  

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69. Audit into the frequency of reactions to intravenous iron infusions
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70. Safety of accelerated infliximab infusion in inflammatory bowel disease in a district general hospital
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73. Fecal HSF2 concentration maybe used as an evaluation index for predicting mucosal healing of ulcerative colitis
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74. Infliximab therapy and deviations in platelet indices in Crohn’s disease patients – A single-center experience
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75. Association between IL12B gene polymorphisms and the risk of Crohn’s disease in Serbian patients with inflammatory bowel disease
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76. Colectomy-free survival and factors associated with it in children with ulcerative colitis managed in a tertiary IBD centre in the UK
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77. Effect of vedolizumab therapy on clinical remission, including remission of peripheral arthropathy, in patient with Crohn's disease and previous tumor necrosis factor antagonist failure
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78.* PROFILE trial: PRedicting Outcomes For Crohn’s dIsese using a moLecular biomarkEr
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80. Evaluation of the thiopurine therapy in children suffering inflammatory bowel disease
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81. Colectomy place in ulcerative colitis patients who received mesalamine treatment

82. Clinical expression of inflammatory bowel diseases – A retrospective population-based cohort study; Vukovar-Srijem county, Croatia, 2010
D. Pezerovic, M. Zulj, I. Klarin, L. Majnaric, I. Vcev, A. Vcev (Vinkovci, Osijek, Zadar, HR)

83.* Opportunistic infections, mesenteric vessels endothelial dysfunction and colonic resistance in IBD have possible genetic background for challenging clinical situations
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84.* Expression of PCNA protein in comparison with inflammatory cells infiltration in Crohn’s disease
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85. Golimumab in ulcerative colitis: A multicentre real world experience

86. Corticosteroid therapy and ursodeoxycholic acid therapy in patient with primary sclerosing cholangitis and psychosis – Case report
M. Razov Radas (Zadar, HR)

87. Inhibition of Ras by farnesylthiosalicylic acid (FTS) is a potential target of treatment of experimental colitis
S. Reif, T. Oron (Jerusalem, Petah Tikva, IL)

88. An investigation of taste preferences and attitudes towards long-term use of oral nutritional supplement drinks in adolescent and adult Crohn’s disease
N. Richards, N. Davies, K. Keetarut (London, GB)
89. Severe extensive ulcerative colitis: A case of good and fast response to treatment
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90. Malnutrition in Tunisian Crohn's disease cohort
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91. Intra-abdominal abscesses complicating Crohn's disease: Clinical and therapeutic features
H. Romdhane, B. Bouchabou, H. Ben Nejma, N. Bellil, R. Ennaifer (Tunis, TN)

92. Severe disease activity in ulcerative colitis associated with mucosal hypoxia measured endoscopically
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93. Risk factors for ocular involvement during Crohn's disease
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94. Crohn's disease or Behçet's disease?
D. Saadouli, S. Yahyaoui, A. Sammoud, M.A. El Efrit (Tunis, TN)

95. Insights into mechanisms and new treatment options of ulcerative colitis in patients with latent autoimmune diabetes
I. Sarvilina (Rostov-on-Don, RU)

96. Systematic review of the clinical disease severity indices for inflammatory bowel disease

97. Can the inflammatory bowel disease biologics registry lead to improved quality of care?
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98. The development of a nurse-led inflammatory bowel disease outpatient clinic: Meeting the needs of adolescents with inflammatory bowel disease
S. Sider, S. Chadokufa, R. Buckingham, B. Huggett, F. Kiperissi (London, GB)

99. Biosimilar infliximab (CT-P13) is effective in induction of remission and mucosal healing in paediatric Crohn’s disease: A single-centre experience
M. Sladek, M. Chmielowska, A. Wasilewska, I. Herman-Sucharska, S. Pieczarkowska (Krakow, PL)

100. Phenotypic variation in monogenic inflammatory bowel diseases – Glycogen storage disease 1B as an illustration
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101. Inflammatory bowel disease (IBD) in a patient with immunodeficiency – Is bone marrow transplant indicated?
   M. Slae, P. Millman (Jerusalem, IL)

102. Treatment of patients with Crohn's disease and ulcerative colitis with manifestation arthritis and spondylitis
   V. Sulyma, O. Sulima (Dnipro, UA)

103. Systematic review: Psychosocial factors associated with pain in inflammatory bowel disease

104. The role of different E. coli variants emphasizing opportunistic infection and colonic resistance in inflammatory bowel disease

105. Analysis of allele's distribution and the association between the TGF-β1 gene's polymorphism and IBD
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106. Personalizing approach to IBD through pro-, anti-inflammatory cytokines and genetic polymorphisms

107.* Does drug level monitoring help us to understand the superiority of thiopurine and anti-TNF combination therapy in inflammatory bowel diseases?

108.* Dietary patterns in patients with inflammatory bowel disease
   I. Tadin Hadjina, P.M. Zivkovic, A. Matetic, J.A. Borovac, J. Bukic, D. Rusic, A. Tonkic, J. Bozic (Split, HR)

109. Isolated appendiceal orifice inflammation associated with distal ulcerative colitis – A case report
   M. Tagle, Y. Scavino, E. Luna (Lima, PE)

110. Position for vedolizumab in the treatment of ulcerative colitis, rescue therapy. Our modestly experiences
   R. Tamburic, J. Petkovic-Dabic, T. Barac, A. Dobrovoljski, S. Dabic, S. Trbojevic (Banja Luka, BA)

111. TLR 2, 4, 6 as a tool for prediction of the risk of early relapse of ulcerative colitis
   G.N. Tarasova, L. Mamedova (Rostov-on-Don, RU)
112. The role of stool genetic testing (SGT) for differential diagnosis of early stage IBD and IBS
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113. Immunohistochemical expression of proliferation markers in colitis ulcerosa
W. Ustymowicz, J. Zinczuk, M. Baszun, A. Pryczynicz, K. Guzinska-Ustymowicz (Bialystok, PL)

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W. Ustymowicz, J. Zinczuk, M. Baszun, A. Pryczynicz, K. Guzinska-Ustymowicz, K. Zareba (Bialystok, PL)

115. Virtual biologics clinic for IBD in a district general hospital
A. Vaishnavi, K. Johns, F. Ali (Pembrokeshire, GB)

116. Primary immunodeficiency and ulcerative colitis: Are there any points of interaction?
A.S. Volkov, O. Bashtovaya, A.A. Iakovlev (Rostov-on-Don, RU)

117. Acute severe colitis in pregnancy: A case report
I.K. Williams (Poole, Dorset, GB)

118.*Infliximab or ciclosporin for steroid-resistant acute severe ulcerative colitis?
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119.*Serum MMP-9 – A novel biomarker for prediction of clinical relapse in patients with quiescent small bowel Crohn's disease

120. Profound loss of neprilysin accompanied by decreased levels of neuropeptides and increased CRP in ulcerative colitis
B. Yildirim, Z. Gok Sargin, N. Erin, G. Tazegul, G.O. Elpek (Antalya, TR)

121. Significance of metalloproteinase 9 (MMP-9) expression in ulcerative colitis
J. Zinczuk, K. Zareba, P. Kuczynska, W. Ustymowicz, M. Baszun, K. Guzinska-Ustymowicz, A. Pryczynicz (Bialystok, PL)
122. Impairment of cognitive and psychomotor performance in patients with inflammatory bowel disease
P.M. Zivkovic, I. Tadin Hadjina, M. Vilovic, D. Rusic, A. Tonkic, Z. Puljiz, J. Bozic (Split, HR)

* = Posters of Distinction
Session I

Predicting good or bad prognosis
Genetics and clinical features for natural history

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Genomic technologies have widely dissected the complex genetic basis of polygenic inflammatory bowel disease (IBD). Genome-wide-association studies (GWAS) as well as meta-analysis have defined approximately 250 disease loci linked to IBD. GWAS have disclosed disease mechanisms by identification of genetic variants and gene networks that impact on host-microbe interaction, more specifically microbe sensing within the NOS2 pathway, but also somewhat surprisingly identifying autophagy as pathogenetic mechanisms, and also highlighted the important role of inflammatory signalling pathways as IL-23 driven T helper cell responses and JAK kinase. GWAS have demonstrated similarities and differences among ethnicities, IBD subtypes, disease location and age at diagnosis. In addition, have disclosed an important overlapping of deranged functional and inflammatory pathways (pleiotropy) with other immune mediated disease such as among others ankylosing spondylitis, psoriasis and primary sclerosing cholangitis, and thus might enable stratification of patients to predict development of extra-intestinal manifestations. Genetic testing might be clinically relevant to identify small numbers of misclassified patients and patients with very-early-onset clinical presentation, assist to differentiate those with monogenic inheritance or immunodeficiency syndromes. Although some clear genotype-phenotype association has been described (i.e. NOD2 and ileal Crohn’s disease), no robust evidence supports the use of genetic marker for patient profiling and prognosis. Genetics can be used in the identification of potential novel targets, to avoid potential toxicity (i.e. for thiopurines), to predict response to biologic therapy and selected them more individually. Finally, transcriptomics can identify genetic signature to potentially predict treatment response. Whereas GWAS have investigated the contribution of common genetic variant, next-generation sequencing technologies offer the possibility to study are and ultra-rare genetic variants. Finally, the identification of protective variants offer the opportunity to identify drug targets

References:

Endoscopy to tailor choices

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Using solely clinical judgement for addressing disease severity and prognosis is unreliable, both for Crohn’s disease (CD) and for ulcerative colitis (UC) patients’ management.

Ileocolonoscopy is an essential tool to be integrated in clinical practice supporting disease severity and prognosis stratification. In CD, the presence of extensive large/deep ulcerations was associated to an increase likelihood of requiring surgical procedures, and the occurrence of more advanced endoscopic lesions after curative ileocolonic resection is associated to higher chances of clinical and surgical recurrence. Similarly, in UC the occurrence of deep ulcers was associated to lower chances to respond to steroid treatment during a severe flare of disease. Taken together across the two diseases, deep and large ulcerations are not only a sign of disease disrupting the mucosal surface, but also a marker of poorer disease outcomes.

Moreover, different degrees of amelioration of endoscopic inflammation were associated to better disease outcomes for both Crohn’s disease and ulcerative colitis. Healing of endoscopic lesions was associated to better prognosis in terms of fewer disease flares, fewer hospital admissions and lower risks of surgical procedures for both CD and UC patients. Complete healing of ulcers was associated to even better disease outcomes, even if the exact amount of amelioration of endoscopic lesions associated to relevant clinical benefits is not confirmed in both CD and UC. Therefore healing of endoscopic lesions is a favourable prognostic marker for IBD patients.

Finally, it should be kept in mind that scoring endoscopic activity might be used to minimize the unreliability of clinical judgement, but substantial inter-observer variability was shown and should be acknowledged for all scoring systems for CD and UC. Central reading (with different reading paradigms), focused training and automated reading processes were proposed to reduce even more the variability in the interpretation of endoscopic severity and of healing.
Radiology to predict natural history

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Crohn’s disease (CD) is a chronic, destructive, progressive and disabling inflammatory bowel disease (IBD). All CD-related complications result in a permanent bowel damage, that usually requires surgery, that removes complications but causes further structural damage. However, disease recurs in more than 50% of patients overtime and may lead to further surgery, with consequent increase in the cumulative bowel damage.

Longitudinal follow up studies have shown that most patients present a non stricturing non penetrating disease at diagnosis evolve to stricturing or penetrating phenotype in up to 60% of cases. Moreover, recent data show that up to 40% of CD diagnosis already have got bowel damage at the time of diagnosis.

Usually, a change in disease behaviour according to the Montreal classification from non stricturing-non penetrating to stricturing or penetrating behaviour is considered disease progression. Based on this outcome measure, longitudinal cohort studies show that from 30% up to 60% of subjects develop bowel damage in the long term. CT and MRI can be useful for monitoring CD, and CD-related complications detected by CT or MRI at diagnosis or during the follow-up time are associated with higher risk of surgery and hospitalizations compared to those without complications.

The assessment of bowel damage needs a complex and integrated evaluation of the entire gastrointestinal tract. The combination of endoscopy to assess inflammatory lesions and complications, such as strictures, together with imaging techniques, such as MRI, CT or US, to assess the involvement of the bowel wall and extra-luminal complications (including fistulas and abscesses), as well as perianal disease can give a precise overview of the damaged digestive tracts.

Assessing and addressing disease progression and evolution by radiological techniques to guide therapeutic strategies may be the ultimate goal for the therapeutic management of CD.

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Biomarkers and prognosis

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It has become increasingly clear that both the quantitative and qualitative expression of these immune responses serve as an immunologic risk marker for IBD phenotypes. The notion that the utility of serologies goes beyond differentiation of IBD subtypes was first introduced by Vasiliauskas et al when they reported that high ASCA levels were found to be associated with fibrostenosing (FS) and internal-penetrating (IP) disease as well as the need for small bowel surgery. Multiple studies confirmed this association for ASCA as well as other anti-mannan antibodies. The other anti-microbial responses OmpC and Cbir1 have also been shown to be associated with a more aggressive disease phenotype and rapid progression to disease complications. It appears that having at least 2 antibodies (antibody sum of 2 or above) is associated with increased risk of disease complications. Multiple models have been developed to try and determine whether there are other predictors of disease phenotype such as genotype. Interestingly, serotype remains an independent risk factor for CD complications and in some studies have been shown to have the highest prognostic power. That being said NOD2 genotype has been shown to be associated with stricturing small bowel disease and was shown to be additive to the risk of complication when combined with serotype (AUC = 0.801; 95% confidence interval: 0.757–0.846). The rapidity of disease progression was higher in patients positive for NOD2 variants and multiple high levels of serologies as compared to those with serologies alone. In general classic statistical methods are used in the majority of prognostic studies. System Dynamics Analysis (SDA) is a valuable alternative to classic regression models as it addresses the inherent dynamic complexity of interaction of all of these variables and provides real time individualized prediction of patient outcomes. Such technique has been employed on both a pediatric and adult CD cohort. In both cohorts, serologies were strongly predictive of a poor prognosis. Neutralizing autoantibodies against granulocyte-macrophage colony-stimulating factor (GM-CSF Ab) reduce neutrophil antimicrobial function in patients with primary alveolar proteinosis (PAP). Subsequently these antibodies have been found in CD patients with ileal location and stricturing behavior. The RISK cohort confirmed that serologic immune markers are important at predicting disease behavior in an inception pediatric CD cohort. The strength of the RISK prediction model was enhanced by including ileal gene expression data suggesting that the biology of the disease pre-treatment may be used to risk stratify patients so to personalize therapy accordingly. Proteomics and single cell sequencing may be promising in the future to optimize the accuracy of our prognostic models.
Session II

Conventional therapies: Optimizing therapies to patient profiles
Steroids: Old and new formulations

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In 1950, the first Oxford cohort of 129 cases of ulcerative colitis reported a 22% mortality in the first year of diagnosis [1]. This represented 15/72 new cases between 1938 and 1948. In 1955, the seminal study on steroids for colitis reported 7% mortality in the steroid-treated group (109 patients) and 24% in the placebo group (101 patients) [2]. In 1962, oral prednisolone (20 mg daily, with steroid enemas) induced sigmoidoscopic remission in 78% of 118 patients with mild or moderate colitis within 2 weeks [3] and a dose-ranging study established 40 mg as optimal dose, while ≤ 15 mg day was ineffective for active disease [4].

Conventional oral corticosteroids are effective, but systemic side effects limit their use. Budesonide is effective for active ileo-ascending colonic CD, but 13% less effective than prednisolone [5]. It is associated with fewer steroid side effects (33% vs. 55%, [5]). A non-inferiority study reported that budesonide 9 mg was no less effective than mesalazine 4.5 g daily for mild-moderately active Crohn’s [7]. Other preparations are being developed: in the largest study of beclomethasone dipropionate for active left-sided or extensive colitis in 177 patients, the effect of 5 mg/day was similar to that of 2.4 g mesalazine [8]. Budesonide MMX® is an extended-release preparation that targets the entire colon. In a pooled analysis of two phase III studies (CORE I and II), combined clinical and colonoscopic remission rates were significantly greater than placebo (6.2%) for the budesonide MMX 9 mg group (17.7%; p = 0.0002), but not the budesonide MMX 6 mg group (10.9%) [8]. Budesonide MMX caused no more corticosteroid-related or other side-effects than placebo.

Other studies include CONTRIBUTE, in which 510 adults with mild-moderately active UC were randomized to budesonide MMX 9 mg or placebo for 8 weeks in addition to oral mesalazine ≥ 2.4 g/day [9]. A 12 month extension study in 122 responders to budesonide MMX compared 6 mg daily with placebo. There was no cumulative adrenal suppression, no change in bone density and the median time to relapse was 181 days on placebo, but never reached on budesonide MMX 6 mg daily. The 6 mg dose is not licensed for use.

Steroids with low systemic bioavailability are appropriate for those with mild-moderately active UC or CD who are intolerant of conventional steroids: obese, diabetic, or hypertensive patients, those with emotional lability or osteoporosis.

References:


5-ASA in UC: Outdated or still state-of-the-art?

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5-ASA-derivatives have been successfully used for the treatment of ulcerative colitis (UC) for several decades and remain a fundamental strategy for induction and maintenance therapy of mild to moderate 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. Recently several studies have demonstrated that also mucosal healing and improvement of Qol and work productivity, all important endpoints in clinical trials, but also for patients well-being are significantly improved compared to placebo in patients with UC. Recent interest focuses on the optimization of 5-ASA use for the treatment of UC. Recent studies assess new dosing schedules, new formulations with different release kinetics and combinations 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 with same or sometimes even better efficacy both for induction and maintenance treatment of mild to moderate UC. 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 also have demonstrated to exert chemopreventive effects in patients with long-standing UC.

A number of unsolved questions remain to be addressed in the future regarding optimal use of 5-ASA’s in IBD.
Azathioprine: Outdated or still a valid option for UC and CD?

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For a long time immunomodulator treatments (azathioprine and 6 mercaptopurine) have been the mainstay maintenance treatment for moderate to severe ulcerative colitis and Crohn’s disease. Often times they are used successfully as steroid sparing agents. Mainly because this is old drug, its use was not always supported by strong evidence. Moreover it’s potential for mucosal healing in Crohn’s disease is rather poor. However it’s widespread and better use, in the appropriate dose and awaiting for its slower action, has reduced importantly the use of deleterious steroids but not the need for surgery in Crohn’s disease. The elucidation of the metabolites and the genetics of the main metabolizing enzyme (TPMT thiopurine methyltransferase) has allowed to predict in part toxicity and optimise its efficacy. Nevertheless side effect profile, although well know and manageable, is unfavourable compared to the biologics. After years of debate Cesame, a large French safety register, has identified the long term safety risk in terms of lymphoma and cancer.

In recent years more and more options, including several new classes of biologics, became available that are both more potent and often to be considered safer and easier to use in IBD. But several studies have documented the additional benefit of the combination therapy between immunomodulators and anti-TNF therapy in particular. Combination therapy is not only superior but leads invariably to higher concentration of the anti-TNF agents hereby preventing loss of response and cost efficacious. This may not be the case for the newer classes. However especially the newer biologics come at considerable cost. Most biologics do have a much better documented mucosal healing rate and therefore the potential to modify the disease course.

It is therefore anticipated that with more and more agents available and with the advent of the biosimilars lowering the price considerably that the use of immunomodulators will decline over time.

So far it is early days to predict whether the JAK inhibitors, so far only registered for UC will replace immunomodulators as first line therapy in moderate to severe ulcerative colitis. Studies in Crohn’s disease are still ongoing.

Weighing costs and benefits, except for the vulnerable patients (frailty, elderly, patients with co-morbidities), immunomodulators remain a very valid option as a first line maintenance treatment for patients failing adequately dosed and administered 5-ASA in ulcerative colitis and for moderate Crohn’s disease without poor prognostic markers. Some absolute indications for immunomodulators remain such as preventing (or overcoming) immunogenicity when starting infliximab or high risk situations for immunogenicity such as restarting infliximab after a long drug holiday.

Meanwhile cost constraints in many countries and for many insurers will still mandate the use IMM before biologic treatment. Better prognostic markers and comparative cost efficacy studies are needed to further rationalise our rapidly evolving treatment paradigm in IBD.
Session III

Anti-TNF: A tailor made approach
Predicting response: The best patient

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Treatment of inflammatory bowel disease (IBD) patients is evolving and drugs based on new mechanisms of action are continuously added to the treatment armamentarium. To date, no single drug has demonstrated sufficient response rates, and loss of response to treatment is common. The causes for insufficient therapeutic effects are protean and are actively investigated. Despite the gaps in our knowledge, observations related to IBD pathogenesis, clinical characteristics and pharmacologic studies provide clues for future successful management of these diseases.

IBDs are heterogeneous in their clinical presentation with major differences noted between Crohn's disease (CD) and ulcerative colitis (UC), regarding involved bowel segments and pathologic characteristics. However, detailed analysis of these disease entities supports the possibility that both are in fact syndromes rather than distinct entities. Furthermore, clinical, endoscopic, pathological, genetic and transcriptional data reveal both differences and overlaps between them. These observations, combined with the shared treatment efficacy on the one hand, and incomplete response rates of the different drug classes on the other, suggest that a change in the paradigm by which treatments are selected is needed.

Because the understanding of IBD pathogenesis did not reach a level which allows tackling basic disease mechanisms, to date, treatments are aimed at abrogating the immune response which is responsible for tissue damage. This approach, which is not gut selective leads to side effects associated with the various modes of immune suppression, some of which can be life threatening including infections and malignancy. Therefore, the decision to embark on treatment should take into account prediction of disease course, such that patients with propensity for a complicated course will be those who undertake the significant risks. To date, little is known regarding disease course prediction, although studies have suggested CD8 cells gene expression, serology and microbial signatures as potential predictors.

Finally, there is accumulating evidence that molecular characterization of pretreatment drug target availability and understanding mechanism of action (MOA) using unbiased systems approach, may serve to identify biomarkers for response before treatment. This, combined with therapeutic drug monitoring, will predictably allow to effectively predict treatment efficacy and sustain its effect. An additional approach may be to match between known drug MOA and a characterized biologic deficiency such as in the case of autophagy. A systematic approach may be adapted from oncology wherein some drug combinations may be calculated in advance based on known disease mechanisms and complementary drug effects. The challenge of balancing efficacy with side effects and effectively predicting their occurrence remains to be solved. However, a more personalized approach to treatment offers improved future outcomes.
Predicting loss of response

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Treatment with anti-tumor necrosis factor alpha agents revolutionized our approach to inflammatory bowel disease. Yet, significant challenges, specifically a high proportion of loss of response need to be addressed in order to achieve optimized outcomes for patients.

A specifically challenging issue remains the prediction of loss of response in patients induced with anti-TNF's, or those already achieving response and remission. Approximately a third may lose response within one year. Prediction of loss of response is thus a fundamental step for more efficient use of anti TNFs. The reasons for loss of response, a dynamic process influenced by complex pharmacodynamic and pharmacokinetic factors are only partially known. We will review factors contributing to loss of response in primary responders. Biomarkers that may be used in practice to predict loss of response, specifically C-reactive protein and fecal calprotectin normalization, drug levels and immunogenicity will be discussed, as well as the timing of assessment and practical approach to patient evaluation. Exploratory biomarkers as well as suggestions for prevention of loss of response would be mentioned as well.
Optimizing anti-TNF therapy

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In the last decades, several pharmacological tests have become available, including monitoring of serum levels of monoclonal antibodies such as the anti-tumor necrosis factor (anti-TNF) agents, infliximab, adalimumab and golimumab. Furthermore, different assays became available to measure anti-drug antibodies. Although these tests are commercially available, their implementation in daily clinical practice is still variable, due to costs and varying availability, and partly also due to ignorance. Based on three clinical scenarios we aim to show the clear added value of measuring TNF serum levels and anti-drug antibodies in daily clinical practice.

Reactive therapeutic drug monitoring

In a patient with secondary loss of response to biological therapy, objectifying disease activity by measuring C-reactive protein and/or fecal calprotectin, performing endoscopy or transmural imaging has been well implemented. However, these analyses will only confirm disease activity but will not be sufficient to guide therapeutic management. In contrast, therapeutic drug monitoring will provide a clear algorithm to decide on unaltered treatment continuation, treatment optimization, switching of therapy within class, or switching of therapy out of class (see Table underneath). Treatment optimization can be achieved by increasing the dose of the biological agent, decreasing the interval between two doses, or adding an immunosuppressive agent. However, before making a therapeutic decision one should always check adherence to treatment, especially for subcutaneous therapies.

Proactive therapeutic drug monitoring

The use of therapeutic drug monitoring in a patient in clinical remission is still debated. Although the primary endpoint was not met in the TAXIT trial (Vande Casteele, Gastroenterology: 2015), the pre-randomization phase showed that less than half of the patient with durable response to infliximab had a serum level within the therapeutic range. One quarter had sub-therapeutic serum levels (9% even undetectable) and benefited treatment optimization, while another quarter had supra-therapeutic serum levels and could be dose de-escalated without a risk of clinical deterioration. Furthermore, patients randomized to the serum level guided group experienced clinical relapse significantly less frequent than patients randomized to the clinical guided group.

Retrospective studies have shown a clear association between anti-TNF serum levels after induction and long-term outcome. However, the prospective TAILORIX study failed to show a clear benefit of infliximab optimization based on infliximab serum levels (D’Haens, ECCO Congress. 2016). Based on the currently available data, a yearly measurement of drug serum levels in an asymptomatic patient seems justifiable.

Therapeutic drug monitoring can be helpful in making decision on treatment discontinuation. For example, in a patient on combined therapy with infliximab and a thiopurine, discontinuation of the thiopurine did not lead to loss of response in patients
with an infliximab serum level above 5 µg/ml (Drobne, Clin Gastroenterol Hepatol. 2015). In STORI, higher infliximab serum levels were associated with clinical relapse after discontinuation of infliximab therapy (Louis, Gastroenterology. 2012).

**General remarks**

In general, one should always take into account the type of assays provided, since therapeutic ranges of anti-TNF serum levels may vary between different assays. Furthermore, drug tolerant or drug resistant antibody assays are clearly more informative than a drug sensitive antibody assay, since they are able to measure anti-drug antibodies in presence of (high) anti-TNF serum levels.

One of the major limitations with the current ELISA assays is the fact that they are quite time consuming. However, new platforms for drug monitoring with a fast turn-around time (less than 20 minutes) are becoming available and will make a huge difference in daily clinical practice.

<table>
<thead>
<tr>
<th>Drug serum levels</th>
<th>Anti-drug Antibodies</th>
<th>Suggested intervention</th>
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| High              | Absent               | Objectify loss of response  
|                   |                      | If confirmed switch out of class |
| Adequate*         | Absent               | Objectify loss of response  
|                   |                      | If confirmed switch out of class |
| Low               | Intermediate or absent | Check compliance  
|                   |                      | Increase serum levels  
|                   |                      | by decreasing the interval  
|                   |                      | or increasing the dose  
|                   |                      | or adding an immunomodulatory drug |
| Absent            | Intermediate or absent | Check compliance  
|                   |                      | Increase serum levels  
|                   |                      | by decreasing the interval  
|                   |                      | or increasing the dose  
|                   |                      | or adding an immunomodulatory drug |
| Absent            | High                 | Switch to another drug within class or out of class |

*Therapeutic ranges based on the ELISA platforms developed by the Laboratory of Pharmaceutical Biology, KU Leuven, Leuven, Belgium*

For infliximab 3–7 µg/ml  
For adalimumab probably 4–10 µg/ml  
For golimumab probably > 1.5 µg/ml  
For vedolizumab probably > 14 µg/ml  
For ustekinumab no clear cut-off yet
Tailoring interruption of anti-TNF in IBD

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Biologic treatments have revolutionized the way we treat inflammatory bowel disease patients (IBD). Anti-TNF antibodies are superior to conventional therapies to achieve sustained remission without steroids, and mucosal healing. The objective of IBD treatment has evolved from symptoms alleviation to a combination of absence of symptoms and intestinal healing. Nevertheless, biologics are expensive and anti-TNF antibodies are associated with an increased risk of infections and possibly skin cancers. Therefore the duration of these treatments may be questioned and stopping them may be contemplated by some patients and clinicians, while it is sometimes even imposed by some jurisdictions across the world. However, the relapse rate in both Crohn’s disease and ulcerative colitis, when stopping anti-TNF after prolonged sustained remission is around 40% after one year. Furthermore in ulcerative colitis, up to 10% may have to undergo colectomy for intractable recurrence. Therefore a systematic withdrawal in all patients in sustained remission is certainly not recommended. The withdrawal may still be an option in some patients and although there is currently no definitive cure for IBD, those patients may have long-standing remission (up to 8 years for around 20% of the patients) without biologics and even without any therapy. When relapsing they may then enter a new successful cycle of biologic therapy. For this strategy, the patient must be carefully selected and then followed-up.

The selection of the patients for a withdrawal strategy must be based on a variety of factors, among which the previous patient history, treatment refractoriness and cumulative tissue damage, the age and comorbidities, the tolerance to the anti-TNF therapy and the patient’s preference, the depth of remission including mucosal or transmural healing and biologic remission on the top of the clinical remission. Combining these factors, one might end up with different profiles, being more or less favourable to an attempt of treatment withdrawal. When a decision of withdrawal is made, the follow-up strategy must also be tailored and intensified. Particularly a regular monitoring with fecal calprotectin and CRP may help to disclose early preclinical relapse, and allow early retreatment.
Session IV

Vedolizumab and ustekinumab
Vedolizumab in UC: For all patients or best patient profile

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Vedolizumab, a humanized anti-α4β7 integrin antibody, is indicated for the treatment of ulcerative colitis (UC) and has been used widely since its approval in 2014. Phase 3 clinical trials in ulcerative colitis demonstrated a variety of outcomes, including induction of remission, clinical response, and endoscopic remission at week 6, while data at 1 year demonstrated prevention of relapse and sustained corticosteroid-free remission. Additionally, vedolizumab showed excellent safety with no increased risk of serious infections or malignancies. The pivotal GEMINI 1 study did not show different outcomes regardless of prior or concurrent treatment with corticosteroids, immune modulators, or TNF blockers, duration of disease, disease severity, or extent of disease with regard to induction or maintenance outcomes. Real world data demonstrates that, unlike in Crohn’s disease, shorter disease duration is not associated with higher rates of response in UC. Some real-world cohorts have demonstrated better efficacy in patients with no prior TNF blocker treatment, with lower baseline disease activity (Mayo Score ≤ 9) and lower CRP (≤ 20 mg/l at induction). One study identified leukocyte count > 9000 x 10⁹/l as reducing the likelihood of steroid-free clinical remission at week 54. Preliminary reports also describe novel laboratory markers predicting response, including higher α4β7 expression on T, B and NK subsets. However, none of the proposed clinical or laboratory predictors of response possess sufficient likelihood ratios to be clinically useful. Until such markers are developed, vedolizumab may be considered for all outpatients with UC, noting the limitation that no studies have been performed in patients with severe, intravenous corticosteroid refractory UC.
Safety of biologics in IBD: Recent updates

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The therapeutic armamentarium for inflammatory bowel disease (IBD) is rapidly growing. Over the last years, novel biological treatments have been developed for Crohn’s disease and ulcerative colitis, namely anti-tumour necrosis factor agents and anti-integrin molecules. Biological treatments have proven their clinical efficacy in IBD; however, their mechanism of action, including the regulation of activation and maintenance of inflammation, may result in patient harm. There has been a debate on whether biologics are associated with important risk of adverse effects (such as serious and opportunistic infections, tuberculosis reactivation, and malignancies), the magnitude of this risk, and whether the risk varies between different treatments or classes.

To date, a large number of randomized controlled trials (RCTs) has examined biological therapies in IBD. Given that the evidence from RCTs ranks high in the proposed hierarchy of evidence, a synopsis of meta-analyses examining safety of biologics in IBD will be discussed. In addition to conventional pairwise comparisons, indirect treatment comparisons, allowing assessment of comparative harm, will be presented. The aim is to summarize and discuss the existing evidence, and identify gaps that warrant further research.
State-of-the-Art Lecture

Predicting the future of treatment for IBD

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The therapy for the two main forms of IBD, Crohn’s disease and ulcerative colitis, has continuously evolved since the fortuitous discovery of the beneficial effects of sulfasalazine in ulcerative colitis patients. In the last couple of decades this evolution has witnessed a switch from an empirical to a pathophysiology-based approach due to an expansion in the understanding of IBD pathogenesis. Today the practicing specialist has a wide range of drugs available at his/her disposal and the benefits to the IBD patients have never been greater. Nevertheless, there is a general consensus that even the most advanced forms of treatment are far from optimal, with some patients failing to respond to any therapy, some needing long-term medications, some constantly switching among drug classes, and many still needing surgical interventions. For all these reasons the search for newer and better forms of treatment is still ongoing, and the therapeutic armamentarium keeps expanding in number as well as type.

The success of anti-TNF biologics has opened the door to the development of monoclonal antibodies against multiple cytokines and cytokine receptors, resulting in both success and failures, and this approach is likely to be pursued by the pharmaceutical industry for another decade or so.

Small molecule therapy has emerged more recently with the aim of blocking the biological activity of signaling molecules, like the JAK/STAT inhibitors, or receptors that regulate lymphocyte sequestration, like ozanimod. Small molecules are easier and cheaper to produce, and the field of small molecules for therapy of IBD will continue to grow for the foreseeable future.

Combination therapies of two or more monoclonal antibodies are already under way, such the current trial with adalimumab and vedolizumab, and more will appear including combination of antibodies and small molecules.

An area that is already being pursued in cancer therapy and will be soon adopted in IBD and other immune-mediated diseases is that of epigenetic therapy. This approach target chromatin modifications involved in pathogenic gene expression patterns, and several classes of drugs are already available. The most common undergoing trials in cancer target histones, such as histone methyltransferases (HMTs) and histone deacetylases (HDACs) with promising results. HMTs and HDACs in particular will soon be used in clinical trials for IBD, and this new trend will grow in the decades to come.
Drugs aimed at modifying the gut microbiome have been used for a very long time, such as pre-, pro- and antibiotics but with limited success, and the same seems to be the case for fecal microbiota transplants, whose occasional success appears to be of only temporary duration. Drugs that block the enzymatic activities of specific microbes are under development, as also are ways to produce microbe-derived beneficial metabolites with anti-inflammatory activity.

Boosted by their well-known microbiota modifying effects, selective diets will eventually be incorporated into IBD therapy, in sharp contrast with what was not done in the past. Diets make a lot of sense, but they require life-long behavioral modifications that fail in most patients because of lack of strict adherence by the patients who still prefer “the magic pill to cure my IBD”.

The study of metabolism of immune cells is presently raising a tremendous amount of interest because the function of different types of immune cells depends of their internal metabolism. Once a better understating of this new field is achieved, it is very likely that metabolism-modifying drugs will be developed, but only time will tell whether or not this novel approach holds real promise.

The continuous and increased ability to manipulate genes, like the CRISPR/Cas9 technology, will eventually also offer therapeutic opportunities for IBD, but this will evolve slowly due to ethical and practical considerations. Before genetic approaches will become reality systems-biology-based approaches will be implemented, and the controlling molecules (hubs) of the IBD regulatory network (the IBD interactome) will be precisely identified, allowing extremely precise drug targeting and ultimately delivering the eagerly expected “precision medicine” for IBD.
Session V

New molecules
JAKs

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Current available treatments for inflammatory bowel disease (IBD) have some limitations and new options are needed. Although targeted biological therapies have been a significant advance, parenteral administration and the potential for immunogenicity are major drawbacks. A new drug class of small molecules, the Janus kinase (JAK) inhibitors fulfills this criteria and has recently shown efficacy in IBD. Convincing clinical data show that the complex cytokine-driven inflammation that characterizes IBD and other immune-mediated diseases can efficiently be modulated by therapeutic inhibition of the JAK proteins.

From a pathophysiology standpoint, the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway has received increasing attention as a novel target for therapeutic intervention because of the potential to modulate numerous pathways in the inflammatory cascade. In addition, compared to currently available antibody-based biologics the small molecules used for JAK inhibition cost less to produce, and the small molecular size allows for oral formulations, which will likely increase treatment compliance. These molecules are also less immunogenic and have a short half-life, allowing for rapid discontinuation, if necessary (e.g., in cases of infection). They also offer additional advantages, including prolonged storage at ambient temperature, fewer outpatient visits, and mitigation of the need for specialized staff to administer drug infusions/injections compared with antibody-based therapeutic agents. Inhibition of the JAK-STAT pathway is, however, not without challenges. Given the complexity of the pathway, inhibition of the Janus kinases simultaneously affects the signaling of several cytokines and hormones, meaning that care must be taken as to what the consequences are and the long-term side effects.

JAKs have previously been approved by regulatory authorities for the treatment of rheumatoid arthritis, psoriasis, dermatitis, and myelofibrosis but have demonstrated a therapeutic benefit in IBD as well. In May 2018, tofacitinib became the first JAK to be approved for IBD in moderately to severely active UC by the FDA, and in June 2018 it received a positive evaluation of the CMPH at EMA. Several other JAKs are in phase 2/3 development in IBD (filgotinib, upadacitinib) while others including gut-restricted JAKs are in earlier phases. There are, however, some safety concerns, because JAK signaling is also involved in a number of important physiologic functions, including hematopoiesis, innate and adaptive host defense, and growth. Hence side effects such as infections (e.g., risk of herpes zoster infections for tofacitinib especially among patients with prior TNF failure and not vaccinated with recombinant zoster vaccine and the risk of cytopenia are major concerns, and in the US the drug's label carries a boxed warning about the potential for serious infections as well as lymphomas and other malignancies. Accordingly, vaccination against shingles should be considered before treatment with tofacitinib and potentially other JAKs as well. Additionally, dose-dependent hypercholesterolemia has been observed, presumably due to inhibition of IL-6 signaling. In this context, it is advised to evaluate lipid profiles 1 to 2 months after treatment initiation. Nevertheless, pooled long-term extension data (1 year) of...
dermatologic patients (receiving 5 or 10 mg tofacitinib twice daily) did not show any clinically relevant increase in the incidence of major adverse cardiovascular events compared with patients receiving placebo. Moreover, the development of JAKs with selective inhibition of specific JAKs (figotinib, upadacitinib) and gut-specific JAKs may result in less pronounced influence on lipid profiles and perhaps fewer side effects in general although long-term follow-up of randomized and real-world cohorts of patients with IBD are needed to accurately determine the general safety profile.

The fact that a significant number of patients with IBD are non-responders to different novel compounds (e.g., TNF inhibitors, anti-integrins, and/or anti-IL12/23) implies that the pathogenesis driving the inflammation does not always depend on these pathways. Furthermore, patients with a secondary loss of response to a given biologic treatment – despite normal trough levels and without antibodies against the active substance – might experience a shift in the predominant pathophysiologic mechanism underlining an innate dynamic potential of the pathogenesis. As a consequence, predictive response biomarkers are highly warranted to guide the optimal treatment strategy for individual patients. Unfortunately, this is currently not a feasible option, and given that JAKs seem to be unaffected by prior biologic treatment, one could argue that JAKs should be kept in reserve for treatment-refractory patients. However, in the end, an individual case-by-case evaluation has to be made on whether to use JAKs as a first, second, or third treatment choice.
New anti-adhesion molecules

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Natalizumab (anti-α4 integrin MAb) established anti-adhesion molecules for treatment of inflammatory bowel disease. Safer agents such as vedolizumab (anti-α4β7 MAb) are now widely used in ulcerative colitis and Crohn’s disease for induction and maintenance of remission or response. Interaction of α4β7 with MAdCAM-1 is key to gut homing of immune cells especially T lymphocytes and hence anti-MAdCAM-1 MAb has been explored in IBD, with generally better results in ulcerative colitis than in Crohn’s disease. In ileal Crohn’s disease interaction between α4β1 and VCAM-1 may also be important. Etrolizumab (anti-β7 integrin MAb) is currently in late phase development. Abrilumab is a further anti-α4β7 MAb that has shown efficacy in phase 2 studies in ulcerative colitis and also in Crohn’s disease. AJM 300, a phenylalanine derivative is an oral inhibitor of α4 integrin that has shown efficacy in ulcerative colitis. Other oral compounds in development are firategrast and TRK170 targeting integrins.

A number of strategies are available to design new anti-adhesion molecules including receptor ligand blockade, allosteric inhibitors affecting affinity/avidity, inhibitors of signaling pathways and inhibitors of transcription – translation pathways that regulate ligand expression. In addition to monoclonal antibodies, oral compounds and anti-sense molecules therefore may provide new molecules that may target different components of intestinal trafficking of immune cells.
Sphingosine-1-phosphate receptor modulators in the treatment of IBD

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The success of the lymphocyte trafficking inhibitor vedolizumab as a therapy for ulcerative colitis and Crohn’s disease has validated the importance of targeting this mechanism in both diseases. Just as complex protein-protein interactions govern the egress of lymphocytes from the vasculature into the gut, similar mechanisms facilitate the exit of these cell via the lymphatics. Interference with the latter process is a potential treatment strategy in IBD.

The sphingosine-1-phosphate (S1P) receptor is expressed on the cell membranes of lymphocytes and endothelial cells in lymph nodes. Lymphocytes follow an S1P concentration gradient in their migration from regional lymph nodes into the blood. S1P agonists interact with these cell surface receptors resulting in internalization and degradation of the target. Thus these agents act as functional antagonists and effector lymphocytes are unable to follow the S1P1 gradient on the lymphatic endothelium, functionally trapping them in lymph nodes and preventing their participation in pathological processes in the gut (1).

Fingolimod, a first generation S1P receptor modulator developed and approved for the treatment of multiple sclerosis (MS), is a nonselective small-molecule agonist to four of the five S1P receptors (S1P1,3–5) (2). Although fingolimod is highly effective for the treatment of MS, it has important side effects including bradycardia, increased risk of herpes infection, macular edema and interstitial lung disease (3) that may result from its relative lack of selectivity. Next-generation S1P receptor modulators with greater selectivity were subsequently developed to overcome this limitation. Ozanimod (RPC1063; Celgene), a S1P receptor 1 and 5 agonist, demonstrated efficacy phase II clinical for the treatment of UC (TOUCHSTONE, NCT01647516) (4). In this study 197 patients were randomly assigned to either placebo, 0.5 or 1-mg of oral ozanimod daily. The 1-mg dose showed an increased rate of clinical remission as compared to placebo (16% vs. 6%, p = 0.048 at week 8 and 21% vs. 6%, p = 0.01 at week 32). Ozonomod was well tolerated, the most common adverse effects were headache and anemia. Ozanimod is currently being tested in a phase III trial in UC (NCT02435992) and a phase II trial in CD (NCT02435992). Another selective S1P modulator, Etrasimod (APD334; Arena) is being evaluated in UC and preliminary positive results have been reported from a placebo-controlled phase II trial in UC (NCT02447302, NCT02536404).

The efficacy, safety and future role of S1P agonists in IBD treatment algorithms will be discussed.
References:


Anti-fibrotic drugs for Crohn’s?

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Crohn’s disease (CD) is characterized by the frequent occurrence of fibrotic strictures and subsequently the need for surgery. Up to two thirds of patients with CD may develop either a structuring or penetrating disease course within 10 years after diagnosis (1). Up to 80% of all CD patients undergo surgery at least once during the course of their disease (2, 3). In half of these patients intestinal obstructions and strictures are the indication for surgery. Subsequently, intestinal fibrosis is the reason for resective surgery in approximately one third of all CD patients (4). It is still unclear which factors induce fibrosis in some patients and not in others. Epithelial-mesenchymal transition (EMT) is involved in the pathogenesis of intestinal fibrosis. It represents a process in which disaggregated epithelial cells reshape with increased mobility and changed metabolic functions (5). To develop effective anti-fibrotic drugs, fibrosis needs to be viewed as a pathological process distinct from inflammation.

At present, there are no approved or effective anti-fibrotic therapies approved for CD. Therapy of fibrosis is complicated by the fact that a wound healing response is essential in CD. Another important problem for the development of anti-fibrotic therapies in CD is the lack of clinical trial endpoints. The International organisation for the study of IBD (IOIBD) and others have stared initiatives to define such clinical endpoints or imaging endpoints for fibrosis studies in CD. In lung fibrosis pirfenidone has been studied in several clinical trials and approved in this indication (6). As αv-integrins can activate matrix-bound latent TGF and αvβ6 integrin plays a role in EMT (see above) specific antibodies against αvβ6 integrin are studied in lung fibrosis. As circulating mesenchymal cells express the CXCR4 chemokine receptor antagonizing antibodies against this receptor have been tested and show promising activity. Blockade of the TGFβ signalling pathway also seems to be promising (6). Specific inhibition of Smad3 by SIS3 does not affect Smad2 phosphorylation but completely blocks activation of Smad3 and has beneficial effects in diabetic nephropathy (6).

Further therapeutic options are second generation and wide spectrum tyrosine kinase inhibitors. They inhibit growth factor receptor signalling thus reducing fibrosis in animal models and some patients with tumor associated fibrosis. PPARγ inhibitors had beneficial effects in lung, liver and kidney fibrosis. LDE223, an inhibitor of hedgehog signalling has been beneficial in bleomycin-induced fibrosis. Further treatment strategies tested in various fibrotic diseases are inhibition of specific molecules by microRNAs.
References:


New anti-IL23 blockers

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Chronic mucosal inflammation is the main pathologic signature of Crohn's disease (CD) and ulcerative colitis (UC), the major forms of inflammatory bowel disease (IBD). The inflammatory process is believed to be caused and sustained by an aberrant immune response against harmless bacteria contained in the gut microbiota. Although the primum movens causing the loss of tolerance against normally tolerated antigens remains unclear in these patients, the number of cell subsets and cytokines involved in the inflammatory process significantly increased in the last two decades. Initially believed to be mediated by T helper of type (Th) 1 cells, characterized by the expression of the transcription factor Tbet and by the signature cytokine IFN-gamma, it is now known that the activity of Th17 cells is pivotal in the inflammatory process occurring in CD and UC. Th17 cells, characterized by the expression of the transcription factor RORc and by a set of cytokines including IL17A, are normally present in the gut mucosa where they are essential to maintain the immune homeostasis. However, their number and the expression of their signature cytokines result increased in active IBD. Moreover, data from experimental models of colitis indicate that Th17 cells are required for the development of intestinal inflammation. Based on its role in the intestinal inflammatory process, the Th17-axis has become the target of several experimental drugs and IL23 inhibition have shown efficacy in CD and more recently in UC. While several cytokines are involved in the differentiation of Th17 cells (i.e. IL1beta, IL6, IL21, TGF-beta), IL23 is essential for their maintenance and pathogenic activity. The first IL23 blockers to be developed were the monoclonal antibodies briakinumab and ustekinumab directed against the p40 subunit shared by both IL12 and IL23. In contrast to briakizumab, ustekinumab showed efficacy in clinical trials and it is now approved in US and EU for CD.

Since experimental data indicate that IL23 might contribute more specifically to mucosal inflammation, with IL12 mediating more systemic effects, selective targeting of IL23, via the unique IL23p19 subunit, was thought to be more effective. Rinsakizumab and brazikumab (MEDI2070) were developed to target IL23p19. Both the IL23p19 blockers showed efficacy in phase 2 trials and although differences in trial design make these trials not directly comparable to those testing ustekinumab, the selective block of IL23 might be as efficacious as the concomitant block of IL12 and IL23 through p40 neutralization. Mirikizumab, another IL23p19 selective blocker, met the primary efficacy endpoint in a phase 2 trial in UC and is currently evaluated in CD. Finally a phase 2/3 trial evaluating the efficacy of the anti p19 guselkumab, recently approved for the treatment of plaque psoriasis, is currently recruiting patients affected by moderately-to-severely active CD.

IL12/IL23 and the selective IL23 blockers represent the next generation anti-cytokine agents that have shown efficacy in IBD. These successes reflect the advance of knowledge in the pathogenesis so as the multiple strategies under development aimed at modulating the IL23/Th17 axis.
Session VI

Tailoring surgery to patients
Tailoring surgery in CD

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In the treatment of Inflammatory Bowel Diseases (IBD) despite advances in medical therapies, surgery has maintained a leading role in the management of complications of the disease, as well as in cases of failure of medical therapy. We will discuss the role for a personalization in debated fields of surgical treatment of Crohn's disease and ulcerative colitis. Tailored surgical treatment in IBD starts way before the operation "per sé". Indeed, the optimization of the patient nutritional status prior to surgery as well as the timing of surgery play a key role with regards to the outcome. Furthermore, In order to plan a personalized operation, preoperative MRI enterography, has shown up to 90% sensitivity in predicting findings and optimizing surgical approach in Crohn's disease. Surgery has become more and more minimally invasive, struggling for a difficult balance between guidelines and personalized treatment tailored on the single patient's need. New techniques, such as single-port approach and transanal proctectomy have shown the potential to reduce the impact of surgery and the possibility to improve the short term outcomes. In conclusion, there is no room for fixed management for surgery in IBD and a tailored approach is key to better outcome in each specific patient.
Perianal Crohn’s disease

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Disease of the perianal region is common in Crohn’s, occurring in ~50% of patients. Perianal manifestations are often quite debilitating, and are thought to represent a more aggressive form of disease on the Crohn’s spectrum. In ~5% of patients, the perianal region is the first manifestation of the disease. Typical symptoms range from pain and itching, to purulent drainage and bleeding. Occasionally, the treatment can add to the perianal symptoms – such as topical steroids or setons. The pathology in the perianal region can include abscess/fistula, stenosis, fissure, scarring, large “elephant ear” skin tags, and rarely malignancy. It is important to not only manage the local manifestations, but also work-up the more proximal bowel for active disease. In this manner, the perianal region can act as a “window” into the abdomen. Anoscopy (often utilizing a pediatric scope), CT or MR enterography and endoscopy are typical adjuncts to assess the presence and extent of disease. EGD, in addition to colonoscopy, is useful to look for gastroduodenal disease. Management of the perianal disease depends on the actual pathology that is present. However, often an examination under anesthesia is required to assess the perianal region, as concomitant disease processes are often present, and patients may not tolerate office examination. While medical management is typically required – especially for patients with proximal disease – principles of early intervention remain to control sepsis by draining pus, and often included placement of setons, biopsy indeterminate lesions to rule out malignancy, and protect the perianal skin. For patients with severe disease diversion or proctectomy are occasionally indicated.
Perioperative medications

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The medical therapy for Inflammatory Bowel Diseases (IBD) has greatly evolved in the last decades, leading to increased control of the diseases with the sequential introduction of immunomodulators and biological drugs targeting TNFα molecules and the α4β7 integrin. Despite these results, up to 60% of patients with ileocolonic CD and up to 20% of those with ulcerative colitis will eventually require a surgical treatment during the course of their disease. The short-term outcomes after surgery for IBD have also markedly improved in the last decades due to better perioperative management as well as the introduction of more effective and safer techniques. Nevertheless, postoperative complications, most of them being of infectious origin, might present in up to 40% of patients undergoing surgery. Many risk factors for these complications have been identified, including poor preoperative nutritional status, severity of the disease at the time of surgery, presence of comorbidities, experience of the surgical team. Undoubtedly, the perioperative drug regimen is another possible risk factor, particularly if we consider that most of the treatments used for IBD profoundly affect the immune system.

The most frequently utilized drugs in IBD are mesalazine, steroids, thiopurine and calcineurin inhibitors, anti-TNF and anti-integrin. While mesalazine has no effect on the surgical outcome of IBD surgery, steroids are well known risk factors for post-surgical complications, so that steroid weaning should be attempted in patients being treated with prednisone > 20 mg/daily for more than 6 weeks. However, on one side, steroid tapering cannot be too fast in order to avoid the so called Addisonian crisis; on the other side, a delay in surgery may be deleterious. Thus, in all cases in which surgery is promptly needed, the easiest and less risky surgical approach should be undertaken, such as a staged procedure in cases of ulcerative colitis, a laparoscopic approach and a temporary protective ileocolostomy in Crohn’s disease. As far as thiopurines and ciclosporine are concerned, literature data support their safety when used in the perioperative time.

The possible effect of the preoperative administration of anti-TNF on postoperative results has remained controversial for quite a long time. However, more recently, a meta-analysis and some large studies appear to indicate an increased risk of postoperative sepsis, intra-abdominal abscesses, anastomotic leak, wound infections in both Crohn’s disease and ulcerative colitis patients treated with anti-TNF before surgery. Concurrent use of steroids and Anti-TNF drugs enhances the risk of such complications. Thus, treatment withdrawal must be considered but the safest period of discontinuation before surgery in order to reduce the risk is currently unknown. A wise surgical strategy is obviously encouraged (i.e. staged proctocolectomy, possible protective ileostomy) also in these cases.

After controversial results reported in early studies, very recently a systematic review and meta-analysis was conducted on 4 studies reporting data on patients treated with Vedolizumab preoperatively. This meta-analysis did not detect an increased risk of
postoperative complications with preoperative VDZ exposure; the risk of overall complications appeared to be lower in UC patients in comparison with those with anti-TNF exposure. These results deserve further verification in future studies.

In conclusion, perioperative medications may play an important role in determining the success of a surgical procedure. The evaluation of all perioperative medications as possible risk factors for potential post-surgical complications should be performed routinely as a part of treatment personalization in IBD.
Session VII

Challenging clinical scenarios
Patients with 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 contra-indications 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. No data are available for ustekinumab and tocilizumab. 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.

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A patient with previous opportunistic infections

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The key goals of managing Inflammatory Bowel disease are to induce clinical remission and then maintain this whilst also achieving mucosal healing to prevent disease progression. Over the last decade, we have seen the introduction of biologic and small molecule therapies that target specific aspects of the inflammatory cascade driving intestinal inflammation. Many of these have shown efficacy for clinical endpoints that include mucosal healing. Although these drugs have revolutionised the care of patients with IBD they now make up in excels of 70% of the direct health care costs. Unlike conventional medications for IBD such as steroids, thiopurines and methotrexate, the new generation of therapies, in part due to their targeted mode of action, are associated with class specific risks of opportunistic infections. These often manifest as re-activation of latent infections in patients with prior exposure. For example, anti TNF agents may cause re-activation of latent mycobacteria resulting in refractory infections associated with high morbidity. Likewise, tofacitinib is associated with reactivation of herpes zoster and subsequent shingles infections. Therefore, clinicians managing patients with IBD must be aware of the importance of appropriate screening for prior exposure to infections and appropriate vaccination of naïve patients. At a minimum this will include a thorough history, appropriate blood tests and a chest x ray. It is also important to consider the increase in incidence of both Crohn’s disease and ulcerative colitis in developing countries where exposure to infection in childhood may be more likely. The global society in which we live means that our IBD clinics include patients from many countries that may have very different infection exposure profiles. IBD physicians should ensure that their MDT includes expertise in opportunistic infections and access to appropriate specialist advice.
Crohn’s disease and tuberculosis in endemic areas

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Tuberculosis (TBC) is one of the most important diseases in human history. Although from a developed world perspective the relevance of the disease has clearly diminished in recent decades, from a global perspective it remains a very significant problem causing 9.6 million cases of active diseases and 1.5 million deaths in 2014. Poverty has been the main risk factor for the disease, and remains so today, although HIV infection has fueled a global reactivation of the disease. Crohn’s disease (CD) is an emergent disease, with quickly increasing incidence, clearly related to economical development. A world map shows a completely contrary distribution of both diseases from a global and many times national perspectives. Paradoxically, intestinal TBC and CD can share identical clinical pictures. Both diseases show, for instance, granulomas as very characteristic histopathological feature. Treatment is completely different, however. Immunosuppressive drugs frequently used in CD aggravate tuberculosis, and tuberculostatic treatment is unuseful in TBC. Further complicating the scenario antiTNF drugs, key in the current armamentarium for CD, can make latent tuberculosis becoming active disease. Differential diagnosis is not always easy, very particularly in those geographical areas with endemic TBC in which CD incidence is rapidly increasing. Rectal bleeding, sigmoid affection, and several types of endoscopic lesions favor CD, while pulmonary symptoms may suggest TBC. Differential has to consider a combination of clinical, endoscopical, radiological, pathological, serological and microbiological data. Several indexes combining various factors have been suggested, and in fact one is available in internet with AUC > 90% for differentiation (Limsrivilai J. AJG 2017; www.pathology.med.ucmich.edu/shiny/tbcrohns/). However, no test or combination can substitute for high index of clinical ability and follow-up of the patient to considere any discrepancy which could suggest a failed diagnosis. Tuberculin skin test (TST) and IGRA (Quantiferon Gold® is the most commonly used) should be part of first evaluation in any inflammatory bowel disease patient. In case of doubt, a trial of antituberculous treatment should be always considered before immunosuppresants in highly endemic areas.
Fistulising CD: 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 fistulising perianal CD, since the findings influence the therapeutic strategy. Examination under anaesthesia (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 effect 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 fistulising 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 fistulising 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.
Fistulising CD: Pro surgical treatment

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Fistulising CD represents the most aggressive phenotype of CD, usually followed by chronic inflammation and stenosis, during the evolution of the condition over time. There are clear limitations of medical therapy in the fistulising form of CD used in isolation. Abdominal fistulas (internal or external) are usually associated to an important inflammatory component, and represent clear indications for surgical therapy in association to medical treatment, mostly via minimally invasive techniques. Patients who are referred to surgical therapy are often under treatment with biologics, and special attention must be given not only to the drugs on board, but also to the nutritional status, previous use of steroids and the abdominal environment, in order to make the right decision for the surgical strategy: primary anastomosis or diverting stoma. The primary source of CD must be primarily resected and target organs, usually recruited to the inflammatory process can be sutured if not affected by the disease and have good tissue conditions. In perianal fistulising CD, a combined approach with medical therapy (mostly anti-TNF therapy in association with antibiotics) and surgery represents the gold standard of treatment in 2018. The surgeons need to clean the fistula tracks during examinations under anesthesia, reduce the perianal sepsis and dilate associated anorectal stenosis which can perpetuate the disease activity. After this “perianal hygiene” patients can start anti-TNF therapy to reduce the inflammatory process not only in the fistula tracks but also in the rectal mucosa, aiming mucosal healing. Additional surgical techniques can be used after mucosal healing and fistula epithelialisation in order to treat the mechanical component of the fistulas, with advancement flaps, LIFT procedure, or other techniques. In this presentation, all these concepts of the surgical management of abdominal and perianal fistulising CD will be discussed in detailed illustrations of two case scenarios. A multidisciplinary team with intense surgical participation, before, during and after the main parts of therapy is essential for good outcomes in patients with fistulising CD.
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POSTER ABSTRACTS

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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 α was 0.88, item-total correlations were good and there was no ceiling or flooring 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 α = 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.
Inflammatory bowel disease in the UK: Is care improving?

Laith Alrubaiy, Ian Arnott, Aimee Protheroe, Michael Roughton, John Williams

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.
Conservative treatment of patients after excision of chronic anal fissure

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Introduction: Anal fissure have been reported in 11–15% of patients with pathology of the colon.

Methods: The main group (group I) consisted of 25 patients (48%), which is 7 days after excision of chronic anal fissures with the anal sphincter divulsa was appointed a suppository Salofalk® worth us scheme is 250 mg 2 times a day for 14 days.
The control group (group II) accounted for 27 patients (52%), which is 7 days after excision of chronic anal fissures with the anal sphincter divulsa was appointed a suppository natalise scheme 2 times a day for 14 days.
Statistically significant differences between groups of patients by sex ($\chi^2 = 1.44; p < 0.05$), age ($t = 0.01; p < 0.05$) were not fixed.
Patients with chronic anal fissure was considered cured after complete epithelisation of the surgical wound.

Results: The level of pain on a visual-analog scale for the seventh day in group I – 3.6 ± 0.4 and group II – 5.6 ± 0.6, statistical difference $t = 2.77; p < 0.05$; on the 14th day in group I – 0.96 ± 0.33 and group II – 3.9 ± 0.63, statistical difference $t = 4.13; p < 0.05$; on the 28th day in group I – 0 ± 0.005 and group II – 0.45 ± 0.33, statistical difference $t = 1.36; p = 1.05$.
In the main group of patients on the 28th day complete epithelisation of wound was noted in 18 (72%) patients, while in patients of the control group – 14 (52%).

Conclusion: Epithelisation of wounds in the early stages, as well as faster relief of manifestations such as blood in the chair, pain syndrome, create an advantage for both patients and coloproctologists in the use of Salofalk® suppository after surgical treatment of chronic anal fissure.
Cognitive behavioural therapy for the management of inflammatory bowel disease-fatigue: A pilot randomised controlled trial

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Introduction: Fatigue is the third most prevalent symptom for patients with inflammatory bowel disease (IBD), yet optimal strategies for its management are unclear. Targeting cognitions, emotions and behaviour related to fatigue through cognitive-behavioural therapy (CBT) may be a viable option to improve fatigue and quality of life (QoL) in IBD.

Methods: This single centre, two-arm, pilot randomised controlled trial (RCT) aimed to assess the feasibility and initial estimates of efficacy of a CBT intervention for the management of IBD-fatigue. Participants were recruited from one tertiary referral centre. Intervention Group 1 received a CBT manual for the management of fatigue, one 60-min session and seven 30-min telephone sessions with a therapist. Control Group 2 received a fatigue information sheet without therapist help. A nested qualitative study evaluated patients’ and therapists’ experiences, and IBD-healthcare professionals’ (HCPs) perceptions of the intervention.

Results: Eighty-nine participants were assessed for eligibility. Of these, 31 of the 70 eligible participants consented to participate (recruitment rate of 44%). Of the 15 participants randomised to the intervention group, 13 (87%) started it and 10 (77% of those who started) completed all 8 sessions. Twenty-two (71%) participants completed baseline and 3-months’ follow-up questionnaires. Initial estimates of efficacy showed a reduction in fatigue scores and an improvement in QoL scores at 3-months post-randomisation. The difference in change in scores between Group 1 and Group 2 was significant for impact of fatigue (mean difference = -26.89, confidence intervals = -51.39, -2.39, p = 0.034). The intervention was acceptable to participants and feasible for therapists to deliver. HCPs reported that the intervention would be broadly applicable but resource constraints may limit its implementation.

Discussion/Conclusion: A full-scale effectiveness RCT testing CBT for IBD-fatigue is feasible and has a potential for improvement of fatigue with some changes to the protocol.
Gastroduodenal Crohn’s disease – Report of 4 cases

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Introduction: Crohn’s disease can affect all the gastrointestinal tract, but up to 4 percent of patients with Crohn’s disease have gastroduodenal involvement. Gastroduodenal Crohn’s disease has distinct clinical, therapeutic and prognostic features.

Methods: Four patients; two males of 53,44 years old two females of 25,40 years old followed up Crohn’s disease with colonic involvement. They admitted with epigastric pain, weight loss. They underwent endoscopic examinations in various time. Upper gastrointestinal endoscopy revealed aphthous in stomach. Geographic duodenal ulcers were also observed in three of them. Histopathologic findings of biopsy specimens were conclusive. Granulomas were found. All of them had already using mesalazine. Corticosteroids and proton-pump inhibitors were started for two of them. One have using infliximab, three patients had their disease controlled. The other patient developed pyloric obstruction and had to be operated. After operation vedalimumab were started to control the disease.

Discussion/Conclusion: Crohn’s disease can affect all the gastrointestinal tract, but gastroduodenal involvement is rarely seen. In our clinic we determined 4 patients in 2000 patients followed up Crohn’s disease for 10 years.
Disease phenotype and features for natural history of paediatric-onset ulcerative colitis

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Introduction: Ulcerative colitis (UC) is an immune-mediated disease characterized by mucosal inflammation that generally begins in the rectum and involves a variable extent of proximal colon. UC manifests more aggressively in children than in adults with more extensive disease and moderate-to-severe symptoms that require intensive treatment and close monitoring. The aim of our study was to evaluate the disease phenotype and natural history of paediatric-onset UC diagnosed at a tertiary referral centre for Paediatric Gastroenterology.

Methods: A retrospective study was conducted of all newly diagnosed patients with UC over a 6-year period (between June 2011 and November 2017). Demographic data and clinical characteristics were assessed at diagnosis and at the follow up. Records were reviewed for disease extent and severity, complications and treatment escalation.

Results: 46 UC patients – 24 girls (52.2%) and 22 boys (47.8%) were included. Median age at disease onset was 14 years (range 2–17 years). Bloody diarrhoea was the debuting symptom in most of our UC patients 21/46 (45.7%). Other presenting features were non-bloody diarrhoea 16/46 (34.8%) and abdominal pain 6/46 (13.0%). At the time of diagnosis more than half of our patients 26/46 (56.5%) had extended disease (extensive or pancolitis). According to the Paris classification, 19/46 (41.3%) presented with pancolitis (E4), 7/46 (15.2%) with extensive colitis (E3), 15/46 (32.6%) with left-sided UC (E2) and 5/46 (10.9%) with ulcerative proctitis (E1). Severe disease (PUCAI > 65) was observed in 16/46 (34.8%) of our UC patients. No clinical variables at the diagnosis were identified to be related to the subsequent extension of the disease. An extensive and severe disease at the diagnosis were associated with treatment escalation and increased risk of surgery.

Discussion/Conclusion: Paediatric-onset UC is characterized by extensive bowel involvement and severe clinical presentation. The disease behaviour is difficult to predict especially in paediatric population.
Anti-tumour necrosis factor drug cessation in IBD – A source of anxiety?

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Introduction: This retrospective study evaluated the reasons for stopping infliximab and adalimumab in patients treated for inflammatory bowel disease (IBD) with specific attention to patients developing anxiety.

Methods: A database of all IBD adult patients commencing and discontinuing infliximab and adalimumab has been maintained prospectively at our centre since 2008. Using this database, electronic clinic notes were examined to establish the reasons why anti-TNF therapy had been discontinued.

Results: Since 2008 we have treated 333 IBD patients with infliximab and 272 with Adalimumab. Infliximab therapy was discontinued in 199 (59.8%) patients. Infliximab was stopped following clinical response/remission in 15% of patients (in accordance with NICE guidelines\(^1,2\)). 12% of patients were primary non-responders. Only 20% of patients were documented to have secondary loss of response. Side-effects accounted for 23% of those who stopped infliximab, 6 patients (3%) due to debilitating mood disturbance or anxiety.

<table>
<thead>
<tr>
<th>Reason for stopping Infliximab (199 patients total)</th>
<th>Total</th>
<th>Crohn's</th>
<th>UC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>29 (15%)</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>Primary non-responder</td>
<td>24 (12%)</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Secondary loss of response</td>
<td>40 (20%)</td>
<td>29</td>
<td>11</td>
</tr>
<tr>
<td>Side-effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Infection</td>
<td>45 (23%)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>- TB</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Severe allergic type reaction</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Mood disturbance/anxiety</td>
<td>6 (3%)</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>- Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss to follow up/moved out of area</td>
<td>11 (6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other or unable to establish</td>
<td>50 (25%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adalimumab was discontinued in 136 patients (50%). This was due to clinical response/remission in 24% (in accordance with NICE guidelines\(^1,2\)). 10% of patients were primary non-responders, with 23% experiencing secondary loss of response. In 6% of those who stopped Adalimumab, debilitating mood disturbance or anxiety was cited as the cause.

Female patients accounted for the majority of those affected by mental health disturbance (62% with adalimumab, 83% with infliximab).
Discussion/Conclusion: In this study we identified that debilitating mood disturbance or anxiety was a common reason for anti-TNF cessation, affecting 1.8% and 2.9% of the total number of patients treated with infliximab and adalimumab respectively. Previous studies have reported psychiatric disturbance in approximately 1% of patients receiving anti-TNF medications\(^3\)\(^4\). The frequency of psychological side effects should warrant routine discussion during follow-up appointments. Future studies and National registry data may help identify whether infliximab or adalimumab has a greater effect especially in patients with prior mental health disease.

References:

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Comparison of long-standing pediatric-onset and adult-onset inflammatory bowel disease

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Introduction: Multiple studies show that onset of inflammatory bowel diseases (IBD) during childhood has a different disease pattern and more aggressive evolution compared to adult onset.

The aim is to analyze the rate of complications of childhood-onset disease and to compare them with characteristics of adult-onset disease in patients

Methods: A retrospective comparative study was conducted from January 2014 to December 2017. Seventy-nine patients with Crohn’s disease (CD) and 50 patients with ulcerative colitis (UC) were retrospectively divided into pediatric onset (age at diagnosis ≤ 18 years) and adult onset (> 18 years) patients.

Results:
Among the CD patients, 13 (16.4%) had pediatric-onset. The comparison of the rate of intestinal complications between age groups yielded the following results: strictures were more frequent in pediatric-onset patients (66.6% vs. 46.1%, p = 0.01). The overall prevalence of abdominal penetrating disease was the same between the 2 groups (53.8% vs. 43.9%, p = 0.2). In addition, the rate of perianal fistulizing disease was similar (30.7% vs. 28.7%, p = 0.1). The rate of resectional surgery was not different in pediatric- and adult-onset CD patients (61.5% vs. 68.1%, p = 0.1). The rate of the assessed treatment with anti-TNF-α antibodies were higher in pediatric CD onset (69.2% vs. 46.9%, p = 0.04).

In UC patients, 20% (n = 10) of patients had a pediatric-onset disease. Pediatric-onset disease was associated with a higher rate of acute severe colitis (60% vs. 23%, p = 0.006) at diagnosis and increased risk for colectomy (30% vs. 10%, p = 0.004). The rate of treatment with anti-TNF-α antibodies was higher in pediatric-onset patients without colectomy (60% vs. 22%, p = 0.03).

Discussion/Conclusion: In our study, patients with pediatric-onset IBD exhibit a more severe disease: more stricturing in pediatric onset CD and more acute severe colitis in pediatric onset UC, explaining the more frequent require of immunomodulators therapy in this population.
An association between anti-Saccharomyces cerevisiae antibodies (ASCA) and recurrent ileitis following total colectomy: A case series

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Introduction: Inflammatory changes of the distal ileum in ulcerative colitis (UC) may be observed in backwash ileitis and after total colectomy (TC) with ileal pouch. The IgG anti-Saccharomyces cerevisiae antibody (ASCA) positivity rate is known 60–70% in patients with Crohn’s disease, 10–15% in patients with UC and less than 5% in patients with non-inflammatory bowel disease colitis. The goal of this paper is to determine the role of ASCA status on recurrent ileitis following TC that lead to altering the initial diagnosis to indeterminate colitis.

Case Series: A case of a 28-year-old female is presented with a 15-year history of UC. TC was done at age of 18. 10 years later, recurrence was observed endoscopically in TI and treatment with infliximab resulted in remission. A second patient presenting was 28-year-old female with a 10-year history of UC. 8 years later TC, during endoscopic control, pathology showed TI and she has been treated with infliximab for a year. The third patient was 65-year-old male with a 36-year history of UC, had a TC 7 years later from diagnosis. TI was seen after 20 years later. After treatment with infliximab and adalimumab, mesalamine has been used for maintenance. The fourth patient presenting was a 55-year-old female with a 26-year history of UC, underwent TC 14 years ago. After 10 years later, routine endoscopy revealed TI. With receiving infliximab, remission has been maintained for more than 4 years. The IgG ASCA positivity was found in all patients.

Discussion: These four cases demonstrate that ASCA positivity is associated with recurrent ileitis following colectomy for UC and support using ASCA as a prognostic marker in patients with UC.
Recurrent Sweet’s syndrome secondary to ulcerative colitis: An uncommon association

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Introduction: Sweet’s syndrome (SS) or acute febrile neutrophilic dermatosis, is a condition characterized by the sudden onset of fever, leukocytosis, and tender, erythematous, well-demarcated papules and plaques which show dense neutrophilic infiltrates on histologic examination. SS can present in several clinical settings: classical (or idiopathic), malignancy associated and drug-induced SS. The association between inflammatory bowel disease (IBD) and SS was first described in 1988. It is a rare extraintestinal cutaneous manifestation (ECM) of IBD and ECMs are seen more common in Crohn’s disease (70%) than in UC (30%). The most common skin or mucocutaneous lesions associated with IBD are erythema nodosum (EN), pyoderma gangrenosum (PG), and aphthous stomatitis.

Case report: 33-year-old male diagnosed with UC at the age of 20 and at the time of the diagnosis, he presented to the Dermatology Clinic with erythematous papular lesions, scattered over his face and neck. He denied using any drug or having systemic symptoms. Skin biopsies found neutrophil rich dermal inflammation consistent with SS. His skin lesions dramatically improved with systemic corticosteroid (CS) treatment. After tapering prednisolone, intermittent exacerbations were reported and colchicine, cyclosporine were added to CS. Under treatment with infliximab and mesalazine patient has been in clinical remission for 6 years. During the remission of UC, no recurrence of SS was observed.

Conclusion: Because different skin lesions can develop in patients with UC, SS associated with UC often misrecognized. Co-existence of SS and UC were not defined in large series of studies in literature and case experiences should be combined so that the co-existence can be understood when present.
Leucopenia in a patient with Crohn’s and Von Gierke’s (glycogenosis 1b) disease

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Introduction: A strong association exists between glycogen storage disease type 1b (Von Gierke’s disease) and inflammatory bowel disease. However, the occurrence of inflammatory bowel disease in patients with glycogen storage disease lb is rare. Leucopenia is a common hematologic manifestation in patients with Von Gierke’s disease. But the basis for leucopenia/neutropenia and neutrophil dysfunction in Von Gierke’s disease are poorly understood. Furthermore, leucopenia in patients receiving imunosuppressive therapy is a well known clinical manifestation.

Methods: Case presentation.

Results: A 41-year-old female patient was diagnosed with Von Gierke’s disease when she was 10 months old. Her disease was clinically presented by not growing fast enough, not gaining enough body weight, enlarged liver, swollen belly and low muscle tone. At the age of 20 she was diagnosed with Crohn’s disease. Two years later, while on topic therapy (automedication), she has undergone right hemicolecotomy with formation of ileotransverse anastomosis due to subtotal stenosis of ascendent colon. In laboratory findings, leucopenia, hyperuricemia, hypertrigliceridemia and microcytic anemia were observed. In 2013. a floride disease of anus, sigmoid colon with stenosis of anastomosis was diagnosed. While she was treated with azatioprin in reduced dose progression of leukopenia was observed. Since leucopenia was still present and further hematologic testing were needed, in 2016. azatioprin was changed into metotrexate. Under low dose metotrexate therapy progression of leucopenia was again evident and 6 month later therapy was stopped since her disease was in remission (clinically and endoscopically). Latest reevaluation of disease showed that a patient is still in remission and leucopenia present as well. A standard procedure before application of biologic therapy started, but the patient is reluctant to make a decision about this treatment.

Discussion/Conclusion: Patients with concomitant Crohn’s and Von Gierke’s disease can experience severe leucopenia due to clinical activity of Von Gierke’s disease and cytotoxic effect of azatioprin and metotrexate. Careful application of these two medications is needed, considering all possible benefits and complications of specific therapy.
Surgical rates for Crohn’s disease: A monocentric cross section study from Turkey

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Introduction: Despite the medical treatment remains the first choice for most inflammatory bowel disease (IBD) patients, up to 70% of patients with Crohn’s disease (CD) will require surgical treatment during their lifetime.

Methods: We conducted a monocentric retrospective study including all inpatients with a previously confirmed CD followed in Ankara University Ibni Sina Hospital Gastroenterology and Hepatology Clinic between June 2016 and March 2018. Epidemiologic and clinical data were collected through the electronic medical records.

Results: We studied 213 patients with CD: 100 (46%) females and 113 (54%) males (The sex ratio F/M = 0.88). The mean age was 40 ± 13.8 and the mean IBD duration was 6.7 ± 5.5 years. Due to endoscopic imaging performed in our center, 73% of these patients had ileocolonic involvement, 16% of them had only ileal involvement and solely colonic involvement observed in 9% of the patients. 75% of patients received mesalazine and 60% of them were treated with azathioprine. Patients received the following biologics in their treatment regimen: infliximab (40%), adalimumab (25%), certolizumab pegol (7%), vedolizumab (8%). A total of 86 (40%) patients underwent surgery (32 females, 54 males; the sex ratio F/M: 0.59), 32% of these patients had required more than one surgical procedure. 34% of 86 patients had surgeries due to perianal fistulas. 12% of patients had perianal/intra-abdominal abscess. 9% of patients had total colectomy and 27% of patients had right hemicolectomy. 23% of patients had ileocecal resection.

Discussion/Conclusion: Our findings indicate that even though the frequent use of new biologic agents in CD, surgery still have a crucial role in treatment.
Possible complications during treatment of patients with M. Crohn – Case report

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General Hospital "Euromedic", Belgrade, Serbia and Montenegro

- M. Crohn cause unknown, occurs as consequence of interaction between genetic factors and environment
- Patients with compromised immune system which has significant effect and reaction to given treatment for IBD

Patient S.R. diagnosed with M. Crohn in 2008
- Damages on colon and ileum
- Because of the extensive changes in first blood test results, patient was given treatment with corticosteroids 60 mg Prednisolon
- Fast relaps because of lower dose of corticosteroids 10 mg
- New treatment: Immunosuppressant AZATHIOPRINE, first dosage 50 mg
- Development of acute pancreatitis at 100 mg of azathioprine
- (Strong abdomen pain with elevated serum lipasa, result at MSC)
- Canceled treatment with azathioprine
- Results of studies show that acute pancreatitis develops with patients with M. Crohn which had therapy with azathioprine, between 2 and 7.3% treated patients and its usually mild not severe
- Disease extremly active (clinically, lab, endoscopic) New treatment
- ADALIMUMAB induction protocol 160….80 mg s.c.
- Before giving third dose, patient has high body temperature, throat pain, severe lymphadenopathy). No reaction to antibiotics
- Development of urticaria, symptoms taken as reaction to
- New treatment: Cortico therapy (Pronison 60 mg), all symptoms are gone

Unwanted effects of adalimumab
- Soar throat
- High body temperature (visoka temperatura,)
- Urticaria
- Palmar Erythema
- Alopecia areata....
- Appearance of all side effects simultaneously is extremly rear
- Symptoms get worse with decrease of cortico dosage to 40 mg
- Urticaria intensifies
- with Palmar Erythema
- DEVELOPE alopecia areata
Biologicall treatment canceled
New treatment: METHOTREXATE 25 mg s.c.
Symptoms reduce after 3rd dosage
Patient develops toxic hepatitis (elevated transaminase x10 from normal methotrexate canceled)

M. Crohn disease still active clinically, endoscopically, lab
All symptoms developed as consequence of adalimumab persist

New treatment: vedolizumab
For now, disease and symptoms developed as consequence of adalimumab are under control, treatment in progress

Conclusion:
Compromised immune system has significant influence on development of disease, and reaction to treatment.
Clinical outcomes after elective discontinuation of anti-TNF therapy in patients with Crohn’s disease

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Introduction: In patients receiving anti-TNF therapy for Crohn’s disease (CD) UK National guidelines mandate a review after 12 months to determine whether on-going treatment is required. We undertook a study to identify clinical outcomes in our own patients who electively stopped anti-TNF treatment.

Methods: A retrospective search of the IBD database identified patients with CD where anti-TNF therapy was electively discontinued from 2002–May 2018. Clinical records were reviewed to identify clinical outcomes.

Results: 46 CD patients out of 453 patients (10%) treated with anti-TNF therapy electively discontinued treatment, with adequate follow-up documented in 30. The median duration of CD prior to treatment was 108 months (range 1–432) with a median anti-TNF treatment duration of 19.5 months (range 12–108) prior to stopping anti-TNF (20 adalimumab and 10 infliximab). 5 patients stopped on basis of clinical review and CRP, 9 patients following clinical review, CRP and FC with 16 patients having had clinical review, CRP, FC and either colonoscopy and/or MRI. Relapse rates in these groups were 3/5 (60%), 5/9 (55%) and 50% respectively. 18 patients (60%) received an immunomodulator at the time the anti-TNF was discontinued. 16 patients (53%) had a recurrence of disease requiring further anti-TNF therapy, median biologic free period 15.5 months (range 6–30 months), there were no significant differences in those receiving an immunomodulator 17 months (range 6–30) versus no immunomodulator 14.5 months (range 9–26) (p 0.28). 14 (47%) patients did not require further biologic therapy and were biologic free at the end of the study period, median 19 months (range 13–54 months). All those requiring re-treatment had a clinical response to the original anti-TNF agent.

Discussion/Conclusion: Only 10% of CD patients electively discontinued anti-TNF. 47% of those patients were biologic free at the end of the study. In those who relapsed re-treatment success rates were high.
Changing patterns of frequency of ulcerative colitis in Lima, Peru

Hugo Cedrón
Clinica Anglo Americana, Lima, Peru

**Introduction:** Ulcerative colitis is a chronic disease that is characterized by diffuse inflammation of the rectal and colonic mucosa. For years, ulcerative colitis was considered an extremely rare disease in Latin America, however, we have noticed an increase in the number of ulcerative colitis cases in our country.

**Objective:** To record the changing patterns of ulcerative colitis frequency in the last years in Lima.

**Methods:** We reviewed all published articles in relation to the frequency of ulcerative colitis in the different hospitals of Lima in the last 40 years. We found nine case series on ulcerative colitis frequency published in our Revista de Gastroenterología del Perú between 1980 to 2018.

**Results:** Nine series of cases were found between 1978 and 2018. The majority of patients with ulcerative colitis were between 30 to 40 years old at diagnosis. A second peak of incidence was between 60 to 69 years old, the serie of Paredes had its main peak of cases in people older than 60 years old, completely different with the others, and could be in relation with a late diagnosis. The distribution between genders were similar.

<table>
<thead>
<tr>
<th>Published year</th>
<th>Author</th>
<th>Hospital</th>
<th>Number of cases</th>
<th>Period of study</th>
<th>Case per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980</td>
<td>Velásquez</td>
<td>Rebagliati</td>
<td>45</td>
<td>30</td>
<td>1.5</td>
</tr>
<tr>
<td>1984</td>
<td>Barreda</td>
<td>FAP</td>
<td>10</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>1986</td>
<td>Illescas</td>
<td>Almenara</td>
<td>52</td>
<td>45</td>
<td>1.16</td>
</tr>
<tr>
<td>1988</td>
<td>Arana</td>
<td>Carrión</td>
<td>15</td>
<td>17</td>
<td>0.88</td>
</tr>
<tr>
<td>1990</td>
<td>Llerena</td>
<td>Cayetano</td>
<td>20</td>
<td>18</td>
<td>1.11</td>
</tr>
<tr>
<td>1999</td>
<td>Illescas</td>
<td>Almenara</td>
<td>74</td>
<td>52</td>
<td>1.42</td>
</tr>
<tr>
<td>2004</td>
<td>Vera</td>
<td>Rebagliati</td>
<td>8</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>2006</td>
<td>Cedrón</td>
<td>Cayetano</td>
<td>27</td>
<td>7</td>
<td>3.85</td>
</tr>
<tr>
<td>2016</td>
<td>Paredes</td>
<td>Almenara</td>
<td>81</td>
<td>10</td>
<td>8.1</td>
</tr>
</tbody>
</table>

**Conclusion:** In Lima, Peru, we still have a low incidence of ulcerative colitis, but there is an increase of reported frequency of ulcerative colitis in the last forty years.
Impact of mesalamine on histological remission in patients with ulcerative colitis

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²Department of Pathology, Ankara University Faculty of Medicine
³Department of Internal Medicine, Ankara University Faculty of Medicine, Ankara, Turkey

Introduction: Histologic measurements are gradually used in ulcerative colitis (UC) to determine response to therapies. We aimed to compare the efficacy of treatment options in terms of mucosal healing in patients with UC.

Methods: The initial and follow-up biopsy specimens from patients with UC (including TI and five colonic segments) examined retrospectively from 2014 to 2018. Histological parameters of activity (cryptitis, crypt abscesses, ulceration) and chronicity (crypt distortion, mucin depletion, pyloric/paneth cell metaplasia) were analyzed in all localizations. They were classified as normal, active and chronic. Comparisons between the diagnostic groups and initial/follow-up biopsies were committed using Chi-square test and a p value less than 0.05 was considered statistically significant.

Results: 167 patients with UC (mean age, 42.3 years) were included in study. 53.7% of patients were male. 116 patients (70%) received mesalamine (MMX) and 30 patients (18%) were on anti-TNF therapy while 18 patients (10.7%) were treated with azathioprine, MMX and steroid. In initial biopsies; pancolitis pattern was observed in 60% and left colon involvement was 35.6% and after treatment, pancolitis pattern resulted in 33.6% in follow up biopsies. Mucosal healing rates were significantly higher in patients on MMX.

Discussion/Conclusion: In conclusion, we discovered the importance of MMX treatment on mucosal healing. MMX treatment are significantly more likely to achieve improvement on pancolitis.
Successful use of the ImproveCareNow (ICN) Quality Improvement Tool: Our 7 year outcomes and achievements

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Introduction: ImproveCareNow (ICN) is a Quality Improvement (QI) Program established in 2007. ICN uses patient data to drive improvements in the care and health of PIBD patients. It’s a network of 96 international centers with over 27,000 PIBD patients that benchmarks care against agreed targets. We share our 7 year experience in using this QI tool.

Methods: All eligible IBD patient enrolled in the program had their data collected at every clinic visit and ambulatory review and were entered into an electronic database. Pre-visit planning meetings were held to discuss all patients prior to the clinic visit. The data that is entered consisted of diagnosis, using the Paris classification, growth and nutrition, lab results, medications, physical assessments, disease activity and extraintestinal manifestations. Data from each visit was analysed and reports were generated within 24 hours. Each patient’s results were stratified and scored weekly, so that individual treatment plans could be instigated. Reports were reviewed on a monthly basis and changes to clinical management were implemented on an individualized basis, adhering to local treatment policy. Monthly QI meetings set and reviewed 90 day goals, enabling the team to strive for better results.

Results: At present 138 (61 female, mean age 12.6 y) patients are registered in the ICN database. Patient who have been transitioned over the years have been removed. Our overall remission rates of 60% in 2011 increased to 72% in 2017, Steroid free remission rates from 50 to 71%, patients off steroids from 60 to 98%, satisfactory nutritional status from 82 to 93%, satisfactory growth status from 92 to 93%. At risk for nutritional failure decreased from 9 to 7%, patients in nutritional failure from 9 to 0%. At the point of joining ICN we did not know patient numbers and did not do any pre-visit planning (PVP), we now have all our IBD patients registered and we do PVPs on each patient before their clinic review, please see table attached.

Conclusion: ICN has shown to be an excellent tool of improving the quality of care of PIBD patients, managing their treatment and improving outcomes. Monitoring disease severity and having the ability to provide tailored treatment plans have been achieved, by using this QI tool. Clinics have been streamlined, patient care has been standardized and key outcome measures have significantly improved.
<table>
<thead>
<tr>
<th>Category</th>
<th>Before 2011</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission rate</td>
<td>60%</td>
<td>72%</td>
</tr>
<tr>
<td>Steroid free remission rate</td>
<td>50%</td>
<td>71%</td>
</tr>
<tr>
<td>Off prednisone 60%</td>
<td>60%</td>
<td>98%</td>
</tr>
<tr>
<td>With satisfactory nutritional status</td>
<td>82%</td>
<td>93%</td>
</tr>
<tr>
<td>At risk of nutritional failure</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>In nutritional failure</td>
<td>9%</td>
<td>0%</td>
</tr>
<tr>
<td>With satisfactory growth status</td>
<td>92%</td>
<td>93%</td>
</tr>
<tr>
<td>Number of IBD patients</td>
<td>Not known</td>
<td>138</td>
</tr>
<tr>
<td>Number of clinics pre-visited</td>
<td>None</td>
<td>100%</td>
</tr>
<tr>
<td>% of complete data entered</td>
<td>n/a</td>
<td>100%</td>
</tr>
<tr>
<td>Family education day</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Parents involved in advisor group</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Parent in QI meetings</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
Skin manifestations in monoclonal therapy of pediatric inflammatory bowel disease (PIBD)

Lucia Cococcioni, Oluwakemi Ogunmoye, Sara Sider, Rachel Buckingham, Sibongile Chadokufa, Bonita Dyball, Fevronia Kiparissi
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Background: Skin lesions in PIBD can occur as extraintestinal manifestations of IBD, with an averagely reported incidence of 15%. However, skin lesions triggered by monoclonal therapy in PIBD are little known and under-reported in literature.

Aim: To describe skin changes after commencement of monoclonals in PIBD patients.

Methods: Retrospective review of medical records from PIBD patients who developed skin lesions while on monoclonals and were further referred for dermatology opinion between 2013 and 2017. Minor local cutaneous manifestations at injection site were excluded.

Results: 22/752 (2.9%) PIBD patients were referred, 8/12 Crohn’s disease (59%), 5/12 UC (32%) and 1/12 IBD-U (9%). 11 patients were on Infliximab and 11 on adalimumab. Females were twice frequently affected, age ranged from 6 to 17.7 years (mean of 8.4). 8/22 patients (36.6%) needed skin biopsies in order to clarify the diagnosis. Four groups were identified, group A: Patients with skin lesions highly likely to be secondary to monoclonal treatment 10/22 (45.5%); group B: patients whose lesions were secondary to the disease 5/22 (22.7%); group C: incidental findings 3/22 (13.6%) and group D: patients whose lesions were a combination of the above 4/22 (18.2%). For skin manifestations likely secondary to monoclonals, 4/10 followed Infliximab exposure and 6/12 followed adalimumab. Mean latency for lesions onset was 1.6 years (range 0.4–3.3). No cases of malignancy or cutaneous infections were reported. Monoclonal therapy was maintained in all cases. Clinical features of patients with monoclonal-induced lesions are summarised in table 1.

Table 1

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (years)</th>
<th>IBD subtype</th>
<th>Biologic</th>
<th>Latency (years)</th>
<th>Skin manifestation</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>13.7</td>
<td>CD</td>
<td>IFX</td>
<td>0.4</td>
<td>Psoriasis</td>
<td>Ears, knee, elbow</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>15.3</td>
<td>IBDU</td>
<td>IFX</td>
<td>0.5</td>
<td>Psoriasis</td>
<td>Scalp, face, ears, hands, feet</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>13</td>
<td>CD</td>
<td>IFX</td>
<td>0.8</td>
<td>Psoriasiform rash</td>
<td>Scalp, chin, ears, knees</td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>16</td>
<td>CD</td>
<td>IFX</td>
<td>1.3</td>
<td>Eczematous patches</td>
<td>Left antecubital, knuckles</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>10.4</td>
<td>ADA</td>
<td></td>
<td>2.4</td>
<td>Psoriasiform eruption</td>
<td>Generalised including scalp</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>13</td>
<td>UC</td>
<td>ADA</td>
<td>1.4</td>
<td>Psoriasis, eczema exacerbation</td>
<td>Arms, legs</td>
</tr>
<tr>
<td>7</td>
<td>Female</td>
<td>14.4</td>
<td>UC</td>
<td>ADA</td>
<td>1.6</td>
<td>Spongiotic dermatitis</td>
<td>Lower legs bilaterally</td>
</tr>
<tr>
<td>8</td>
<td>Female</td>
<td>12.9</td>
<td>CD</td>
<td>ADA</td>
<td>2.3</td>
<td>Alopecia areata</td>
<td>Scalp, eyebrow</td>
</tr>
<tr>
<td>9</td>
<td>Female</td>
<td>9.8</td>
<td>CD</td>
<td>ADA</td>
<td>2.0</td>
<td>Scaling depigmented rash</td>
<td>Face</td>
</tr>
<tr>
<td>10</td>
<td>Female</td>
<td>6.3</td>
<td>UC</td>
<td>ADA</td>
<td>3.3</td>
<td>Discoid eczema</td>
<td>Sheen and torso</td>
</tr>
</tbody>
</table>
Conclusion: Skin lesions in PIBD patients receiving monoclonals were considered to be drug-induced in almost half of the cases. Psoriasis and psoriasiform lesions were commonly seen with infliximab; however, no pattern could be identified for adalimumab-induced skin lesions. Prompt referral for dermatology assessment in PIBD patients receiving monoclonals is advised.
Clinical relevance of probiotic on long-term maintenance therapy outcomes

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²Floreasca Emergency Hospital, Department of Gastroenterology, Bucharest, Romania

Introduction: Oral S-aminosalicylic acid formulations are recommended as first-line therapies for active, mild to moderate ulcerative colitis (UC); however, little is known about long-term outcomes with maintenance therapy following induction. Controlled clinical trials have shown efficacy with some probiotics.

Methods: This open-label, prospective study evaluated outcomes at 12 months in UC patients achieving complete or partial remission after 8 weeks of induction therapy with mesalazine. The patients were adults with active, mild to moderate UC, with modified UC Disease Activity Index (UC-DAI) total score of 4–10, endoscopy score ≥ 1, and Physician Global Assessment ≤ 2. Patients received 8 weeks of mesalazine (Salofalk® 4 g/day) during induction; patients achieving complete or partial remission at 8 weeks received maintenance mesalazine 2 g/day, alone (group A) or mesalazine plus probiotic (Saccharomyces cerevisiae: IBSI-SUN) (group B).

Results: Of the 125 patients included, 112 completed the induction phase and 94 entered the maintenance phase (group A: 45 patients, group B: 49 patients). Mean age was 44.2 years. All patients had histology compatible with UC. After 12 months of maintenance therapy, 48.8% (22 pts) in group A and 71.4% (35 pts) in group B had sustained complete or partial remission. Symptom improvement (≥ 1 point reduction from baseline) was observed in 58%, 40% and 31.1% of patients for rectal bleeding, stool frequency or both in group A, compared to 63.2%, 61.2% and 49%. The mean (± SD) UC-DAI score was 4.3 ± 2.24 in group A and 3.2 ± 1.82 in group B (p < 0.0011) at the end of the study. CRP levels were 9.9 ± 1.4 mg/l in group A vs. 6.5 ± 1.1 mg/l in group B. Adverse events during treatment were mild (6.4% vs. 2%).

Discussion/Conclusion: Association of probiotic to mesalazine for maintenance therapy in mild to moderate forms of UC provides better results and a lower incidence of adverse effects.
Developing a faecal transplantation donor bank for the treatment of ulcerative colitis

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Introduction: Faecal microbiota transplantation (FMT) is an infusion of a faecal suspension from a healthy individual (donor) to the GI tract of a recipient patient, to treat a specific disorder associated with an alteration of gut microbiota. Evidence has shown FMT from unrelated donors is as effective as related donors. This has provided an opportunity for a better standardised and safer method for donor selection, screening, and faecal suspension preparation.

Ulcerative Colitis (UC) is a chronic relapsing-remitting mucosal inflammatory bowel disease with features including rectal bleeding, diarrhoea, faecal urgency, fatigue and weight loss. The aetiology of UC is believed to be multifactorial including the interaction of the gut microbiota with the human host.

Methods: Faecal donors were recruited from the local university through advertising campaigns including visual posters, word of mouth and oral presentations to target groups including university sports teams. Donors were extensively screened according to European guidelines for eligibility and invited for a medical interview if suitable. Successful volunteers underwent both blood and stool testing for transmissible diseases prior to donation which were taken within 28 days of screening. Further questionnaires were completed on day of donation prior to in-house sample processing.

Results: Eleven volunteers registered interest in becoming a potential faecal donor of which five (45.5%) were eligible for screening. Reasons for failure included healthcare students, recent/current use of antibiotic and excludable medical disorder. Of the eligible volunteers, three of the original eleven (27.3%) were suitable to supply donations. Positive infectious screens included Hepatitis E, Amoeba, clostridium perfringens, EBV and CMV. Previous but not active EBV and CMV infections were not excluded but matched to recipients also showing evidence of past infection.

Discussion/Conclusion: We report the success of implementing a non-related FMT donor stool bank for the experimental treatment of UC and highlight common pitfalls in current donor recruitment and screening.
Corticosteroid therapy in patient with synchronous Crohn’s ileitis and non-Hodgkin lymphoma type DLBCL

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Polyclinic Marinmed Dubrovnik, Department of Hematology, General Hospital of Dubrovnik, Hungary

Introduction: Corticosteroid therapy has been recognized as the first-choice drug for Crohn’s ileitis due to its extremely good anti-inflammatory, immunosuppressive and antiproliferative action. Budesonide is a corticosteroid of limited local activity on the gastrointestinal tract and as such no systemic effect of corticosteroids alone and less side effects.

Methods: Case presentation: A 27-year-old patient, male, appears in a gastroenterological ambulance with aching pain in the lower right abdominal region. The US scan shows a noticeably thickened ileal wall in length of 80 mm and thickness up to 10 mm, irregular lumen. Recommended colonoscopy performed three months after initial diagnosis due to patient delay of colonoscopy. As a result of colonoscopy, there was found a large infiltrative formation of the ileum which affects 100% of circumference, and the ileoceleal valve is affected. Ileum biopsies taken. Established diagnosis of NHL-DLBCL (non-GCB phenotype) after PHD. In samples of ILEUM mucosa PHD also responds to Crohn’s disease. Due to NHL, therapy with ciclofosfamide, doxorubicin, vincristine, methylprednisolone and mesalazine 4 x 2 tbl and 500 mg and 9 mg of budesonide is started. Control of MSCT after 6 months shows better ileum passage but unfortunately with extraintestinal symptoms and development of NHL. Continue NHL treatment with hyper-CVAD and mesalazine total of 6 g and budesonide 9 mg. One year after the onset of NHL treatment and Crohn’s illness, the patient unfortunately died of NHL complications, septic and MOF. During the entire therapy for both illnesses patient did not experience obstruction of the ileum despite the initial finding of stenosis of the ileum and ileoceleal valve.

Discussion/Conclusion: The use of budesonide can introduce and maintain remission of stenosing illitis without the need for operational treatment.
Development of the method for monitoring thiopurine metabolites in the patients suffering Crohn’s disease

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Introduction: Until 2015 year in Poland there were registered 6000 patients with Crohn’s disease (CD). However, there may be even about 15,000 people suffering CD due to undiagnosed conditions. 6-mercaptopurine (6-MP) and azathioprine (AZA) are two thiopurine drugs that are currently used in the clinical practice for the patients with inflammatory bowel disease (IBD) including CD. Both, 6-MP and AZA, exhibit short half-life in the circulation after oral administration. Major metabolites of clinical interests are 6-thioguanine nucleotides (6TG) and 6-methylmercaptopurine nucleotides (6-MMP). They were shown to slowly accumulate in the red cells where they reach a steady-state concentration after 1–4 weeks. Monitoring thiopurine metabolites has two main aims: (1) to increase effectiveness of the therapy and (2) to decrease potential side effects caused by these drugs. Pharmacokinetics Laboratory in our Hospital is the only one center in Poland where the 6TG level is measured. The aim of this study was to develop method for the azathioprine and 6-mercaptopurine quantitative determination in the erythrocyte lysates in children with CD.

Methods: Erythrocytes (RBC) from the patients undergoing thiopurine therapy were obtained from 1.2 ml of whole blood collected on the K2 EDTA or K3EDTA. After centrifugation at 3500 rpm for 5 minutes at room temperature the plasma was discarded. RBC were washed with 0.9% NaCl and centrifuged again in the same conditions. This step was repeated twice. Aliquot 100 μl of the RBC was transferred into another tube and internal standard (6-mercaptopurine), NaCl, DTT and HClO4 were added. Next, the samples were centrifuged and supernatant was decanted and then hydrolysis was performed (100°C, 45 minutes). Cooled samples are analysed by the HLPC and chromatograms were recorded at 340 nm following the developed procedure.

Discussion/Conclusion: The method, after its validation, is used in our Hospital since 2011 year and was shown to significantly increase the safety and efficiency of the thiopurine therapy in CD children.
Characterising and managing issues with food-related quality of life in inflammatory bowel disease – A qualitative study of patients and healthcare professionals

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Introduction: Inflammatory bowel disease (IBD) has a profound impact on diet and nutrition that creates limitations in psychosocial functioning and impacts quality of life (termed food-related quality of life, FR-QoL). The issues experienced and the management methods used by patients with IBD and healthcare professionals (HCPs) regarding FR-QoL are not well understood.

Methods: Individual semi-structured interviews with 15 IBD patients reporting issues with FR-QoL; and two focus group interviews with 11 HCPs were audio recorded and transcribed verbatim.
Pragmatic thematic analysis was used to analyse data, with NVivo 11 used for data management.

Results: Fifteen patients with IBD (10 CD/5 UC) were purposively selected from UK hospital outpatient clinics (7 female, mean age 34.4 y; range 21–51 y). Individual interviews ranged from 39–70 minutes. Eleven HCPs (3 consultant gastroenterologists, 3 IBD registrars, 2 specialist dietitians, 2 IBD specialist nurses and one psychologist) participated in two focus groups over 2 hours each. Patients perceived IBD as having a direct impact on their diet, particularly their food choices and enjoyment of food. This limited their daily life such as going out, socialising with friends and family, or personal relationships. Several factors, including limited understanding of IBD impact on body function and food digestion, fear of triggering a flare through eating, anxiety about making the right food choices, were perceived to contribute to impaired FR-QoL.
Patients attempted various methods to improve FR-QoL including trial and error, food avoidance or exclusion, reducing portion size or frequency of eating; but few approaches were perceived to have the desired improvement in FR-QoL. Limited or no dietary advice from HCPs left patients feeling that food-related issues do not receive the same level of attention as medical management. During the focus groups, HCPs identified the factors affecting patients’ diet and FR-QoL that needed greater attention and they were: IBD-related (e.g. newly diagnosed, acute inflammation, functional symptoms, strictures and stoma) and non-IBD related (e.g. pregnancy, allergies, likes/dislikes). HCPs acknowledged FR-QoL advice as a low priority in a consultation. HCPs recognised insufficient time in clinical consultations to address more complex issues. Some felt inadequately prepared to offer diet-specific advice, or assumed that other members of the multidisciplinary team provide diet-related care and advice.
Discussion/Conclusion: Both, patients and HCPs emphasised the need for more individualised care in relation to food and IBD and required quality and timely sources of information. The development and testing of interventions designed to address FR-QoL is required.
Intestinal microbiota changes in urban and rural patients with inflammatory bowel diseases

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²Kazan State Medical University, Kazan, Russia
³Scientific Research Institute of Physical-Chemical Medicine, Moscow, Russia
⁴Moscow Institute of Physics and Technology (State University), Moscow, Russia
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Introduction: The gut microbiota is considered to play an important role in the pathogenesis of inflammatory bowel diseases (IBD). Its qualitative and quantitative composition depends on numerous factors as food habits, environmental conditions, age, etc.

Methods: The aim of our study was to reveal the influence of environmental conditions on the intestinal microbiota in IBD patients. Materials and methods: the study included 91 IBD patients, 22 of them living in rural, and 69 – in urban area. The control group consisted of 96 subjects without any symptoms of gastrointestinal diseases (27 – rural, 69 – urban). Total DNA was extracted from stool samples followed by whole genome sequencing on SOLiD 5500W platform.

Results: The following bacterial genera showed decreased abundances both in rural and urban IBD patients in comparison with control group of rural or urban subjects: Clostridium, Butyrivibrio, Eubacterium, Coprococcus, Roseburia, Faecalibacterium, Ruminococcus and Akkermansia.

The abundance of Bacteroides genus was significantly higher in groups of rural and urban IBD patients: (14.45 ± 18.02)% and (21.81 ± 19.11)% compared to rural and urban control group – (2.73 ± 1.75)% and (9.81 ± 12.078)%, respectively, p < 0.05. The abundance of only two bacterial genera – Methanobrevibacter and Catenibacterium differs significantly between urban and rural IBD patients and was higher in rural compared to urban patients.

The decrease of alpha diversity indices was observed in urban patients (2.06 ± 0.44) compared to control urban residents (2.34 ± 0.33), p < 0.001. However no significant difference was found between the rural IBD patients and the rural controls by Shannon diversity index.

Discussion/Conclusion: Disturbance of the intestinal microbiota composition can be one of the causal factors of IBD. Only two genera – Methanobrevibacter and Catenibacterium – differed significantly between urban and rural IBD patients. The abundance of butyrate-producing bacteria with anti-inflammatory properties (Eubacterium, Faecalibacterium, Roseburia, Coprococcus, etc.) significantly decreased both in urban and rural IBD patients comparing with control group.
The role of microbiological research in the treatment of patients with severe attack of ulcerative colitis

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Introduction: Ulcerative colitis is a chronic inflammatory disease of the colon, in which there is an immune inflammation and destructive changes in the intestinal wall.

Methods: The main group (1 group) consisted of 37 patients (48%) with severe attack of ulcerative colitis, which was treated with Salofalk® granules of 1000 mg supplemented with antibacterial drugs, prescribed on the basis of sensitivity to them microflora, isolated from biopsies of the colon wall.

In the control group, 40 patients with severe disease attack (52%), treatment was carried out according to the current clinical guidelines, mesalazine therapy (Salofalk® granules were prescribed 1000 mg) was supplemented with standard antibacterial drugs.

Statistically significant differences between groups of patients by sex (t = 1.44; p < 0.05), age (t = 0.01; p < 0.05) were not recorded.

Results: In 1 group, improvement of the state on the 4–6 day was noted by 28 patients, the time of onset of remission was 22 days. In the second group, the improvement occurred on 8–11 days in 21 patients, the time of remission was 32 days. When assessing the severity of the disease attack on 30 days in patients of the main group, improvement was noted in 32 people, while in the control group only in 21 patients.

Conclusion: Appointment of antibacterial therapy in patients with severe attack of ulcerative colitis on the basis of microbiological examination of biopsies of the colon wall, in addition to standard therapy with Salofalk®, allows you to quickly stop the attack of the disease, to achieve remission.
Assessment of quality of life in patients with inflammatory bowel diseases

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The management of the health-related quality of life (HRQOL) is increasingly considered as an important treatment goal in chronic diseases including inflammatory bowel diseases.

Introduction: The aim of our study was to determine the impact of IBD on HRQL and identify the factors involved in the deterioration of HRQL in these patients.

Methods: Thirty-one patients filled in IBD questionnaire (IBDQ-32), Pittsburgh sleep quality index questionnaire, and sociodemographic questionnaire. Disease activity was assessed by ulcerative colitis activity index and Crohn’s disease activity index. The correlations of sleep quality, sociodemographic variables, and disease characteristics with IBDQ were investigated.

Results: The factors involved in the alteration of HRQL were: disease activity, poor socioeconomic conditions, use of corticosteroids, age < 30 years, a number of surgeries ≥ 2 and anterior hospitalization history. A multivariate regression analysis identified the predictors of decreased HRQOL as not consuming folic acid (p = 0.007), poor sleep quality (p = 0.012), and disease severity (p = 0.039). IBDQ-32 mean score was lower in patients who had hospitalization (p = 0.01), poor sleep quality (p < 0.002), anemia (p = 0.04), more severe disease (p = 0.01), and those who had not consumed folic acid (p = 0.01) relative to their counterparts.

Discussion/Conclusion: Impaired the health-related quality of life was significantly associated with poor sleep quality, lack of folic acid consumption, and disease severity in inflammatory bowel diseases patients.
The prevalence of viral markers at patients with inflammatory bowel diseases

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Patients with inflammatory bowel disease often require immunosuppressive therapy and blood transfusions are at a high risk of contracting infections due to hepatitis B and hepatitis C.

Introduction: The aims of this study were to investigate the prevalence of hepatitis B virus and hepatitis C virus infection in inflammatory bowel disease patients and the risk factors related to the infection and nonimmune status.

Methods: This retrospective study included 89 patients with inflammatory bowel diseases (ulcerative colitis, n = 57; Crohn's disease, n = 32). The prevalence of viral markers and risk factors related to HBV and HCV infection and nonimmune status were analyzed in IBD patients. Prevalence data of the study were compared with that of the general Roumanian population.

Results: The prevalence of HBV, HCV was 2.6% and respectively 1.7, in the 89 patients with inflammatory bowel diseases. Among the 57 patients with ulcerative colitis, 2.8% (2/57) had HBV and 1.1% (2/57) had HCV. Among the 32 patients with Crohn's disease, 3.1% (1/32) had HBV and 6.2% (2/32) had HCV. One patient with Crohn's disease had HBV and HDV coinfection. The prevalence of HBV and HCV in patients with colorectal cancer associated with inflammatory bowel diseases was 2.2% (2/89) respectively 1.1% (1/89).

Discussion/Conclusion: The prevalence of HBV and HCV in roumanian patients with IBD is similar to the prevalence of these viruses in the general community. Screening of patients for viral markers should be mandatory in patients with inflammatory bowel diseases.
Inflammatory articular disease in patients with inflammatory bowel disease

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Extraintestinal manifestation like arthrytis and episcleritis are two common comorbidities of inflammatory bowel diseases.

Introduction: The aim of this study was to evaluate the prevalence and the clinical characteristics associated with inflammatory articular disease in patients with inflammatory bowel diseases.

Methods: We analyzed 78 patients diagnosed with inflammatory bowel diseases. The presence of arthritis was diagnosed by the reumatologist and with inflammatory articular disease was defined as persistent or recurrent joint pain with an inflammatory pattern (night pain, progressive relief during the day, morning stiffness lasting at least 30 minutes). Were analysed the characteristics of the disease independently associated with the presence of inflammatory articular disease.

Results: A total of 78 patients with IBD, 45 with Crohn’s disease, and 33 with ulcerative colitis were included. 48.7% patients fulfilled the criteria for inflammatory articular disease, whereas 17.9% presented with other extraintestinal manifestations. Inflammatory articular disease was associated with Crohn’s disease, with older age, female sex and generally in patients with more active intestinal disease. Only in ulcerative colitis, inflammatory articular disease was further associated with increasing body mass and with tobacco smoking. Episcleritis has been associated with the intense activity of inflammatory bowel disease.

Discussion/Conclusion: Patients with inflammatory bowel disease have a high prevalence with inflammatory articular disease. Inflammatory articular disease was more strongly associated with Crohn’s disease than ulcerative colitis and the risk factors were were female sex, advanced age, active digestive disease, and tobacco consumption.
Osteo-articular manifestations in inflammatory bowel diseases – Diagnosis and treatment

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Osteo-articular manifestations are the most common extraintestinal manifestations belonging to inflammatory bowel diseases. Arthritis may be peripheral (pauciarticular or polyarticular) and axial, may present periarticular manifestations, dactilitis, entesopathies, osteomalacia, tendinitis, osteoporosis.

Introduction: The objective of the study was to evaluate the effectiveness of treatment with immunosuppressants, anti-TNF-alpha agents or corticosteroids in patients with osteo-articular manifestations.

Methods: We analyzed 87 patients with inflammatory bowel diseases (Crohn’s disease and ulcerative colitis) diagnosed between October 2013–December 2017 based on a detailed anamnesis of laboratory criteria (VSH and faecal calprotectin), endoscopic criteria, radiomaging (nuclear magnetic resonance of sacroiliac joints, DEXA osteodensitometry) and anatomopathological of biopsy pieces.

Results: 87 patients have been investigated, 37 with Crohn’s disease and 50 with ulcerative colitis. Of these, 35 had osteo-articular manifestations, 20 patients developed peripheral arthritis with large joints and received acetaminophen treatment to relieve pain. 4 had axial arthritis (sacroileitis and ankylosing spondylitis) and received NSAID (to reduce inflammation but not to reduce disease progression) and anti-TNF agents (infliximab). 2 had osteopenia, 6 patients developed osteoporosis and received treatment with calcitonin, bisphosphonates and raloxifene, and 3 patients had fractures.

Discussions/Conclusions: Initiation of treatment requires an early diagnosis of inflammatory bowel diseases as well as osteo-articular manifestations. Infliximab treatment was reserved for moderate-severe forms. Treatment with anti-TNF alpha agents has been used to induce the remission phase of the disease but also to maintain it.
The incidence of extradigestive manifestations in intestinal inflammatory diseases

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Intestinal inflammatory diseases represented by Crohn’s disease and ulcerative colitis most commonly affect the distal small intestine and colon, but can also associate manifestations of other organs and systems, mainly the joints, skin, eyes, kidneys, liver and vascular system.

Introduction: The objective of the study was to evaluate the incidence of manifestations of extradigestive manifestations in patients diagnosed with inflammatory bowel diseases as well as treatment administered according to the type of disease to induce and maintain the remission of the disease.

Methods: We have analyzed 65 patients diagnosed with inflammatory bowel diseases, 25 of whom with Crohn’s disease and 40 with ulcerative colitis in May 2015–December 2017. All patients have been diagnosed on the basis of X-rays, DEXA osteodensitometry, biopsy histopathological examination, slit lamp, endoscopic retrograde cholangiopancreatography, nuclear magnetic resonance of affected joints.

Results: 65 patients have been included in the study. Of the group studied, 27 patients had osteo-articular manifestations (16 had peripheral arthritis, seven patients developed osteoporosis and four had axial arthritis) and received treatment with anti-TNFalpha agents, corticosteroids, bisphosphonates and calcitonin. 7 patients had ocular manifestations, 5 with episcleritis and 2 with uveitis and received local corticosteroid therapy. 4 patients experienced dermatological manifestations and they were administered corticosteroids (topical, local and intralesional), immunosuppressive therapy and anti-TNF alpha agents.

Discussions/Conclusions: Osteo-articular manifestations are the most common extradigestive manifestations in inflammatory bowel diseases. Combined therapy has been used to increase the efficacy and duration of therapeutic response to the biological agent.
Adverse effects of infliximab therapy in inflammatory bowel diseases

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Infliximab is a monoclonal antibody used in the treatment of inflammatory bowel diseases to induce remission in cases resistant to conventional therapies in extraintestinal manifestations (dermatological, ocular), ankylosing spondylitis, rheumatoid arthritis and psoriatic arthritis.

Introduction: The objective of the study was to evaluate the incidence of adverse reactions occurring during treatment with infliximab in patients diagnosed with inflammatory bowel diseases.

Methods: The study included patients with Crohn’s disease and ulcerative colitis with moderate and severe form of the disease who received treatment with infliximab. The adverse reactions that occurred during the administration of the biological agent but also at the treatment distance were followed. Infusion reactions occurred were mild, moderate and severe.

Results: 87 patients were diagnosed with inflammatory bowel diseases, 37 with Crohn’s disease and 50 with ulcerative colitis. Adverse reactions occurred in 23 patients. Adverse reactions were mild and moderate in 16 patients and severe in 7 patients. 8 patients had headache, 2 had rash, 4 had palpitations and 2 had fever. Severe reactions have been reported in 7 patients who received infliximab treatment, 4 had chest pressure and 3 patients suffered from dyspnea.

Discussions/Conclusions: The occurrence of acute infusion reactions was in most cases after the first administration so that the rate of administration was decreased and in 3 cases the infliximab administration was temporarily stopped. Treatment with infliximab is well tolerated by patients with Crohn’s disease and ulcerative colitis, causes healing of extraintestinal manifestations and is effective in severe cases of disease activity.
Efficacy and safety of hepatitis C treatment with direct antiviral agents (DAAs) and ribavirin in patients with ulcerative colitis (UC) with stable disease under treatment

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The efficacy the safety of the newer DAAs against hepatitis C in patients with concomitant UC under treatment, with stable disease, is still unclear. For this reason we conducted a retrospective review of all patients who underwent treatment with DAAs and ribavirin during the last 2 years.

Materials/Methods: This multicenter study included 482 HCV patients, cirrhotics (compensated) or with advanced fibrosis (≥ 2), treated with DAAs and ribavirine (1200 mg daily) for 12 weeks. 8 (1.65% – 5 males, 3 females) of them suffered simultaneously from UC and were treated for this disease with 5-ASAs (3), thiopurines/corticosteroids (2) and anti-TNF agents (3). The stage of fibrosis in this population was F2-F3 and the genotypic distribution of HCV was G1a 3 (2M, 1F) patients, G1b (2M) 2, G3 2 (1M, 1F) and G4 (F). The pre-treatment viral load was between 0.54–0.92 x 10⁶ IU/ml and the aminotransferase levels were: ALT 248–99 U/l, AST 179–98 U/l, γGT 54–203 U/l. HCV-RNA was measured at weeks 4, 12, 24, general blood count, ESR, liver biochemistry, CRP were monitored monthly, and measurements of AFP levels, stool calprotectin and upper abdominal ultrasound were performed every 3 months. Dasabur/ombitasvir/paritaprevir/ritornavir for the G1, sofosbuvir/velpatasvir or sofosbuvir/daclatasvir for the G3, and elbasvir/grazoprevir for the G4 were the DAAs used.

Results: Although, viral load was undetectable at the end of week 4 in all patients, aminotransferase and γGT levels were abnormal during the first 12 weeks (but with a trend of normalization) in 2 (both M, one treated with 5-ASAs and one with anti-TNF). 12 weeks after the end of treatment all patients achieved undetectable HCV-RNA. No side effects or exacerbation of UC were observed. Calprotectin levels were within normal limits during the study period.

Conclusion: DAAs and ribavirin is a safe and effective treatment for patients with chronic hepatitis C and UC under treatment, with stable disease.
Vedolizumab: Effects on liver function in an IBD and IBD/PSC cohort

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Introduction: Primary sclerosing cholangitis (PSC) is a disease characterized by inflammation and destruction of the hepatic bile ducts often associated with inflammatory bowel disease (IBD). Vedolizumab (VDZ) is a gut-selective antibody for the treatment of IBD. We sought to look at the effects of VDZ therapy on liver biochemistry in patients with IBD and IBD/PSC.

Methods: We conducted a retrospective study looking primarily at changes in alkaline phosphatase levels of patients at our centre treated with VDZ. As a control group we matched each patient with PSC with two patients who had PSC never treated with VDZ. Basic demographics alongside data on phenotypes of IBD and a concurrent diagnosis of PSC were collected. Liver biochemistry was analysed at 0, 2, 8, 12, 24 and 36 weeks.

Results: In total 45 patients were treated with VDZ. Patients were divided into three separate groups: Group 1; IBD on VDZ (n = 32), Group 2; IBD/PSC on VDZ (n = 13), Group 3; IBD/PSC not treated with VDZ (n = 26). The median age was 42.5 years (17-75). 91.7% of patients with PSC on VDZ were post liver transplant. Median alkaline phosphatase (ALP) levels are as follows: Week 0: IBD cohort 68.00, PSC/IBD cohort 126.00, Control cohort 88.00. Week 36: IBD cohort 80.50, PSC/IBD cohort 254.50, Control cohort 114.00. There was a significant rise in ALP levels seen in Group 2 at 8, 24 and 36 weeks (p-values 0.010, 0.003 and 0.006 respectively).

Conclusion: VDZ therapy has no effect on liver biochemistry in patients with IBD alone. However in individuals with PSC, serum ALP increased significantly while on VDZ therapy.
Peach pit as a cause of small bowel obstruction in patient with Crohn’s disease

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Introduction: Foreign body in digestive tract is a rare cause of intestinal obstruction. Most foreign bodies pass digestive tract spontaneously. Endoscopic intervention will be needed in approximately 10–20%, and surgical intervention in less than 1% of cases. People with increased risk of foreign body obstruction are those with previous abdominal operation, hernia, tumour, Crohn’s disease or congenital intestinal malformations.

Case report: In this paper we present a case report of a patient with Crohn’s disease, known stenosis of terminal ileum and mild prestenotic dilatation who refused prior proposed resection of terminal ileum, and was in remission for a longer period of time. Patient was admitted to hospital due to development of obstructive symptoms; abdominal pain and vomiting, without diarrhoea or fever. CT revealed a presence of foreign body in the area of ileocecal valve with prestenotic dilatation of thickened terminal ileum. Foreign body showed characteristics of hyperechoic ring with hypoechoic centre, and was taught to be gallstone (gallstone ileus). Shortly after admission patient developed fever, progression of abdominal pain and eventually acute abdomen, therefore an emergency operation was performed. Inflamed and thickened terminal ileum was resected and showed no signs of perforation, and extracted foreign body was showed to be peach pit which was stuck in the ileocecal valve.

Discussion/Conclusion: Except of the most common causes of small bowel obstruction, it is necessary to bear in mind the rare causes of obstruction and consider them in differential diagnosis, especially in patients with Crohn’s disease, and those with stenosis of terminal ileum. This approach is important due to timely intervention and lowering the possibility of developing complications such as perforation, bleeding or fistula formation, which could lead to severe morbidity, as it has been shown in the literature.

Key words: peach pit, small bowel obstruction, Crohn’s disease
Tuberculosis infection in inflammatory bowel disease patients on anti-TNF therapy: Experience from an endemic country

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Introduction: The advent of anti-TNF treatment has provided an effective therapeutic approach for induction and maintenance of remission in inflammatory bowel diseases (IBD). However, an increased risk of tuberculosis (TB) infection is a well-recognized iatrogenic adverse event following the use of anti-TNF agents, which may be potentially a life-threatening condition.

Objective: To determine the prevalence and clinical features of IBD patients who developed active TB during anti-TNF therapy.

Methods: In this retrospective study, all patients with IBD treated with anti-TNF between 2008 and 2017 were enrolled. Data regarding demographics, interval between start of anti-TNF therapy and active TB development, tests for latent TB, concomitant medications, and details of diagnosis and treatments for TB were collected.

Results: Of the 72 patients treated with anti-TNF agents, 5 (7%) had active TB: 4 with Crohn's disease and 1 with ulcerative colitis, 3 males and 2 females, with a mean age of 47 years (30–66 years). Four patients received infliximab and 1 was on adalimumab. Three patients were on combotherapy with azathioprine. Past history of treated pulmonary TB was found in 1 patient. All patients had TB screening and none of them had evidence of latent TB. Time from initiation of anti-TNF treatment to TB diagnosis ranged from 3 to 36 months with a median of 14 months. Three patients had culture confirmed TB and 2 had presumed TB. Regarding TB localization, 2 patients had pleuro-pulmonary TB, 1 miliary TB, 1 intestinal TB, and 1 neuro-meningeal TB. All patients were successfully treated with anti-TB drugs during a period of 6–12 months.

Discussion/Conclusion: Despite screening for latent TB, 7% of patients developed active TB in our series. These data highlight that physicians should be aware of the potential risk of TB development throughout all anti-TNF therapy course, especially in endemic countries.
Phenotype and clinical outcomes of older-onset Crohn’s disease

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Introduction: Crohn’s disease has classically been considered a disorder with onset in young people. The late onset could represent a particular form of expression of this disease. The aim of this study was to determine the epidemiological characteristics specific to Crohn’s disease in the elderly and to compare these characteristics with the form of presentation in young people.

Method: Retrospective cohort study to analyze consecutive Crohn’s disease patients from January 2010 to December 2017. Clinical and phenotypic characteristics and treatment outcomes were evaluated. The patients were stratified in two groups according to age at symptom onset: The first group consisted of patients with onset at age 50 years or above (older patients) and the second group was the group of patients aged less than 50 years old (young patients).

Results: Ninety-four patients were included (55 men, 39 women). Mean age was 39 ± 15 years. 24 patients were aged more than 50 years old (25.5%). The main presenting symptoms were diarrhea and abdominal pain (64.8% and 39.3% respectively) without difference between young and older patients (p = 0.4; p = 0.7). Ileocolonic disease was the most dominant site of involvement in both groups (51.4% vs. 50%; p = 0.9). The behaviors of the disease were inflammatory (50% in group 1 vs. 50% in group 2; p = 1), penetrating (33.3% in group 1 vs. 34.2% in group 2; p = 0.9) and structuring (31.4% in group 1 vs. 20.8% in group 2; p = 0.3). The severity of the disease was similar in the two groups (p = 0.4). There was no differences in rates of complications, surgical resection, steroid treatment and azathioprine treatment between the two groups (p = 0.8; p = 0.9; p = 0.6 and p = 0.09).

Conclusion: The results of the present study suggest that there are no epidemiological and therapeutic differences in Crohn’s disease among the elderly.
Gender-related differences in clinical course of Crohn’s disease:
A Tunisian retrospective study

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Introduction: Crohn’s disease is a chronic inflammatory bowel disease that can affect men and women. Information regarding gender-related differences in Crohn’s disease is relatively scarce and conflicting. The aim of this study is to analyze the clinical characteristics between women and men affected by Crohn’s disease.

Methods: Retrospective cohort study to analyze consecutive Crohn’s disease patients from January 2010 to December 2017. Clinical and phenotypic characteristics and treatment outcomes were evaluated.

Results: 94 patients (55 males and 39 females) were diagnosed with Crohn’s disease. The mean age was similar in men and women (38.5 vs. 40.5; p = 0.5). Smoking history was observed only in men (63.6% vs. 0%; p = 0.0001). Diarrhea and abdominal pain were the most frequent presenting symptoms. No gender-related differences in clinical characteristics were observed. Ileocolonic disease was the most dominant site of involvement in both men and women. Structuring and penetrating behavior were more frequent in men (40.0% vs. 12.8%; p = 0.004; 43.6% vs. 20.5%; p = 0.02 respectively) whereas inflammatory behavior was more frequent in women (71.8% vs. 34.5%; p = 0.0001). The disease activity was more severe in men (51.0% vs. 18%; p = 0.001). More male patients experienced complications (47.2% vs. 18%; p = 0.003), surgical resection (52.7% vs. 18%; p = 0.001) and steroid treatment azathioprine treatment (69.0% vs. 38.4%; p = 0.003).

Conclusions: Crohn’s disease seems to be more severe in men than in women. History of smoking was observed only in men who are more exposed to complications, surgical resection and immunosuppressive therapy.
The spectrum of pathological changes in patients with Crohn’s disease under long-term mesalamine treatment

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Introduction: Crohn’s disease (CD) can affect any part of the gastrointestinal tract. Nearly 50% of patients have involvement of terminal ileum (TI) and colon, while 30% have only small-bowel involvement, and 20% present with isolated colonic CD. The purpose of the study was to evaluate the effects of mesalazine treatment on the pathology and involvement pattern in patients with CD.

Methods: We reviewed initial and follow-up biopsies from TI and five colonic segments in 101 patients with CD. Clinical data were recorded at the time of both initial and follow-up biopsies performed after treatment. Involvement patterns and histopathologic changes were evaluated in initial and follow-up biopsies of patients receiving mesalazine and compared with the effects of other treatment modalities.

Results: Of the 101 patients evaluated 59.9% were females and the median age was 38.5 years. Fifty-two percent of the patients received treatment with mesalazine. The majority of initial biopsies (85%) were abnormal with terminal ileum involvement while on follow-up biopsies terminal ileum involvement was found in 73.8% (p = 0.07) in the mesalazine group. Active ileitis with or without ulceration was the predominant pattern in 68% of the initial biopsies compared to 49% found in follow-up biopsies after treatment (p = 0.085). Right colon involvement didn’t show significant difference between initial and follow up biopsies (37.5% vs. 37.7%, p = 0.98). No significant difference was observed between initial and follow-up biopsies in the group receiving other treatment modalities.

Discussion/Conclusion: Our results indicate that mesalazine treatment improves the inflammatory process considerably in the terminal ileum mucosa in CD.
Predicting good or bad prognosis in IBD: The role of disorders of the rheological properties of erythrocytes

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The study included 37 patients (6–17 years old) with IBD (17 with CD and 20 with UC). Erythrocyte deformability, spontaneous (shear-induced) platelet aggregation, dynamic blood viscosity, morphology of erythrocyte aggregates, the state of erythrocyte cytoskeleton by the method of thermoinduction, the condition of hemostasis on thromboelastograph, medium molecular peptides (MMP), erythrocyte sorption capacity, binding ability of albumin were researched.

It was found that in CD the disorder of the majority of studied parameters is not only more significant than in UC, but they also remain much more stable even after the treatment. Like rheological disorders, endogenous intoxication continues in CD even after treatment. Thus, disorders of the rheological properties of blood are an important factor causing ischemic damage of the intestine. This gives grounds for recommending the use of adjuvant methods to reduce hypoxia and microcirculatory disturbances in IBD.

According to the obtained data it can be concluded that IBD is accompanied by a significant degradation of hemorheological properties of blood. It is an important factor in the pathogenesis of these diseases and is at the core of microcirculation disorders at IBD.

Key words: inflammatory bowel disease, IBD pathogenesis, hemorheology, endogenous intoxication.
Morphological criteria for prediction of the causure of ulcerative colitis in children

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Introduction: Ulcerative colitis is a chronic disease, which is based on the inflammatory and destructive damage to the mucous membrane of the colon of an autoimmune nature with the development of hemorrhages, erosions and ulcers, the formation of extraintestinal manifestations, as well as local and systemic complications. It was noted that in almost 40% of patients the manifestation of the disease was observed before reaching the age of 18 years. There are two main clinical variants of the disease: favorable or relapsing and unfavorable or continuously-recurrent. The risk of complications and disability of patients depends on the course of the disease. Therefore, it is very important to determine the course of ulcerative colitis as soon as possible and to prescribe an effective treatment. Until now, there are no unified methods for the early prognosis of ulcerative colitis in children. It is believed that changes at the cellular, morphological level outstrip the endoscopic, sonographic signs, which was the basis of our choice of the method of early prognosis.

Goal: Predicting the course of ulcerative colitis in children at the stage of disease manifestation.

Objective: to determine the morphological criteria for predicting the course of ulcerative colitis.

Materials and methods: In the initial treatment of patients in order to identify prognostic criteria for the disease, biopsies in 26 children with recurrent course, in 25 children with continuously recurrent ulcerative colitis and in 26 patients with ulcerative colitis, operated on for complications or because of ineffective therapy, were retrospectively studied. A complex of morphological methods of investigation, nonparametric statistical estimation methods (exact Fisher) was applied.

Results: Ulcerative colitis of recurrent course even at a high degree of activity determined by the presence of "crypt abscesses" is characterized by monomorphic epithelium and absence of sharp disturbances of interstitial interactions in the mucous membrane.

Ulcerative colitis of the continuously-recurrent course was characterized by the appearance of new structural features at the tissue level and in the system of two interacting tissues of the organ level – epithelial and loose unformed connective tissue of the lamina propria. In this case, deformed crypts, "crypt abscesses" in deformed crypts are always determined, micro-polypoid formations of the epithelial layer, foci of fibroblastic activity in the propria of the mucous membrane and microfocal lipomatosis.
When the pathological process spreads beyond the mucous membrane of the large intestine: to the neighboring organs (small intestine) or to the entire wall of the large intestine, we can ascertain the organ-system manifestations of the disease and ascertain the aggressive variant of the pathomorphism of ulcerative colitis. In the ileum, these children were identified areas with structural and functional characteristics characteristic of the colon – atrophy of the villi and the "table-like" appearance of the mucous membrane. In histochemical analysis, in these parts of the small intestine, alcyanophilia of the cytoplasm of goblet cells and the predominance of acidic mucins in mucosal superimpositions were manifested as much as possible, which indicates involvement of the small intestine adjacent to the large intestine. This phenomenon is a testimony of the substitutive function of the ileum, a decrease in the function of the mucous membrane of the colon, most manifest in the aggressive variant of the pathomorphism of ulcerative colitis. In parallel with this, a violation of differentiation in the epithelial layer of the large intestine was detected with the formation of foci of apical granular cells in the descending and sigmoid regions, those parts where the named cells are normally absent.

**Discussion:** Structural indices of cellular and tissue elements that make up the mucous membrane, make it possible to predict the course of the disease. These include qualitatively new signs of regenerative histogenesis of the cellular, tissue and interstitial level in the epithelial layer, the intrinsic plate, a significant disruption of interstitial interactions in the organ system.

When the pathological process spreads beyond the mucous membrane of the large intestine: the organ systemic manifestations of the disease, that is, the aggressive variant of the pathomorphism of ulcerative colitis and the ineffectiveness of therapeutic measures, are indicative of the early administration of anticytokine therapy to the adjacent organs (small intestine) or to the entire wall of the colon.

**Conclusion:** Morphological examination of biopsies is an integral part of modern diagnostic technologies, it can be used to predict the course of ulcerative colitis, as well as to determine the tactics of treatment.
Acceptance and commitment therapy improves body image in inflammatory bowel disease patients

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Introduction: Body image dissatisfaction is common in inflammatory bowel disease (IBD). Acceptance and commitment therapy (ACT) involves exercises which promote psychological flexibility. ACT positively impacts stress in IBD patients and has also been utilised for other psychological disorders, including body image dissatisfaction in the general population. ACT has not previously been assessed as a treatment for body image dissatisfaction in IBD. Our aim was to identify the effect of an ACT program on body image in IBD subjects.

Methods: 122 subjects were randomised to an eight-week ACT course (n = 61) or standard care (n = 61) with the original trial outcome being stress (ClinicalTrials.gov RegNo: NCT02350920). Body image was a secondary outcome in the original trial. Baseline data were available for 122 patients, while the follow-up study included 77 who attended five or more ACT sessions and had a baseline body image score of three or more. The Hopwood Body Image Scale was completed at baseline and after 8 and 20 weeks.

Results: Baseline body image dissatisfaction was greater in females (p = 0.007), younger subjects (p = 0.006) and those who had undergone previous surgery (p = 0.03). Body image dissatisfaction decreased by 14% and 37% in the ACT group from baseline to 8 and 20 weeks and by 10% and 9% in the control group with a significant treatment x group interaction (p = 0.001). ACT also impacted favourably on a range of other psychological variables including stress (p < 0.001), anxiety (p = 0.02) and depression (p = 0.002).

Discussion/Conclusion: An eight-week ACT therapy course improves body image in IBD subjects with body image dissatisfaction.
Long-term follow-up in children with inflammatory bowel disease at different age of onset

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Aim: Evaluation of behavior at diagnosis and after 10-year follow-up of children with Inflammatory Bowel Disease (IBD) with different age at debut.

Materials and methods: Retrospective study of children with IBD followed up for 10 years ± 1, diagnosed between 1996–2007 at a Reference Center in Argentina. Diagnosis: clinical, biochemical, imaging, endoscopic and histological. Exclusion criteria: syndromic, monogenic forms. They were divided according to age at diagnosis: Group I: < 6 years old and Group II: > 6 years old. Variables: median age at diagnosis, clinical score at diagnosis/10 years, endoscopic score at diagnosis, relapses, treatment, extraintestinal manifestations and complications.


<table>
<thead>
<tr>
<th>CLINICAL SCORE</th>
<th>DEBUT</th>
<th>P AT 10 YEARS OF FOLLOW UP</th>
<th>P AT 10 YEARS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCDAI/GI 16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>REMISSION</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MILD</td>
<td>9 (56%)</td>
<td>14 (40%)</td>
<td>0.54</td>
</tr>
<tr>
<td>MODERATE</td>
<td>6 (37%)</td>
<td>17 (49%)</td>
<td></td>
</tr>
<tr>
<td>SEVERE</td>
<td>1 (6%)</td>
<td>4 (11%)</td>
<td></td>
</tr>
<tr>
<td>AT DEBUT</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>GI n = 16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GII n = 35</td>
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<td></td>
<td></td>
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<tr>
<td>AT 10 YEARS</td>
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<td></td>
<td></td>
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<tr>
<td>GI n = 16</td>
<td>16 (100%)</td>
<td>20 (8%)</td>
<td>0.05</td>
</tr>
<tr>
<td>GII n = 35</td>
<td>0</td>
<td>7 (21%)</td>
<td></td>
</tr>
</tbody>
</table>

Treatment: Steroids GI: 7 (44%), GII 20 (57%), Thiopurines GI 44%, GII 60%, surgery GI 2 (13%), GII 4 (12%), Biological Therapy GI 1(6%), GII 6 (17%). Complications: GI: liver transplantation, GII: Portal vein thrombosis - Burkitt lymphoma (C.U) – Chronic myeloid leukemia (E.C).

Conclusion: Early onset IBD children had a more benign course in this cohort in the long term follow up. This may be due to local environmental factors or higher U.C prevalence of patients followed at a LATAM center.
**Epidemiological profile of perianal Crohn’s disease in a Tunisian population**

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**Introduction:** Crohn’s disease is a chronic panparietal inflammation. Perianal Crohn’s disease is a common condition, seen in more than 50% of patients with Crohn’s disease. It may precede, concomitant to the disease or arise secondary to the intestinal disease. It represents a therapeutic challenge for the practitioner.

**Aims and methods:** The aim of this study was to clarify the epidemiological profile and risk factors for Perianal Crohn’s disease development in our patients. We conducted a retrospective study carried out in the gastroenterology department of the Hedi Chaker Hospital of Sfax collecting patients with Crohn’s disease hospitalized between January 1, 2017 and December 31, 2015.

**Results:** We included 119 patients with Crohn’s disease during the study period. We included 60 male (50.4%). The average age was 35.5 years (14–87 years). Of these, 37 (31.1%) presented with Perianal Crohn’s disease. The anoperineal manifestations were present at the time of the diagnosis in 19 patients (51.35%) and of secondary appearance in the 18 others. These were fistulas and anal fissures in 17 patients for each and the combination of both in 3 patients. Anoperineal manifestations were classified as complex in 17 patients (46%). Only one patient (2.7%) presented with isolated Perianal Crohn’s disease. The analytical study did not find any difference between the two groups according to sex, age, smoking status, family history of IBD and general condition. In the group of subjects who developed perianal disease, colonic involvement was present in 28 patients (75.7%), isolated in 12 patients and associated with ileal damage in 16 patients. In case of colonic involvement, the rectum was affected in 26 patients (92.8%). Isolated ileal involvement was the least represented in the case of perianal involvement: 8 subjects (21.6%). In the comparative analysis, the difference was significant for ileal involvement (21.6% vs. 48.8%, p = 0.005) and colonic involvement (75.7% vs. 24.3%, p = 0.012). None of the patients with upper gastrointestinal tract involvement had perianal disease. Regarding the phenotype of the disease, the difference was significant only in case of inflammatory profile (18.9% vs. 81.1%, p = 0.004). The comparative analysis according to the evolutionary profile found no difference in the number of hospitalizations or in corticosteroids’ treatments.

**Conclusion:** Perianal involvement in Crohn’s disease is frequently encountered in our patients and is complex in half of the cases. It often associates with distal locations and severe phenotypes of the disease but seems to evolve independently of the intestinal disease.

**Disclosure:** Nothing to disclose.

**Keywords:** Crohn’s disease; perianal; epidemiology
The short-term immunosuppressive therapy for induction of remission of the steroid-refractory ulcerative colitis in elderly patients

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Introduction: We evaluated the efficacy and safety of mesalazine-budesonide combined therapy versus azathioprine in inducing remission in moderate UC in steroid-refractory or steroid-dependent patients with ages more than 60 years.

Methods: We included in this study 37 patients, which were structured in 2 groups: A group composed of 12 older patients (ages > 60 years, mean age 67.3 ± 8.71 years) and B group consist of 25 patients with ages < 59 years (mean age 37.3 ± 9.55 years). In A group 5 patients were treated with oral mesalazine (Salofalk®, 2–3 g/day) and oral budesonide (3 mg x 3 times/day), for 6–8 weeks and 7 patients (with contraindicated corticoids therapy) were treated with azathioprine (1–1.5 mg/kg/day). In B group 15 patients were treated with oral mesalazine and budesonide and 10 patients were treated with azathioprine. We evaluated the Powell-Tuck index and endoscopic classification at baseline, after 1, 3, 6 and 12 months.

Results: Most of the older patients (58.33%) present left-sided UC, 4 patients had proctitis and only one had extensive colitis. In B group the localization was: left-sided UC in 11 cases and proctitis in 14 cases. The distinctive features in elderly patients consist in the high incidences of: rectal bleeding (66.66%), diarrhea or paradoxical constipation (83.33%) and extraintestinal manifestation (58.33%). Also, they have a lower incidence of abdominal pain (33.33%) or weight loss (8.33%). Rapid response to associated treatment was observed in most young patients (60.0%) and only in one case (20.0%) in A group. Two older patients discontinued treatment with budesonide due to osteoporosis. At 3 months, the rate of clinical and colonoscopy confirmed remission after mesalazine-budesonide therapy was: 40.0% in older patients and 73.33% in B group. Comparatively, the remission rate after azathioprine monotherapy was: 57.10% in older patients and 50.0% in B group. Two patients discontinued azathioprine treatment due to leuco-trombocytopenia (A group) and increased aminotransferases levels (B group). The diminution of the mean Powell-Tuck score at 3 and 6 months compared with baseline suggest a more slowly response in elderly patients.

Discussion/Conclusion: The immunosuppressive therapy can represent an effective and safe alternative for the induction of remission in the elderly and steroid-refractory or steroid-dependent UC patients. Mesalazine associated with budesonide achieved high remission rate in short term treatment in moderate UC and assured better result in young patients.
The study of the mechanism of the development of Crohn’s disease in women with endometriosis

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Introduction: The aim of the study was to search for molecular mechanism of the development of CD in women with EM.

Methods: The study included 29 women with EM and CD (32–42 years old). QoL measured by the IBDQ-32, the EHP-30. CDAI was a research tool to quantify symptoms of CD. The diagnosis was based on clinical and anamnestic characteristic, ultrasound, laparoscopic and histological evaluation of EM, blood tests for CD (CBC, ESR, CRP, pANCA, ASCA), ileocolonoscopy with biopsy. Proteomic analysis was made in endometrial samples and colonic mucosa (2DE, MALDI-TOF-MS/MS). Patients took mesalazine 1500/750 mg daily, budesonide MMX 9 mg daily, dienogest 2 mg daily. CG included 15 women with EM. Statistics performed by “Statistica 10.0”.

Results: 29 women with EM stage II–III (mild EM, n = 15; moderate EM, n = 14) and ileocaecal steroid-dependent CD (mild CD, n = 21; moderate CD, n = 8) were identified. In 26 women had been diagnosed endometriosis before CD. In 4 women intestinal endometriosis and CD occurred simultaneously. A significant difference was seen in the scores for “Pain” (p < 0.05) and “Control and powerlessness” (p < 0.05) of EHP-30 in EM and CD vs scores in the CG. IBDQ-32 mean score was lower in EM and CD vs. CG (p < 0.01). The degree of EM correlated with level of ASCA in CD (r = 0.74; p < 0.01). It has been registered the significant increase of expression of transgelin, PRDX6, vimentin, haptoglobin, Rho-GDIα, SM-22α in endometrial samples and colonic mucosa of women with EM and CD vs CG.

Discussion/Conclusion: Participants of molecular mechanism of the progression of endometriosis and Crohn’s disease in women, including processes of apoptosis, immune reaction, glycolytic pathway, cell structure, transcription factors, were discovered.
Molecular mechanisms of sensorineural hearing loss as the extraintestinal manifestation of inflammatory bowel diseases

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Introduction: The aim of the study was to search for molecular mechanism of sensorineural hearing loss (SNHL) in patients with ulcerative colitis (UC) and Crohn’s disease (CD).

Methods: The study included 25 adults with UC E1–E2, S1–S2 (n = 16), CD L1–L2, B1–B2 (n = 9) and SNHL (38–42 years old, female – 18, male – 7). QoL measured by the IBDQ-32, EuroQoL. Diagnosis based on clinical and anamnestic characteristic of patients, instrumental tests for SNHL (otoscopy, tympanometry, pure tone audiometry, SDS, MRI, OTOblot assay), laboratory tests for UC and CD (faecal calprotectin, pANCA, ASCA), capsule endoscopy and ileocolonoscopy with biopsy of mucosa. Proteomic analysis was made in serum and mucosa (2DE, MALDI-TOF-MS/MS). Control group (CG) – 20 patients with UC (n = 10) and CD (n = 10). Patients took mesalazine 1500/750 mg daily, budesonide MMX 9 mg daily. Statistics performed by “Statistica 10.0”.

Results: 23 patients with UC and CD had bilateral SNHL, 2 patients with CD – unilateral SNHL, tinnitus had 21 patients. A significant difference was seen in the scores for “pain” (p < 0.05) and “depression” (p < 0.05) vs. scores in the CG. Anomalous configurations of audiograms were detected in SNHL: the degree of hearing impairment was mild (SDS = 81.7 ± 2.1%, 60% patients) and moderate (SDS = 69 ± 1.8%, 40% patients). The degree of SNHL correlated with pANCA (r = 0.89; p < 0.01) in UC and ASCA in CD (r = 0.72; p < 0.01). Anti-68kDa antibodies were positive in SNHL. It has been registered the significant increase of expression of TGFβ, TNFα, IL-1, IL-12, VCAM-1, HSP70, the decrease of expression of PPARγ, RBP4 in serum and mucosa of patients vs. CG.

Discussion/Conclusion: SNHL is associated with the T-cell mediated immune response, proinflammatory cytokines, vascular changes, and have been described during the genesis of the IBD.
Study on clinical remission and mucosal healing in subtypes of Crohn’s disease patients by short-term combination therapy

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Introduction: This study aimed to analyze the effect of short-term combination therapy on clinical remission and mucosal healing in different subtypes of Crohn’s disease.

Methods: Different subtypes of CD patients diagnosed in Ruijin Hospital, Shanghai Jiao Tong University School of Medicine between Jan 2014 and Jun 2016 were enrolled. They were given infliximab (5 mg/kg) in combination with azathioprine (1 mg/kg) for 30 weeks. Evaluation and endoscopy were performed in week 38. The difference among different subtypes was compared. Clinical remission was judged by CDAI < 150. Endoscopic severity was performed by SES-CD (simple endoscopic score for CD). Mucosal healing was judged by disappearance of ulcers under endoscopy.

Results: 81 CD patients were enrolled in the study with 52 males and 26 females. The age of onset was 12–60 years old. 57 cases presented ileum involvement (70.3%), while 62 cases (76.5%) involved colon. There was no difference between L1, L2 and L3 subtypes in age onset, BMI, lab examine, or CDAI before the combination therapy. Short-term combination therapy induced high remission rate in CD patients and one-third of the patients achieved mucosal healing. There is difference in mucosal healing rate between subtypes of CD patients (as you can see in the following tables).

Discussion/Conclusion: Short-term combination therapy induced high remission rate in CD patients and one-third of the patients achieved mucosal healing. There is difference in mucosal healing rate between subtypes of CD patients, indicating longer combinational treatment for CD patients with involvement of colon.
A patient with Crohn’s disease during remission by biological agent treatment, then developed active pulmonary tuberculosis: Determining the eating habits

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Crohn’s disease (CD) is a chronic intestinal disease. Biological agents are used for the remission induction and maintenance of remission in CD after the full investigation for tuberculosis according to the international guidelines. Malnutrition and specific nutritional deficiencies are common in IBD patients, particularly countries with-low income. So, infection diseases probability such as TB is increased in IBD. Here, we present a patient who developed “Active Pulmonary Tuberculosis (TB)” after the six months therapy with a biological agent (anti-TNF). Particularly, eating habits of the patient is determined.

Case: 22-year-old female patient was diagnosed as moderately active Crohn’s ileocolitis. At this time, intestinal biopsies (PCR and culture results) did not reveal any evidence for tuberculosis. Azatiopurin (AZT) 2.5 mg/kg and oral Mesalazin were prescribed. After 4 months, because of no recovery, an anti-TNF was decided to add. Quantiferon test was negative. The chest examination and chest X-ray were normal. Anti-TNF was started as protocol. She was in both clinical and laboratory remission at the 3rd and 6th month of therapy. She had cough, sputum and night sweats after 6 months of biological agent and AZT treatment. Pulmonary TB was detected by further examinations.

The patient was a senior student in Turkey and living in a dormitory with two girlfriends. The height of the patient is 163 cm and her weight was measured as 46 kg during the first admission of hospital. Her last weight measurement was 53 kg before the diagnosis of TBC was made. There was no evidence of TB in his boyfriend and her doormate. The patient didn’t have any special nutrition program during Crohn’s treatment. The daily energy intake of the patient was 1620.7 kcal. Only 16% of her daily energy was from proteins (62.1 g), 37% from fat (67.9 g), and 47% from carbohydrates (187.5 g). Her daily fiber consumption was 15.6 g. The tool we used for collecting data about nutritional behavior was the 24-hour dietary recall. Her vitamins intakes found to be deficient such as vitamin B₁₂ was 4.7 μg, iron was 8.5 mg and calcium intake was 573.1 mg. The results from 24-hour dietary recall were entered into the BEBIS Nutrition Data System for Research software version 7.2 (April 2013) and dietary intake data were collected and analyzed by using this program.

Discussion: The patient didn’t have any special nutrition program during CD treatment. She didn’t use cigarettes or alcohol, and avoided to consume raw vegetables, fizzy drinks, fatty and spicy foods, particularly fructose syrup. She went to the school in the evening and had irregularity at meal times. She often eats fast foods (high-fructose corn syrup and lard, trans-fat). Chocolate and other similar products such as biscuits and packaged products are frequently consumed by the patient.
In conclusion, malnutrition and specific nutritional deficiencies are common in IBD patients. So, in order to decrease infection diseases probability such as TB risk in IBD patients, nutritional status should be identified and then nutritional therapy with anti-inflammatory activity for improving nutritional status should be provided.

References:


Vitamin D status and polymorphisms of its receptor gene during Crohn’s disease: Results of a prospective comparative study

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Introduction: Vitamin D is of great interest in the etiopathogenesis of CD (Crohn’s disease) since its discovery of its action on the innate and acquired immune response. The prevalence of hypovitaminosis D during CD varies from 16 to 88% depending on the studies, but the cause-and-effect relationship remains to be proven. The goals were: (1) To determine the status of vitamin D during CD; comparing the results to those of a control group and identifying the factors associated with vitamin D deficiency and deficiency in these patients. (2) To study certain polymorphisms of the vitamin D receptor gene during the course of the CD, in particular looking for an association with the vitamin D status.

Methods: Case-control study with prospective collection of data including patients with CD. The determination of the hydroxy vitamin D was carried out by radioimmunoassay. Vitamin D deficiency was defined as 25 OHD < 20 ng/ml and subdivided into insufficiency: 20 < 25OHD < 10 ng/ml and deficiency: 25OHD < 10 ng/ml. The Bsm1, Fok1, Taq1 and Apa1 polymorphisms were studied by Polymerase Chain Reaction and enzymatic restriction method.

Results: There were 63 patients (27 men and 36 women) with a mean age of 35.4 years and 61 age and sex matched controls. There were no statistically significant differences between the 2 groups in phototype, clothing habits, smoking, and the season in which the samples were taken. The mean age of diagnosis of CD was 30.4 years [14–63]. Colon localization was the most common (47%). CD was a penetrating phenotype in 47% of cases. At the time of inclusion, 44% of the patients were in thrust. The mean level of 25OHD was 14.2 ng/ml [4.45–35.6] during CD and 15.6 ng/ml in the control group with no significant difference between the two groups (p = 0.4). Vitamin D deficiency was found in 79% of patients and 84% of controls (p = 0.3). Similarly, there was no significant difference in the frequency of VD deficiency (33% vs. 25%, p = 0.3). Factors associated with the presence of VD deficiency during CD were CDAI, which was higher in case of deficit (169 ± 145 vs. 81 ± 109, p = 0.04). The correlation study of vitamin D versus CDAI was close to statistical significance (p = 0.08, r = -0.216); a tendency to inverse correlation. Factors associated with vitamin D deficiency during CD were: female sex (81% vs. 43%, p = 0.03). In addition, treatment with azathioprine (41% vs. 67%, p = 0.04), anti-TNFα treatment (14% vs. 36%, p = 0.05) and prior vitamin D supplementation (32% vs. 54%, p = 0.04) were associated with the absence of vitamin deficiency. The genetic study of polymorphisms of the vitamin D receptor could be performed in 53 patients and 58 controls due to a lack of precipitation of DNA. A significant difference was found for the Apa1 polymorphism with a less frequent GG genotype during MC (11%) compared with controls (31%) (p = 0.04). Only the homozygous bb genotype of Bsm1 polymorphism was more common in vitamin D deficiency (56%) compared to non-deficient patients (24%) (p = 0.04) and this genotype was associated with vitamin D level on lower (12.5 ng/ml) (p = 0.04).
Conclusion: In Tunisia, vitamin D deficiency is as common during CD as in the general population. Some polymorphisms in the vitamin D receptor gene are associated with CD and vitamin D deficiency suggesting an etiopathogenic link. Systematic supplementation with vitamin D especially in women and the control of the activity of the disease by immunosuppressors and biotherapies are probably the only way to prevent this vitamin deficiency.
Fatal cerebro-meningeal haemorrhage complicating a Crohn’s disease

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Introduction: Central or peripheral neurological manifestations are rarely reported during Crohn’s disease. Cerebral venous thrombosis is the most described complication explained by the state of hypercoagulability characterizing the outbreaks of the disease. Cerebrovascular accidents, severe deficit or psychiatric syndromes are also described in the literature.

Observation: We report the observation of a 35-year-old patient without past medical history, followed for an ileo-colic Crohn’s disease of inflammatory phenotype without anoperineal lesions and not associated with extraintestinal manifestations. The patient experienced two moderate outbreaks of his disease which responded to oral corticosteroid therapy. He was received put azathioprine as maintenance therapy, which was stopped by the patient because of a deep asthenia.

Two months later, the patient was admitted in our department for a third thrust classified as moderate, with a CDAI score equal to 289, made of a liquid diarrhea of 6 to 7 stools/day non-bloody. Physical examination at admission had shown a fever estimated at 38.5°C, a mucocutaneous pallor with a sensitive abdomen without palpable mass. The neurological examination was normal. On the laboratory tests, the patient presented an inflammatory biological syndrome with serum C-reactive protein (CRP) at 118 mg/l and macrocytic anemia at 10 g/dl.

An abdomino-pelvic CT scan was then performed in an emergency to eliminate a complication as an abscess. This imaging demonstrated a continuous non-stenosing circumferential wall thickening from the anal margin to the transverse colon half with densification of the peri-colic fat without fistula or intra-abdominal collection. A medical treatment based on oral corticosteroids at the dose of 1 mg/kg/day combined with antibiotic therapy was started. The initial clinical-biological evolution was favorable with an apyrexia obtained after 24 h and a control CRP at 50 mg/l. At the 5th day of hospitalization, the patient presented acute severe headache associated with two episodes of vomiting without a sensory-motor deficit. In front of this clinical profil of intracerebral hypertension, a cerebral scan was performed, showing multiple left parieto-occipital intra-parenchymal hematoma associated with meningeal haemorrhage and peri-lesional edema with mass effect on median structures and a beginning of temporal and right sub-falcorial engagement. The clinical evolution was marked by an alteration of the state of consciousness with the development of a rigidity of decerebration of the four limbs and tonic-clonic movements of the right upper limb. The patient was transferred to the intensive care unit and a cerebral angio CT scan was performed to support the etiological diagnosis of cerebro-meningeal haemorrhage. Imaging showed a marked increase in intracerebral bleeding with complete temporal engagement and vasospasm of the carotid vessels. Five hours after the onset of neurological symptomatology, the patient was declared brain dead.
In front of this clinical presentation, three main diagnoses were discussed: aneurysm rupture, arteriovenous malformation or cerebral thrombosis complicating the moderate outbreak of Crohn’s disease. But the rapid fatal evolution, the bleeding site, and the lack of specific radiologic signs were not in favor of any of these diagnoses. The autopsy was not done. It might have perhaps identified an unknown pathological entity in which Crohn’s disease plays an etiopathogenic role.

**Discussion/Conclusion:** Our observation is the first case described in the literature of a cerebro-meningeal haemorrhage complicating a moderate thrust of an ileo-colic Crohn’s disease with a fatal course in a few hours. Etiopathogenic links may explain this association.
Choledochoduodenal fistula complicating a Crohn’s disease: A case report

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Introduction: A choledochoduodenal fistula is an abnormal communication between the common bile duct and the duodenum. It is most often secondary to a perforated duodenal ulcer, choledocholithiasis, or cholelithiasis. Crohn’s disease (CD), due to the chronic inflammation of the gastrointestinal tract, is associated with an increased risk of developing gastrointestinal fistulas. Only three cases of bilo-intestinal fistula occurring in the setting of CD have been reported: 2 choledochoduodenal fistulas and one colo-biliary fistula. Choledochoduodenal fistula is generally asymptomatic and is accidentally discovered on imaging.

Observation: A 70-year-old patient with no pathological history, non-alcoholic-smoking, had consulted for diffuse abdominal pain and bilious vomiting without fever or jaundice, evolving since 2 weeks. He had also reported a chronic diarrhea. No abnormalities were noticed at physical examination at admission. On the laboratory tests, the patient presented an inflammatory biological syndrome with serum C-reactive protein (CRP) at 89 mg/l and normocytic anemia at 10.5 g/dl. The abdominal ultrasound had noted a pneumobilia without cholelithiasis in the gallbladder or in biliary ducts. The upper gastrointestinal endoscopy and the colonoscopy have showed multiples ulcerations in the antral and duodenal mucosa as well as in the terminal ileum. The CT enteroclysis had described a wall thickening in the second and third duodenum and a choledochoduodenal fistula with pneumobilia. Anatomopathological examination of intestinal lesions had concluded to a chronic inflammation related to a Crohn’s disease. A treatment based on corticotherapy then on azathioprine combined with infliximab was instaured and a clinical, biological and endoscopic remission was obtained. A CT Scan performed after 1 year of treatment showed the persistence of the choledochoduodenal fistula.

Discussion/Conclusion: Choledochoduodenal fistula is a very rare complication of the CD. It reflects a severe evolutive profile of the disease. Its management is essentially based on treatment of inflammation and may require biotherapy.
Prolonged azathioprine treatment reduces the need for surgery in early Crohn’s disease

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Introduction: The place of azathioprine (AZA) is well recognized among the immunosuppressive treatments. Whether an early use of this molecule could alter the natural history of Crohn’s disease (CD) remains debated. We aimed to evaluate the impact of AZA on disease progression in a cohort of Tunisian patients with early CD.

Methods: This longitudinal cohort study examined patients with early CD defined as disease duration ≤ 18 months and no previous use of disease-modifying agents (immunomodulators/biologics) according to Paris definition. The primary outcome was the proportion of CD-related intestinal surgery. Statistical analysis was performed with SPSS 20.0. Cox regression analysis was performed to identify potential predictive factors of CD progression.

Results: Fifty eight patients with early CD were enrolled in the study. The sex-ratio M/W was 0.93. After a median follow-up of 65 months (interquartile range, 32–78), 20 (34.48%) patients underwent abdominal surgery. The cumulative rate of remaining free of CD-related bowel surgery at 5-year on AZA treatment was 0.57. The median CD-related bowel surgery was 72 months (61.5–81.3). Three independent predictors of CD-related operations were identified: prior bowel resection (0.045), smoking (p = 0.04), and AZA treatment duration < 36 months (p = 0.038).

Conclusion: Prolonged use (≥ 36 months) of AZA was associated with a more favourable disease course of early CD, evident as a lower risk of CD-related surgeries.
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.
Hematological status of Crohn’s disease patients who underwent the same type of surgery

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Introduction: During Crohn’s disease (CD) evolution an important number of patients require surgical management for complications such as strictures, abscesses and fistulas. For some patients, such surgical event is the moment of diagnostic for CD. After resection of a diseased intestinal segment, CD reappears often within a year post surgery.

Methods: We retrospectively rewiewed patients admitted in surgical departments of our hospital and released after suffering various surgery procedures for bowel (small bowel or colon) obstruction during June 2016–June 2018. In order to evaluate their tolerance to surgical stress, value of hemoglobin (HGB) was assessed as main indicator.

Results: Since june 2016,149 patients were submitted to a surgical therapy for small bowel or colon obstruction, ages between 25–91 years, 28 men and 121 women, with mean HGB during hospitalization: 12.10 (7.70–17.2) g/dl. Both 25 and 91 years old were women and had normal HGB, 12.60 g/dl. Mean duration of hospitalization was 7 days. In the same period, from 38 patients hospitalized with CD, twelve adults underwent surgery, 6 men and 4 women, ages between 35–70 years; other five patients were admitted in pediatric surgery, orthopedics and oro-maxilo-facial surgery departments. Six of these patients underwent surgery for obstruction, mean HGB: 10.96 (8.62–16.6) mg/dl, one for colecistectomy, with HGB 12.32 g/dl, one for acute peritonitis, with HGB 8.12 mg/dl. For two patients, surgical event represented the diagnostic moment. Two patients received treatment with adalimumab. No patient needed blood transfusion. Mean duration of hospitalization was 8 days.

Discussion/Conclusion: Patients with CD tolerated sucessfully surgical procedures for the bowel obstructions. It is important a careful postoperative management in order to prevent recurrences.
Introduction: T regulatory (Treg), T helper 17 (Th17) and activated T effector (Teff) cells are often to be found on surfaces, that have barrier functions, such as the bowel mucosa, where they protect the organism from pathogens or suppress excessive T-cell immune reactions. The dynamics between these tree subpopulations determine the development of inflammatory process in inflammatory bowel diseases (IBD). Recently, conflicting data on the effect of anti-TNFα therapy on Th17/Teffs/Tregs subsets have been accumulated, mainly in Crohn’s disease. Our aim is to monitor for a period of 1 year Th17/Teffs/Tregs in patients with ulcerative colitis (UC) on anti-TNFα therapy.

Methods: Eight consecutive active UC patients on anti-TNFα therapy were followed immunologically and clinically. Th17, Teffs and Treg in peripheral blood were tested by flowcytometry in patients (before therapy, on week 6, on 3th month and on first year after induction of anti-TNFα) and 15 healthy controls.

Results: We found that before therapy the mean percentage of Th17 lymphocytes in patients (8.42%) was lower than in healthy subjects (15.3%). During the therapy the patients who are clinical responders increased Th17 level but below the mean percentage found in healthy subjects. The mean of Treg frequency by UC patients was lower than those of the healthy controls before anti-TNFα treatment (5.6% vs. 7.42%, respectively), while at the first year of therapy in clinical responders Tregs were significantly higher than those by the healthy controls (10.0% vs. 7.42%, respectively). We found that in patients who are clinical responders there is a statistically significant down-regulation in Teffs on 1st year. This is directly related to the severity of the disease as well.

Discussion/Conclusion: Our results demonstrated that biological therapy affects Th17, Teffs and Treg subsets in UC patients and the changes in these subsets could be predictive factor of response to anti-TNFα agents.
Comparison of histological reports after various types of treatment and after achievement of clinical and endoscopic remission in patients with ulcerative colitis (UC)

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Introduction: When we talk about the remission in case of UC, we consider: clinical, endoscopic, histological and biomarker remission. Only clinical and endoscopic remission is not fully enough to completely rule out the activity of disease. So the aim of our study was to assess the histology reports after various type of treatment in UC patients in remission and realize in which cases we have more stable healing of lesion.

Methods: 52 patients with previous confirmed diagnoses of UC were examined. Hematology, liver enzymes test, C-reactive protein, fecal calprotectin, ultrasound examination and lower endoscopy with biopsy were performed. They were divided into two groups: first group - steroid-unresponsive and steroid-dependent patients (n = 22) after administration of biological therapy with achievement of clinical and endoscopic remission on follow up endoscopy. Second group – biological naïve patients (n = 30) after administration of 5ASA* and topical steroid with achievement of clinical and endoscopic remission on follow up endoscopy.

Results:

| UC patients (n = 52) with clinical and endoscopic remission after treatment |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|------------------|
| After biological therapy (n = 22) – steroid-unresponsive & steroid-dependent patients | After therapy with 5ASA + topical steroid (n = 30), biological naïve patients | p |
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Microscopic analysis and assessment according to Riley
Scoring: 0 = none, 1 = mild, 2 = moderate, 3 = severe

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Discussion/Conclusion: As a result of our study, on the background of biological therapy intake (for steroid-dependent and steroid-unresponsive patients), when clinical and endoscopic remission is achieved in patients with ulcerative colitis – histological activity index is significantly lower, than in biological naïve patients with clinical and endoscopic remission, receiving basic therapy plus topical steroids.

No conflict of interest.

*5ASA – 5aminosalicylic acid
**PMN – polymorphonuclear leukocytes
***LP – lamina propria
Efficacy and safety of azathioprine and methotrexate for maintaining remission in microscopic colitis: Outcomes from a district general hospital

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Introduction: There is excellent evidence for the efficacy of budesonide to treat microscopic colitis (MC). Unfortunately many patients experience a relapse of their symptoms after withdrawal of this drug. There are limited data which report on the safety and efficacy of using immunomodulators to maintain remission in patients who require two or more courses of budesonide in 1 year for MC. Since 2011 all patients under one physician with a diagnosis of biopsy proven MC requiring two or more courses of budesonide started treatment with an immunomodulator. These patients received treatment for 2 years following which treatment was withdrawn and follow up for disease recurrence continued.

Aim: To report the safety and efficacy of the use of immunomodulators in patients with microscopic colitis at a large DGH.

Methods: We maintain a prospective database of all patients treated with immunosuppressants for MC. Data on disease subtype, age, and duration of treatment, tolerability and complications were reviewed.

Results: 14 patients; 13 (92%) females who required 2 or more courses of budesonide to maintain symptom free remission were identified. Mean age was 62, (range 48–78). Disease type was lymphocytic colitis; 4 (28%), collagenous colitis; 10 (71%). Mean duration of treatment was 14 months (range 12–36 months). 4 (28%) patients tolerated standard dose azathioprine. In 10 (71%) patients side effects required withdrawal of AZA, of these 2 (20%) started low dose azathioprine and allopurinol and 1 started mercaptopurine, 3 (30%) started low dose mercaptopurine and allopurinol (LDMPA). 3 (30%) started methotrexate. 1 patient was intolerant to all thiopurines and MXT.

6TGN levels were available in all 10 (100%) who remained on thiopurines. Mean 6TGN was 499 (204–723). 13 (100%) patients were in a steroid free remission at 1 year and 10 (91%) at 2 years. 8 (57%) stopped all immunosuppression after 2 years of therapy and remain in remission; with a mean follow-up of 14months (range 12– 60 months). 5 (35%) remain in remission on therapy. 1 year after treatment withdrawal 3 (18%) patients had a biopsy proven relapse. Treatment was restarted and all patients entered a clinical remission. Complications of treatment included: oesophageal squamous cell cancer in 1 patient after 18 months LDMPA.
**Discussion/Conclusion:** In this case series of patients with budesonide dependent MC standard dose azathioprine, LDTA and MXT were effective treatment options that provided (at least) medium term remission and avoided long term steroids. Azathioprine was poorly tolerated. These treatments should be considered in patients with steroid dependent disease to avoid the long term risks of steroids.
The imbalance of the homeostasis serine proteases inhibitors in inflammatory bowel disease naive patients: A horizon for new perspectives therapies?

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Background: The pathogenesis of chronic inflammatory bowel disease (IBD) suggest an inappropriate activation of the intestinal immune system against the intestinal host’s flora of genetically predisposed persons. The intestinal microbiota can be involved in different ways in this pathogenesis. Indeed, an excessive proteolytic activity of the intestinal microbiota of IBD subjects was one of the recent and demonstrated hypothesis.

Three aims were fixed to this study. First one is to explore the global fecal proteolytic activity of naive IBD patients comparing to normal persons and to study secondly the effect of serine protease inhibitors on this activity. The third objective was to compare normal serpin concentration in fecal waters in both groups.

Material and methods: A prospective comparative study was enrolled in our medical center from January 2015 to December 2015. Were included to the study all the hospitalized new cases of IBD and a second group of healthy voluntary people. All the subjects (controls and patients) treated with an antibiotic, anti-inflammatory or probiotic in the 6 months prior to inclusion were excluded. All patients have benefited of a physical and biological examination and colonoscopy. Stool samples were collected for fecal water extraction. At the first step we measured the global proteolytic activity of fecal water using azocasein or casein as a substrate in both groups. To highlight the nature of the proteases involved, we studied the inhibitory effect of specific serine proteases inhibitors on fecal proteolytic activity. We used PMSF and SBTI as chemical serine protease inhibitors and serpin ES expressed by a commensal bacterium of the intestinal microbiota. This serpin was previously purified and optimized in the Ifé Laboratory, Metagenopolis at INRA Jouy-en-Josas in France using recombinant strain of E. coli (plasmid pDEST17). The final step was to search a natural serpin deficit in IBD group so we studied in both groups the proteolytic activity of the fecal water after using proteases which degraded all the protein except serpins. For the statistical analysis we used Spss software (20.0) (significant difference for p < 0.05).

Results: Were included in the first group of IBD 28 patients vs. 15 in the second group of controls. The middle age was 46 years vs. 48 years in the second group. The sex ratio [H/F] was 1.33 vs. 1.14. The IBD group were divided in 15 cases of Crohn’s disease and 13 cases of ulcerative colitis (UC) disease. The activity of the disease was variable from minimal to severe. Proteolytic activity was greater in patients vs. healthy controls (294.3 U/ml vs. 22.9 U/ml, p < 0.05). Particularly high activity has been observed in the severe forms of both UC and Crohn’s disease. We found a significant decrease in protease activity in the presence of both inhibitors: PMSF (1 mM) (294.3 ml/l vs. 63.60 U/ml p < 0.01) and SBTI (1 mM) (294.3 U/ml vs. 79.6 U/ml p <
Using the serpin ES (14 μg/μml) non-significant decrease in the proteolytic activity was found (294.3 U/ml vs. 242.2 U/ml, p > 0.05). In reverse zymography only one band was found in the first group vs. three bands in the healthy groups.

**Conclusion:** Our study demonstrated a higher proteolytic activity of fecal water in IBD group comparing to healthy people and this activity was concordant to the severity of the thrust. Serine inhibitors were able to decrease the proteolysis. Thus, majority were serine proteases. The lower concentration of serpin ES may explain the lesser inhibition. Finally, in IBD patients there is a natural deficiency in serpins therefore an imbalance in the homeostasis can be suggested as hypothesis to the pathophysiology of the IBD disease. Restoring this balance proteases-inhibitors can lead to new therapeutic perspectives especially by manipulating the microbiota using genetically modified probiotics.
The prevalence of extraintestinal manifestations in patients with IBD

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Introduction: The prevalence of extraintestinal manifestations in patients with IBD is estimated to be between 25–40%, and most commonly affect joints, skin, hepatobiliary system and eyes.

Methods: We thoroughly studied 140 patients who enrolled in our outpatient department from 2015 to 2017. The study group included 65 men and 75 women with a mean age of 39.25 years and a mean disease duration of 9.54 years. The CD group was comprised by 92 patients, 41 males and 51 females, with the following disease location; 40 L1, 13 L2 and 39 L3. Among 48 patients with UC with equal sex distribution 4 were classified as E1, 28 as E2 and 16 as E3. There was also a detailed recording of the administered medication in all patients.

Results: A total of 35% of the study group exhibited extraintestinal manifestations and more specifically 37% of patients with CD and 31.3% of patients with UC. In a more detailed analysis 13.6% of patients had osteoporosis/osteopenia, 12.9% peripheral arthritis, 3.6% axial arthritis and 5% of patients experienced cutaneous, hepatobiliary and ocular manifestations. We observed a statistically significant correlation between the occurrence of extraintestinal manifestations and the age of the patients (p = 0.001), as well as the administration of biological agents (p = 0.038). There was not any statistically significant correlation between the presence of extraintestinal manifestations and gender (p = 0.072), disease duration (p = 0.46), disease location (p = 0.47) and each disease separately (CD: p = 0.957, UC: p = 0.097).

Discussion/Conclusion: A significant prevalence of extraintestinal manifestations, in accordance to the international literature, was observed in our study group, and particularly in the elderly as well as in patients receiving biological agents.
Causes of switching anti-TNFα agents in patients with IBD – A single-center experience

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Introduction: The aim of this study is to evaluate the causes of switching anti-TNFα agents in patients with IBD.

Methods: The study group included 85 patients, 40 men and 45 women with a mean age of 38.56 years. There were 64 CD patients with a mean disease duration of 10.22 years and the following disease distribution; 27 L1, 6 L2, 30 L3 and 1 L4. The mean duration of anti-TNFα agent administration was 6.36 years, with 40 patients initially receiving infliximab and 24 adalimumab. Among 21 patients with UC, there were 13 with pancolitis and 8 with left-sided colitis, with a mean disease duration of 13.36 years. The mean duration of anti-TNFα agent administration was 4.63 years with 12 patients initially receiving infliximab, 6 adalimumab and 3 golimumab.

Results: There were 31 drug switches 18 concerning infliximab (58%), 11 adalimumab (35.55%) and 2 golimumab (6.45%) in a total of 27 patients. Causes of switching included non-response in 13 patients (42%), allergic reactions in 11 patients (35.5%), loss of response in 6 patients (19%) and psoriatic rash in 1 patient (3.5%). In patients receiving infliximab the most common cause of switching was allergic reactions (55.5%), followed by loss of response (28%), non-response (11%) and psoriatic rash (5.5%). In patients receiving adalimumab, the most frequent cause was non-response (82%) followed by loss of response (9%) and allergy (9%). Finally, non-response was the only cause of switching in the golimumab group.

Discussion/Conclusion: Switching of anti-TNFα agents in patients with IBD is most often due to non-response and the occurrence of allergic reactions.
Risk factors for surgery in Crohn’s disease patients – The experience of a referral center

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Introduction: The aim of this study is to evaluate the association between clinical factors (age at diagnosis, gender, early use of steroids, current smoking, extraintestinal manifestations, location and behavior of the disease) and increased risk of surgical intervention in CD patients.

Methods: This is a retrospective study of 99 patients 49 men and 50 women, 31 of whom had undergone finally a surgical intervention. At diagnosis, 79 patients were under 40 years of age while 20 were over 40 years of age. The study group included 44 L1 patients, 9 L2 and 46 L3, while 17 of them manifested perianal disease. A total of 57 patients were classified according to their disease behavior as B1, 30 as B2 and 12 as B3. At the time of diagnosis, 43 patients were smokers, 13 had stopped smoking at least 6 months prior to diagnosis, 43 were not smokers, and 38 exhibited at least one extraintestinal manifestation. Finally, 26 patients received steroids up to 3 months after diagnosis or at the first flare up.

Results: There was not any statistical significant correlation between surgery and sex \((p = 0.7)\), age at diagnosis \((p = 0.5)\), disease location \((p = 0.3)\), smoking \((p = 0.6)\), perianal disease \((p = 0.7)\) and extraintestinal manifestations \((p = 0.07)\). In contrast, a statistically significant correlation was observed between surgery and disease behavior \((p < 0.05, 48\% \text{ patients who had undergone surgery were classified as B2 and } 29\% \text{ as B3})\) and use of steroids \((p < 0.05, 68\% \text{ of the patients who had undergone surgery received steroids within three months of diagnosis or at the first flare up})\).

Discussion/Conclusion: The stricturing and penetrating disease behavior, as well as the early introduction of steroids seem to be a risk factor for surgery in CD patients.
How effective are treatments in prevention of hypercoagulability and thromboembolic events in ulcerative colitis patients?

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Introduction: Thromboembolic complications are an important cause of morbidity and mortality in ulcerative colitis (UC) diseases. The aim of the study is to examine the frequency of thromboembolic events and coagulation parameters during treatment in patients with UC and compare differences between patients with UC and healthy volunteers (HV).

Methods: The data of the patients with UC was retrospectively analyzed in our center from March 2009 to December 2017. ESR, CRP, MPV, aPTT, INR, endoscopic score, previous thromboembolic events and treatments of all patients with UC were studied and compared with HV.

Results: The data of 100 patients with UC (56 male, 44 female) and 60 HV (26 male, 34 female) were examined. All patients with UC (n = 100) use mesalazine; 18 of them also use AZT and 9 of them also use anti-TNF agents. Thromboembolic events were seen in 3% of patients with UC and 3.3% in HV (p = 1.000). Median (min.–max.) thrombocyte counts were 303 (98–446) in UC group and 280.5 (180–561) in HV group (p = 0.096). Median (min.–max.) value of INR was founded 1.0 (0.9–8.3) in UC group and 1.0 (0.9–1.2) in HV group (p = 0.03).

When we compared the endoscopically inactive (Mayo Score: 0–1) 24 patients and endoscopically active (Mayo score: 2–3) 76 patients on same parameters it’s seen that; no significant difference with MPV, PLT, aPTT, INR and thromboembolic events frequency (p > 0.05).

Patients who gets combination therapy of azathioprine or anti-TNF, thromboembolic events ratio was 4.3% and 2.7%) on the patients who gets monotherapy mesalazine (p > 0.05). In additional these groups compared with the HV groups; no significant difference with thromboembolic events frequency (p > 0.05).

Discussion/Conclusion: The incidence and risk of thromboembolic events in treated patients with UC did not increase significantly when compared with healthy volunteers. This was assessed independently of the endoscopic activity of the disease. When there was a separate risk assessment for the which treatments used, it was found that there was no difference between patients who used mesalazine monotherapy and those who received combination therapy of azathioprine or anti-TNF in addition to mesalazine. These results suggest that mesalazine treatment in patients with UC has a key role in preventing thromboembolic event complication.
Proactive approach of therapeutic drug monitoring (TDM) in pediatric inflammatory bowel disease (PIBD) on maintenance biologic treatment improves clinical remission

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Background and aim: Infliximab (IFX)/adalimumab (Ada) are used as maintenance therapy in PIBD. There is reactive or proactive approach to TDM. We looked at trough levels of IFX/Ada, presence of ADA and correlation to clinical response.

Methods: We conducted a retrospective study (n = 67, Crohn’s disease [CD] = 47, ulcerative colitis [UC] = 11, inflammatory disease unclassified [IBDU] = 7 and early onset IBD [EOIBD = 2]; Male n = 43, age range 4 years 3 months – 17 y; median 13 y 8 m). 42 patients were on IFX only, 25 on Ada.

Results: Group 1 IFX converted to Ada; n = 25 patients; CD n = 15, UC n = 3, IBDU n = 5, EOIBD n = 2. Lowest Ada trough levels n = 15, median 5.6, range 0.3–17, highest median 9.1, range 3.7–12.7. ADA for Ada negative in 16 patients, n = 5 positive over time, n = 2 positive at first measurement. Group 2 IFX only; n = 42; lowest IFX through levels, median of 1.4, range < 0.8–32.5, highest through levels median 5.2, range 0–45. ADA for IFX negative in n = 37, n = 7 developed antibodies, median ADA of 61, range 10 -> 200. 50% (21/42) of patients received double doses. 5 patients were given 15 mg/kg. In 81% (17/21) of patients, double dosing led to an incremented of through levels above > 2, median 4.1, range 2.4–21.9. 15/67 (22%) out of 67 patients had completely normal laboratory tests, 42/47 (89%) CD patients had normal PCDAIs, 10/11 (91%) UC patients had normal PUCAIs. 14/47 (30%) CD patients developed antibodies to IFX, 2/11 (18%) UC patients developed antibodies to IFX.

Discussion/Conclusion: Conclusion The vast majority of patients on IFX/Ada had an excellent clinical response with this proactive approach, thus enabling us to optimize treatment and bring them into clinical remission. We advocate proactive biologic drug monitoring.
Rheumatological manifestations of Crohn’s disease: A monocentric study in Turkish population

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Introduction: Rheumatologic manifestations (RM) are common extraintestinal manifestations in patients with IBD. In the literature 10–20% axial involvement, 1–12% ankylosing spondylitis (AS), 10–20% peripheral involvement are reported. In our study we aimed to show prevalence of musculoskeletal and mucocutaneous involvements of Crohn’s disease (CD).

Methods: In this retrospective study 213 inpatients with CD were included between June 2016 and March 2018. RM were obtained from systematic patients’ questionnaire and rheumatology consultations. Subgroups were described as axial arthropathies, peripheral arthritis, and diagnosed rheumatologic diseases such as AS, rheumatoid arthritis (RA) etc.

Results: Included 213 patients’ 113 were male (53%) and 46% were female. Mean age was found 40 and mean disease age was found 6.77. RM were reported in 69 patients (32%). Axial involvement was 21%, 7.5% of patients had AS. 6.5% patients had both axial and peripheral arthritis involvement, 0.4% RA and 0.4% familial mediterranean fever (FMF). Initial treatment of 52 patients (75%) was mesalamine monotherapy or mesalamine combinations with azathioprine or budesonide. And 25 patients (36.2%) were still under remission with mesalamine and azathioprine combination. 44 patients’s (63.7%) treatment was changed to anti-TNF treatments. 22% of those patients were still use mesalamine combined with anti-TNF treatment.

Discussion/Conclusion: We studied frequency of RM of CD and their response to treatment. In order to prevent from arthritic deformations and complications anti-TNF treatments are frequently used in these patients, mesalamine and its combinations have important role on initial treatment. And more than one-third of the patients were under remission with mesalamine and its combinations.
Biosimilar infliximab in clinical practice of IBD patients

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The aim of this study is to present the 5-year positive experience with the application of biosimilar IFX to patients for treatment with the anti-TNF alpha naive or switched from the original IFX or other anti-TNF alpha antibodies.

Introduction: At present, in the Czech Republic, the biologic agents used for IBD treatment include infliximab (IFX), adalimumab, golimumab, vedolizumab and ustekinumab. Besides the original molecules, copies of them have been developed, i.e. biologically similar (biosimilar) drugs. Biosimilar IFX has been approved for the treatment of IBD in the Czech Republic since December 1, 2013.

Methods: From the beginning of 2014, we started the BT with biosimilar IFX in 26 patients with BT naive patients, in 15 cases with Crohn’s disease (CD) and 11 cases with ulcerative colitis (UC). Most of the patients responded to induction treatment by remission of their intestinal inflammation and proceeded to maintenance therapy. In the observed period, 43 patients (29 with CD and 14 with UC) were transferred from the original to the biosimilar IFX.

Results: To date, IFX has been administered to 69 patients, in 61 patients at a dosage of 5 mg/kg of body weight, in 8 patients at a dosage of 10 mg/kg. In 12 cases of IFX administration, we registered side effects (allergies, headaches, paresthesia). In 2 patients the treatment had to be discontinued, while in the rest of the patients, complete reconstitution occurred upon deceleration of the infusion. Most patients (86.7%) are still in clinical, laboratory and endoscopic remission.

Discussion/Conclusion: In the case of a correct indication and proper monitoring of the patients, administering biosimilar IFX to patients with IBD is an effective, safe, and cost-efficient treatment.
Protective effect of mesalazine on thromboembolic event risk in Crohn’s disease

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Introduction: In patients with Crohn’s disease (CD), thromboembolic events (TE) are one of the major causes of morbidity and mortality. In this study, we aimed to show the effect of mesalazine treatment on thromboembolic events and coagulation parameters in patients with CD in comparison to healthy volunteers (HV).

Methods: A retrospective, analytic study including all patients with CD who under mesalazine treatment in our department between January 2010–March 2018. Patients who have any rheumatologic or hematologic disease were excluded. Patients treated with mesalazine and HV were compared on TE, coagulation parameters, thrombocyte counts and MPVs. We also compared the patients with endoscopically active and inactive disease; and the patients who only use mesalazine and who use additional treatment options.

Results: A total of 100 CD patients with a mean age of 42.6 (18–76) and 60 HV with a mean age of 49.9 (19–78) were enrolled. All patients use mesalazine. TE were seen in 4% of CD and 3.3% in HV (p > 0.05). Median value of INR was founded 1.0 (0.9–1.6) in CD and 1.0 (0.9–1.2) in HV (p = 0.031). Median thrombocyte counts were 299.5 (108–647) in CD and 280.5 (180–561) in HV (p = 0.431). Mean MPV was 9,069 on CD and 10,273 on HV (p = 0.05).

We compared the endoscopically inactive 38 patients (SES-CD score: 0–1) and endoscopically active 62 patients (SES-CD-score: 2–3); it’s seen that, under mesalazine treatment, TE ratio was 2.6% vs. 4.8% (p = 0.509), respectively.

Patients who gets additional treatment options like azathioprine or anti-TNF drugs, TE ratio was 4.8% (n = 41) and 3.4% (n = 59) on the patients who only gets mesalazine (p = 0.561). There is also no significant difference on coagulation parameters and MPV but thrombocyte count is higher in the patients who gets additional treatment (334.38 vs. 290.67, p = 0.038).

Discussion/Conclusion: Our results suggest that using mesalazine in CD is protective from TE independently from additional treatments and endoscopically severity. Despite there is higher INR values and higher thrombocyte count in some subgroups that doesn’t result into a coagulation dysfunction or TE.
Incidence of inflammatory bowel disease across Croatia: Is there a difference between north and south?

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Introduction: It has been suggested that the incidence of inflammatory bowel disease (IBD), which includes ulcerative colitis (UC) and Crohn’s disease (CD), is twice or more times higher in southern than in northern Croatia. Although the incidence rates of these diseases have increased significantly during the last thirty years, there are still considerable data discrepancies between different areas of Croatia. The aim of this study was to investigate this apparent variation by ascertaining the incidence of IBD across Croatia.

Methods: Two prospective and two retrospective studies were conducted in Croatia: one in the central, continental area of Zagreb during the time period 1980–1989, and the other in Adriatic coast in Primorsko-Goranska County from 2000 to 2004. Second study conducted in Adriatic coast in Split-Dalmatia County during the time period 2006–2014 are compared to the results from the 1980s study. Also, incidence and prevalence in Vukovarsko-Srijemska County, continental Croatia, comparisons between the period of surveillance, 2001–2010, and the decade before, 1991–2000.

Results: Incidence rates in Rijeka North Adriatic were 4.3/10⁵ (95% CI: 2.6–6.0) for UC and 7.0/10⁵ (95% CI: 3.4–10.6) for CD – compare with 0.7/10⁵ for CD, and 1.5/10⁵ Zagreb, Central continental area. In other study, in Slavonija North rural county incidence rate were UC 3.5/10⁵ and CD 0.95/10⁵, compare incidence rate in Dalmacija South Adriatic of UC was 9.0 (95% CI: 5.8–12.1)/10⁵ inhabitants, and the annual incidence rate of CD was 4.1 (95% CI: 2.6–6.2)/10⁵.

Conclusion: In our study, analyzing the results from Croatia during the last 30 years, the higher overall incidence rates in southern than northern continental area, we observed a significant incidence rate increase for both diseases. Possible reason for this dynamics is modernization and “westernization” of life style, including dietary and behavioral habits in general. This may reflect recent increases in the incidence of IBD in southern Croatia whereas those in the north may have stabilised.

Key words: IBD, ulcerative colitis, Crohn’s disease, incidence
Audit into the frequency of reactions to intravenous iron infusions

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Background: Iron deficiency anaemia is common place in patients who suffer from gastroenterology conditions, (Kaitha et al. 2015). The reduction or loss of absorption of iron taken orally in diet or as a medicinal supplement being the primary cause. Patients with dysfunctional gastrointestinal tracts will often struggle to absorb oral iron, tablet or liquid, leading to worsening of symptoms. These patients require intravenous iron to relief the symptoms of lethargy, tiredness and also gut dysfunction that can be seen with oral iron, such as pain and diarrhoea, (Gasche et al. 2004).

The Gastroenterology Ambulatory Unit at RGH is set up for all gastroenterology patients and one of the procedures carried out on the unit is intravenous iron infusions.

Method: All patients admitted to the Ambulatory Unit are logged and a discharge summary produced. This summary can be pulled off as a report and the relevant data interpreted. Over a two month period the Ambulatory Unit seen 254 patients for varying procedures and infusions. The patients who underwent iron infusions were given either Ferinject or Cosmofer.

As no patient sensitive information is presented in this audit, ethical approval was not required.

Results: Of the 254 patients 9.4% (n = 24) underwent an intravenous iron infusion. Cosmofer was given to 46% (n = 11) of the patients and the remaining 54% (n = 13) received Ferinject. The only reason for this split was capacity of the unit and the fact that Ferinject can be administered rapidly. Whilst receiving an intravenous iron infusion 17% (n = 4) patients had a reaction of some sort, 1 was receiving Cosmofer the other 3 patients received Ferrinject. The most common symptoms were flushing, nausea and pounding heart. The 2 patients experiencing more significant symptoms included altered mental state and a drop in blood pressure. The 2 less acute patients were treated by stopping and restarting the infusions without further symptoms, however the other 2 required medication. Medication given included chlorphenamine, hydrocortisone and IV fluids to both, one required adrenaline. Following a period of observation, all recovered well.

Conclusions: The reactions these patients experienced are not uncommon when administering intravenous iron, with the exception of the 2 patients who presented with acute confusion. However in retrospect, those 4 patients and in particular the 2 who became confused where generally unwell with their iron deficiency which leads one to suggest that their general health lowered their threshold for experience allergic type symptoms. More investigation would be needed to identify an exact cause.
References:


Safety of accelerated infliximab infusion in inflammatory bowel disease in a district general hospital

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Introduction: Our district general hospital serves a population of around 330,000 with 1325 active inflammatory bowel disease (IBD) patients. A small percentage of these patients receive infliximab infusions. The British National Formulary states that infliximab infusions should follow the following schedule: 5 infusions over 2 hours (hr) with 2 hr of post-infusion monitoring, with subsequent infusions delivered over 1 hr with 1 hr of monitoring. With published data supporting an accelerated infusion regimen, after 10 incident-free infusions we administer infliximab over 30 minutes (min) with 30 min observation. Our primary endpoint was to assess the safety of accelerated infusion protocol, with secondary assessment of efficiency.

Methods: Using the local IBD registry data tool, we retrospectively identified all patients with IBD who underwent infliximab infusions in 2017.

Results: 202 infusions were given to 39 patients with IBD. 59 induction infusions were administered over 2 hr, 10 infusions over 1 hr, and 133 infusions over 30 min. Only 1 infusion reaction was reported in the induction phase (1.7%). The reaction occurred within 10 minutes of commencement of the infusion and was anaphylactoid in nature. The patient was taken off infliximab and is now on ustekinumab. The remaining 201 infusions were reaction free, including all of the accelerated infusions. The accelerated infusions saved a total of 1 hr per patient visit to the infusion unit. This has allowed the Trust to free up 13 days of infusion time per annum on our current case load.

Discussion/Conclusion: Accelerated infliximab infusions over 30 min were safe and the time saved enhances our unit’s capacity, consistent with the wider evidence available in the literature. If other units across the country also share the same safety profile of accelerated infliximab infusions, then the national guideline can be updated, resulting in an overall increase in the efficiency of infusion units.
Is there a role for budesonide in maintenance of remission in Crohn’s disease?

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Introduction: The role of corticosteroids in the therapy of inflammatory bowel disease has been known for long time. Introduction of budesonide as a corticosteroid with predominantly local activity and fewer side-effects has somewhat changed our approach to steroid therapy. It can be used as an induction therapy in mild to moderately active ileocecal CD, but its use in maintaining of remission is doubtful.

Methods: Case presentation.

Results: Our patient, female of now 34, was diagnosed with IBD in 2010. Prolonged diarrhea, endoscopic mucosal appearance on colonoscopy (without ileoscopy), mucosal histology with cryptabscesses and exclusion of infectious disease led to the diagnosis of UC-pancolitis. Mesalazine 3 g a day after a few weeks brought clinical remission. She stopped aminosalicylate and delivered a healthy child in 2012. Two months later she was hospitalised because of cramps with 10 watery stools a day, severe weight loss – 7 kg, afebrile, with mild anaemia and CRP over 200. Aminosalicylate was restarted and after exclusion of infection systemic methylprednisolone was started – 1 mg/kg. Fast clinical improvement followed. Native colonoscopy was performed- spared rectum and deep ulcerations with spared mucosal areas in sygmoid and descending colon were found, biopsies were taken and examination ended-incomplete. Histologic characteristics confirmed high possibility of CD-and this was confirmed by ultrasound signs and segmental ileal stenoses visible on barium follow-through. At admission her CDAI was 200.

Clinical remission was achieved and methylprednisolone was tapered. She refused the introduction of azathioprine or referring to the tertiary centre for possible introduction of anti-TNF therapy. A mild relapse followed after the cessation of methylprednisolone and budesonide was introduced, 9 mg daily, next month reduced to 6 mg. She continued 3 mg daily on her own without symptoms, normal CRP and relapsed after two years. She increased daily dose, repeatedly refused endoscopy and other medication and continued budesonide.

Discussion/Conclusion: Continued budesonide may be effective in prolonging time to relapse in CD (as several studies had shown) – particularly in situations of patient’s non-compliance. Taking into consideration current knowledge of mucosal healing and course of the disease – it cannot be the mainstay of remission maintenance in CD.
Gal-SWITCH: A prospective study of planned switch from infliximab bio-originator Remicade® to Bio-similar Inflectra®

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Introduction: Infliximab (IFX) biosimilars were approved in 2013 by the EMA. Since then, studies have shown the efficacy of IFX biosimilars appear similar to Remicade® when patients are switched. The main reason for switch to bio-similar is the associated cost reduction with recent reports of cost savings up to 69%. Our aim was to prospectively assess the efficacy, safety and patient satisfaction when patients were switched from Remicade® to Inflectra®.

Methods: This is an open-label prospective cohort study involving patients with IBD > 18 years receiving Remicade® who were switched to Inflectra® in October 2017. Data was collected at intervals of 3 months starting 6 months pre to 6 months post switch. Patient CRP, fecal calprotectin, IFX trough levels and antibodies (Abs) to IFX were collected along with patient reported outcome measures (PROMS).

Results: 53 patients were included in the study of which 55% (n = 29) were male and 75% (n = 40) had Crohn’s disease. The average dose of Inflectra® was 450 mg and infusions ranged from 4 to 8 weekly. There were no reported infusion reactions and there were no crisis IBD flare admissions. No patients had developed Abs to IFX at 6 months post switch. 98% of patients were still receiving Inflectra® at 6 months. There was no significant change in CRP or fecal calprotectin post switch. No significant change in PROMs was noted. An approximate 56% cost reduction occurred.

Discussion/Conclusion: Our study demonstrates the efficacy of switching to biosimilar without concern regarding safety or immunogenicity. The majority of patients remained on Inflectra® at 6 months and the switch resulted in a significant cost reduction.
Fecal HSF2 concentration maybe used as an evaluation index for predicting mucosal healing of ulcerative colitis

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Introduction: In our previous study, we found that heat shock transcription factor 2 (HSF2) was differentially expressed in ulcerative colitis (UC) patients and increased in parallel with the severity of UC. HSF2 appeared to be a potential novel marker for UC activity. So this study is aiming at providing a new noninvasive index for predicting the mucosal healing of UC.

Methods: Fecal samples were collected from 51 UC with MES (0, 1, 2, 3) and health controls. The concentration of fecal HSF2 was detected by Elisa. The correlation between fecal HSF2 levels and MES was compared by Pearson correlation analysis. A total of 231 follow-up UC patients were included. The fecal samples were collected in early morning and colonoscopy was performed in the next day for MES scoring. MES = 1 was made as the evaluation standard for mucosal healing. The concentration 1.8 ng/ml of fecal HSF2 was used as a cut-off value to predict mucosal healing. The sensitivity and specificity, positive predictive value and negative predictive value of fecal HSF2 predicting mucosal healing were calculated by the diagnostic test evaluation method. The predictive accuracy was evaluated by ROC curve.

Results: The concentration of fecal HSF2 in the normal control group and UC patients with MES = 0, 1, 2, 3 were (0.64 ± 0.09, 1.30 ± 0.35, 1.84 ± 0.46, 2.38 ± 0.57, 3.38 ± 0.42) ng/ml respectively. The level of fecal HSF2 was positive correlation with MES (r = 0.81). The sensitivity, specificity, positive and negative predictive value of fecal HSF2 to predict mucosal healing was (67.8%, 80.9%, 67.1% and 81.5%) respectively. The AUC of fecal HSF2 to predict mucosal healing was 0.919 (95% CI: 0.846–0.992, p < 0.001).

Conclusions: Fecal HSF2 concentration maybe used as a high accuracy noninvasive evaluation index for predicting the mucosal healing of UC.
Infliximab therapy and deviations in platelet indices in Crohn’s disease patients – A single-center experience

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Introduction: Biological treatment (BT) has become a mainstay in the management of inflammatory bowel disease (IBD). The aim of our investigation was to assess the correlation between platelet (PLT) indices [mean platelet volume (MPV), plateletcrit (PCT), platelet distribution width (PDW)] and C-reactive protein (CRP) in the course of infliximab (IFX) therapy in Crohn’s disease (CD) patients.

Methods: 40 patients with CD, 23 men and 17 women, were enrolled to the study. They were administered infliximab (standard therapy; together six doses). Laboratory tests (CRP and PLT indices) were performed in all patients during therapy – at 0, 2, 6, 14, 22 and 30 weeks.

Results: The survey revealed statistically significant decrease in CRP and PLT in observed patients (p < 0.01). MPV and PDW values increased significantly (p < 0.01); PDW remained in normal range and MPV was too low during whole study. Likewise, PCT measurements had adequate values all the time, however they lowered significantly (p < 0.01). Moreover, we observed a negative correlation between PLT count and MPV (p < 0.05) together with a positive correlation between CRP and PCT (p < 0.01) prior to the first dose of IFX. PLT count correlated positively with both CRP and PCT before IFX therapy and after the administration of its six doses (p < 0.01). Furthermore, a similar, but negative correlation was noticed with refer to PDW and PLT (p < 0.01).

Discussion/Conclusion: Chronic inflammatory process in patients with IBD is connected with elevated PLT count and changes in PLT activation and their morphological parameters. Increase in PCT together with decrease in MPV and PDW seem to accompany the exacerbation of CD. IFX therapy appear to normalize mentioned abnormalities. Our data suggest that PLT indices could be useful biomarkers for determining active CD and for assessing the efficacy of BT.
Association between IL12B gene polymorphisms and the risk of Crohn’s disease in Serbian patients with inflammatory bowel disease

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Introduction: Inflammatory bowel disease (IBD) is a chronic disease of unknown etiology in which genetic factors contribute to development of disease. Genome-wide association studies (GWASs) have confirmed two single nucleotide polymorphisms (SNPs) in IL12B gene (rs6887695 and rs321227), as susceptibility loci for Crohn’s disease (CD) and/or ulcerative colitis (UC), but none of them has been studied in Serbian IBD patients so far. The aim of this study was to investigate the association of rs6887695 and rs321227 with Serbian IBD patients.

Methods: A total of 206 IBD patients, 107 Crohn’s disease (CD) and 99 ulcerative colitis (UC), and 255 healthy controls were included in the study. All subjects were genotyped using TaqMan SNP genotyping assay.

Results: CC genotype of rs6887695 was more frequent in CD group (OR = 2.20; p = 0.04), and could be recognized as a potential predisposing factor, while significantly lower frequencies of G allele carriers of rs6887695 were observed in CD patients (OR = 0.38; p = 0.01). Likewise, C allele and CC genotype of rs3212227 SNP were more frequent in CD patients (OR = 1.53; p = 0.03, and OR = 2.51; p = 0.058 respectively). In contrast, CD patients carrying G allele had significantly increased risk of penetrating behaviour, while CC genotype of rs6887695 had less often penetrating CD (OR = 2.48; p = 0.02 and OR = 2.20; p = 0.03). None of the analyzed markers was associated with UC, or its phenotypic characteristics.

Discussion/Conclusion: The IL12B SNPs rs6887695 and rs3212227 are associated with susceptibility and severity of disease in Serbian CD patients, supporting their potential role as biomarkers of CD.
Colectomy-free survival and factors associated with it in children with ulcerative colitis managed in a tertiary IBD centre in the UK

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Introduction: Colectomy-free survival is an important outcome for children with ulcerative colitis. There is only limited data available about long term outcome of children with ulcerative colitis.

Aims and objectives: To review the outcome of colectomy-free survival and associated factors in patients with ulcerative colitis managed in our centre.

Methods: We have performed a retrospective analysis of all patients diagnosed with ulcerative colitis in our hospital from January 2010 to December 2015. The patients were identified from the medical database of the paediatric gastroenterology unit and paediatric surgical unit. The clinical, laboratory, endoscopy data and medical and surgical treatment were analysed.

Results: 147 patients with ulcerative colitis were identified in the study period, 85 (58%) were male patients. The median age at diagnosis was 12.9 years (2.2 to 17 years) and median duration of follow up was 34 months (12 to 96 months). 105 (72%) recorded pancolitis (E4) at diagnosis while 15 (10%) and 26 (18%) had extensive (E3) and left sided (E2) lesions respectively. Severity of disease at diagnosis, documented as physician global assessment, was mild in 50 (34%), moderate 70 (48%) and severe in 26 (18%) patients. 55 (37%) patients had no relapse in first year after diagnosis. 90 (61%) patients were in clinical remission at both 3 months and 12 months after diagnosis. 86 (59%), 54 (37%) and 46 (31%) patients received steroid treatment at diagnosis, 3 months and 12 months after diagnosis respectively. 145 (99%) patients received treatment with mesalazine during the follow-up period. 93 (63%) patients were treated with azathioprine and 66% of these patients were commenced on Azathioprine treatment within 6 months of diagnosis. 31 (21%) patients received treatment with infliximab and median time to start infliximab was 1.4 years (3 months–7 years). 12 (8%) patients had surgery (sub-total colectomy) and chronic active severe UC was the indication for surgery in all patients. Factors associated with colectomy were steroid treatment at 3 months after diagnosis (75% vs. 34% p value 0.05), steroid treatment at 12 months after diagnosis (92% vs. 26% p value 0.01) and longer time interval from diagnosis to initiation of infliximab treatment (10.4 months vs. 19.8 months p value 0.01). Age, extent and severity at diagnosis, the laboratory parameters at diagnosis including Hb, ESR, CRP, albumin, platelets, number of relapses in first year after diagnosis, number of episodes of hospitalisation for intravenous steroids and need for treatment with azathioprine or infliximab were not associated with colectomy.
Discussion/Conclusion: Only a small proportion (8%) children needed colectomy in our cohort of patients with UC and the need for steroid use at 3 months and 12 months after diagnosis and longer interval to start treatment with infliximab were associated with colectomy.
Effect of vedolizumab therapy on clinical remission, including remission of peripheral arthropathy, in patient with Crohn's disease and previous tumor necrosis factor antagonist failure

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Introduction: There is an increasing need for new treatments for patients with Crohn’s disease in whom previous therapy with tumor necrosis factor (TNF) antagonists has failed. Vedolizumab, as a monoclonal antibody against α4β7-integrin, is effective in inducing and maintaining clinical remission in Crohn’s disease.

Methods: Case presentation.

Results: A 23-year-old male with a history of Crohn’s colitis with extraintestinal manifestation in the form of peripheral arthropathy and sideropenic anemia, was treated by a pediatric gastroenterologist since he was eleven. He was treated with corticosteroids, azathioprine and non-steroidal anti-inflammatory drugs followed by mesalazine and methotrexate. The course of the disease was characterized by periods of remission and exacerbation, without persistent stable remission. At the age of 19, he was transferred to our department. We performed re-evaluation of the disease by using endoscopy and MR enterography. These studies showed pancolonic Crohn’s disease with luminal narrowing of the transverse colon. Due to an active immunosuppressive refractory disease, it was decided to commence treatment by using TNF antagonist (adalimumab). After the initiation of these agent we achieved clinical and laboratory improvement, but four months later, clinical exacerbation was noted. We intensified a dose of adalimumab (applying every week), and six months after the initial remission, a further exacerbation (joint stiffness, worsening of anemia, increase in the number of stools, increased levels of C-reactive protein and fecal calprotectin) occurred. At that time, abdominal CT examination described thickening of the colonic wall, hyperemia of the surrounding fatty tissue and multiplied mesenteric lymph nodes. We didn’t have the ability to measure anti-adalimumab antibodies and serum adalimumab concentration levels. Because of ileocolonoscopy confirmed active colonic disease and despite arthropathy, we switched adalimumab to vedolizumab. Ten weeks afterwards, we achieved complete clinical and biochemical remission. Recolonoscopy and MR enterography after one year showed luminal narrowing of the transverse colon with scarring changes (dysplasia and malignancy were excluded), without elements of mesenterial lymphadenopathy.

Conclusion: Unlike the previous therapy with immunosuppressive agents and TNF antagonist, application of vedolizumab caused stable clinical and biochemical remission for the first time, including remission of peripheral arthropathy.
PROFILE trial: Predicting Outcomes For Crohn’s disease using a molecular biomarker

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Introduction: The course of Crohn’s disease (CD) varies substantially between affected individuals, but reliable prognostic markers are not available in clinical practice. This hinders disease management because patients with aggressive disease can be undertreated by conventional “step-up” therapy, while those with indolent disease would be exposed to the risks of unnecessary immunosuppression from indiscriminate use of a “top-down” approach. Previously, we have described a transcriptional signature identifying two subgroups of patients that is detectable within peripheral blood CD8 T-cells at diagnosis, correlating with subsequent disease course. To overcome the technical challenges of separating cell populations, which would not be possible in a routine clinical setting, we developed a whole-blood qPCR-based biomarker that can recapitulate the CD8 subgroups. Here we describe the development and validation of this biomarker and the resulting clinical trial investigating its ability to personalise therapy in CD.

Methods and results: From a training cohort of 69 newly-diagnosed IBD patients, we simultaneously obtained a whole-blood PAXgene RNA tube and peripheral blood CD8 T-cell sample. Gene expression in both samples was measured by microarray. After detecting the CD8 transcriptional signature and identifying its correlation with prognosis, statistical modelling was used to identify a transcriptional classifier in whole-blood gene expression data that could recapitulate the CD8 findings. This was subsequently optimised into a multi-gene qPCR assay. Independent validation of this biomarker was established using a second, independent cohort of 84 newly-diagnosed patients, which confirmed that the subgroups had significantly different disease courses (HR = 3.34, p = 0.0003) for time to treatment escalation).

Discussion/Conclusion: We have developed, optimised and validated a whole-blood qPCR classifier that is able to predict disease course from diagnosis in IBD patients. This represents a major step towards personalised therapy and is currently under investigation in the PROFILE trial, the first biomarker-stratified trial in inflammatory bowel disease.
V565, a novel oral anti-TNF domain antibody, binds to mucosal macrophages and T cells, and reduces colonic mucosal inflammation after 6 days oral dosing to ulcerative colitis (UC) patients

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Introduction: Monoclonal antibodies to TNF transformed treatment options for patients with Inflammatory Bowel Disease (IBD). V565 is a novel oral anti-TNF domain antibody (Vorabody) engineered for resistance to intestinal proteases. It is in development as an oral treatment for IBD. In vitro V565 suppressed phosphorylation of kinases and signalling proteins and inhibited the release of inflammatory cytokines following culture with biopsies taken from patients with IBD. It was safe and well tolerated after high single and multiple doses in healthy volunteers and patient volunteers with CD and resulted in high concentrations of active drug in ileal fluid and faeces.

Methods: Patients with a Mayo score of 3–10 including an endoscopy score of ≥ 1 had up to 7 days of oral dosing with 555mg tid V565. Sigmoidoscopy with biopsies was performed before and after the dosing period. The primary outcomes of interest were presence of V565 in the colonic mucosa and reduction from baseline in phosphorylation of tyrosine kinases and signalling proteins. Localisation of V565 was determined by immunohistochemistry. Phosphorylation was determined using PathScan Receptor Tyrosine Kinase signalling arrays.

Results: Five patient volunteers with UC were treated. Due to visit scheduling, most received 6 days treatment. Presence of V565 was confirmed in the inflamed lamina propria and co-localised with CD14+ macrophages and CD3+ T cells in post-treatment biopsies. The overall level of phosphorylation of the panel of 39 kinases and signalling proteins was reduced by approximately 50% in four of the five patients. There were no treatment induced ADAs.

Discussion/Conclusion: Six to 7 days of oral administration of the anti-TNF domain antibody V565 to UC patients resulted in localisation of the Vorabody to CD14+ macrophages and CD3+ T cells in the lamina propria and inhibition of mucosal inflammatory processes. The reduction of 50% in the overall phosphorylation level was similar to that seen in an earlier study of UC biopsy cultures with infliximab at a concentration of 67 nM (10 µg/ml), a serum concentration associated with mucosal healing. These results provide encouragement that oral dosing with V565 will be a beneficial oral treatment option for patients with IBD.
Evaluation of the thiopurine therapy in children suffering inflammatory bowel disease

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Introduction: Therapeutic Drug Monitoring (TDM) is the useful tool for the individualized therapy in patients with inflammatory bowel disease (IBD) including both Crohn’s disease (CD) and ulcerative colitis (UC). The TDM is important especially for the pediatric population where the pharmacokinetics and pharmacodynamics of the applied drugs is highly variable among the patients. That may be caused by the physiological and pathophysiological differences between children depending on their age. Up to 50% of the patients must be withdrawn from the thiopurine therapy due to severe adverse effects, failure to respond or lack of response. TDM in the IBD group is applied to monitor drug exposure, adherence to the therapy and toxic metabolites. According to the recommendation of Polish Society for Gastroenterology, azatiopine is administrated in the dose 2–2.5 mg/kg/day, whereas 6-mercaptopurine in the dose 1–1.5 mg/kg/day.

Methods: This study describes results of the TDM that we are applying in our Hospital for the IBD children and achieved clinical outcomes. Statistical analysis of collected data was performed. Dose of the drug and 6-thioguanine concentration was correlated with the known markers of the adverse effects seen during thiopurine therapy. Data from the standard therapeutic drug monitoring were obtained from the 50 patients undergoing IBD therapy between 2016 and 2018 year. 6TG concentration was measured with the HPLC method developed by us. Data about total blood count (including WBC, RBC and PLT), hepatic enzymes, ferritin level and serum iron level are opportunistic collecting data and there was no need for additional blood sample collection from the pediatric patients. Parameters were correlated with the pharmacokinetic data.

Discussion/Conclusion: Our analysis have shown that TDM for the 6-mercaptopurine and azatioprine significantly improved clinical outcomes of our CD and UC children.
Colectomy place in ulcerative colitis patients who received mesalamine treatment

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Introduction: In ulcerative colitis treatment, mesalamine and surgery has the important place. Colectomy is indicated when chronic intractable disease is not controlled with medication or drug side effects are too severe.

Methods: We conducted monocentric retrospective study between January 2017–April 2018. The patients who received treatment at inpatient clinic of Gastroenterology of Ankara University Faculty of Medicine were involved in this study. The patients are classified by sex, colectomy, involvement zone of the disease and received treatment.

Results: We have included 102 patients in this study. The ages of patients is between 19–85. The mean age was determined as 44.3. 42.7% patients are female and 57.3% patients are male (43 patient female, 58 patient male). 30% of the patients were identified as left sided colitis, 22.7% as extensive type and 46.5% as pancolitis. 26.7% of the patients were treated surgically. According to the patients receiving surgical treatment; 14% left-sided colitis (4 patient) 33% extensive type (9 patient) and 51% pancolitis (13 patient) 12.9% of patients with left colon involvement, 39.1% of patients with extensible type involvement, and 29.7% of pancolitis patients were undergone colectomy. While all patients received mesalamine treatment, steroid use rate was found to be 73%, azathiopurine use rate was 55% and anti-TNF agent use rate was 38%.

Discussion/Conclusion: Colectomy was generally performed pancolitis involvement ulcerative colitis patients. According to our study, colectomy can also be applied to those with left-sided colon involvement or extensible involvement.
Clinical expression of inflammatory bowel diseases – A retrospective population-based cohort study; Vukovar-Srijem county, Croatia, 2010

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Introduction: Clinical characteristics of the cohort of 150 patients with inflammatory bowel diseases, ulcerative colitis (UC) and Crohn’s disease (CD) were retrospectively assessed as the second aim of the epidemiologic study (“Incidence and prevalence of inflammatory bowel disease in Vukovarsko-Srijemska County, Croatia, 1991–2000 and 2001–2010: a population-based study”).

Methods: We analyzed clinical features of the cohort group of 150 patients with IBD, 119 with UC and 31 with CD, separately for both diseases. Patients were interviewed retrospectively, by using standardised protocols, on age and symptoms at the time of diagnosis, intestinal and extraintestinal complications and the localization and the extent of disease. Differences among the categories were assessed by using the χ² and Fisher exact tests. The duration of the symptoms was analyzed by the nonparametric Mann-Whitney U-test. The extent of CD and UC were classified according to the Montreal’s classification.

Results: When analysis of phenotypes of CD was made, the results showed the class age 17–40 years as the prevalent age at disease onset (phenotype A2 58% of patients), the ileocolon as the predominant disease localization (phenotype L3 64% of patients) and strictureing complication as the dominant disease behavior (phenotype B3 64% of patients). From these results, the most prevalent integrated phenotype in the sample, A2L3B3, has arisen, presented with 22.58% of patients. With respect to the extent of UC, our results indicate that the most prominent phenotype is localization of disease in the rectum and the left colon (phenotype E2 41% of patients), then follows phenotype E1 (proctitis 36% of patients) and at the third position is the extensive type of disease (proximal to the splenic flexure), including also pancolitis (phenotype E3 23% of patients). Our results are in line with pathologic features, indicating significantly higher participation of intestinal complications, in patients with CD, than in those with UC. These registered complications include: intestinal perforation (CD/UC, 9.7%/0.8%), fistula (CD/UC, 22.6%/0.8%), abscess (CD/UC, 29.0%/0.8%) and ileus (CD/UC, 25.8%/0.8%).

Discussion/Conclusion: This study might be the starting position in developing the national register of patients with IBD, necessary if someone wants to continuously follow-up changes in frequency and characteristics of IBD. Only such, dynamical approach, will allow causal relationships, essential for the purpose of designing advanced therapeutic options.
Opportunistic infections, mesenteric vessels endothelial dysfunction and colonic resistance in IBD have possible genetic background for challenging clinical situations

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Introduction: IDB pathogenesis is commonly realized through metabolic and immune mechanisms involving vascular and digestive systems injury. Immune system has strong influence on both colonic mucosa and endothelium and may have strong molecular-genetic background. However, there is lack of data connecting genetics, vascular-endothelial changes and colonic changes including dysbiosis and inflammation. The aim of this study is to find possible connections of the endothelial function and mesenteric vessels remodelling depending on A1166C polymorphism of angiotensin II type 1 receptor (AGTR1) gene in IBD patients with colonic dysbiosis as a background for opportunistic infection and vascular-endothelial injury as well.

Methods: Observational study includes 104 IBD patients with colonic dysbiosis (CD) in stable remission. Standard aerobic and anaerobic microbiology techniques with nosology identification and quantity composition of microbiota were used. Intima-media thickness (IMT) of abdominal aorta (AO) and other flow mediated parameters of mesenteric vessels evaluated sonographically. NO (nitrite/nitrate) plasma concentration, vascular adhesive molecule (sVCAM-1) level was defined by IEA. AGTR1 (A1166C) genes polymorphisms assessed in PCR.

Results: The microbial overgrowth syndrome of II–IV degree detected in 95.1–95.9% of cases. CC- genotype carriers of AGTR1 gene had heavier dysbiosis of III–IV grades. Patients with A-allele, had lower frequency of dysbiosis (p = 0.004) and moderate severity (p = 0.037). CC genotype of AGTR1 gene characterized by elimination of obligate colonic indigenous constant microorganisms and contamination by pathogenic (E. coli Hly+) and opportunistic (Proteus), Enterobacteriaceae, Peptococci, Clostridium and Candida fungi. In patients with CC genotype of the AGTR1 gene a significant reduction of Bifidobacteria (35.7%, p < 0.001), Lactobacilli (24.1%, p < 0.01) and enterococci (1.5%) was found. On this background, significant increase of enterotopathogenic Escherichiae (8.94 ± 0.08 lg CFU/g), opportunistic Enterobacteriaceae (8.78 ± 0.12 lg CFU/g), Hafniiae (8.69 ± 0.09 lg CFU/g), Proteus – by 55.2%, Staphylococci (5.92 ± 0.14 lg CFU/g), Candida fungi (5.60 ± 0.10 lg CFU/g) was observed.

Discussion/Conclusion: The CC genotype of AGTR1 gene is generally characterized by elimination of normal colonic autochthonous obligate microflora and contamination by pathogenic, opportunistic and conditionally pathogenic microorganisms. The mechanism possibly involves changes of mesenteric arteries and endothelial function and may predict failures of both standard and faecal transplant therapies.
Expression of PCNA protein in comparison with inflammatory cells infiltration in Crohn’s disease

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Introduction: PCNA (proliferating cell nuclear antigen) is a polymerase-associated protein. It is synthesized in early G1 and S phases of the cell cycle. PCNA plays a threefold role in a life and death of cells. It is important element of the DNA replication mechanism, acting as an auxiliary protein for the DNA polymerase δ (necessary for the synthesis of chromosomal DNA), and DNA polymerase ε (necessary for the recombination of DNA and repair of its damage). Whereas lack or low level of functional PCNA can lead to cellular apoptosis. Excessive expression of PCNA is used for monitoring the cycle phase of tumor cells. Therefore the aim of our study was to evaluate the expression of PCNA in nondysplastic glandular cells, dysplastic cells and inflammatory cells in Crohn’s disease (CD) in comparison with inflammatory cells infiltration.

Materials and method: The study consisted of 14 patients with Crohn’s disease. Endoscopic materials were taken from archival paraffin-embedded tissue. Sections were stained with H&E and subjected to routine histological evaluation. In 9 cases dysplastic cells has been found. The expression of PCNA protein in tissue sections was assessed by immunohistochemical methods. The color reaction was observed in nucleus of glandular cells and inflammatory cells. The staining reaction was assessed as % of positive cells with nuclear reaction. To visualize all leukocytes CD45 antibody was used. Infiltration of CD45+ cells was analyzed in stroma of surface epithelium and in lamina propria.

Results: PCNA expression in non-dysplastic glandular cells of CD ranged from 0–20% (mean 6.66%), in dysplastic cells was higher and ranged 0–80% (mean 56.6%). In inflammatory cells expression of PCNA was the highest, ranged 10–100% (mean 60%). Statistical analysis showed that higher expression of PCNA protein in dysplastic cells correlated with lower infiltration of CD45+ cells in lamina propria (p = 0.001, R = -0.904). We didn’t observed such correlation in relation to leukocytes infiltration in surface epithelium. Also PCNA expression in non-dysplastic glandular cells and in inflammatory cells didn’t correlate with amount of CD45+ cells in stroma of surface epithelium and in lamina propria.

Conclusion: Increased PCNA expression in dysplastic glandular cells of Crohn’s disease is a result of the abnormal cell division. Immune infiltrate cells also express high levels of PCNA in CD. But high proliferation rate of dysplastic cells under low activity of inflammatory cells may lead to malignant transformation.
Golimumab in ulcerative colitis: A multicentre real world experience

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Introduction: We assessed the effectiveness of golimumab in patients with ulcerative colitis (UC) in a real world setting.

Methods: A retrospective multicentre study was conducted between 2014 to date. Data was obtained from five West Midland hospitals. All patients with a diagnosis of moderate-severe UC on golimumab were included. Fisher’s test was used for statistical significance.

Results: Of a total of 56 patients, the majority of patients had left sided disease (48%; n = 27) followed by pancolitis (45%; n = 25) and proctitis (7%; n = 4). Twenty-two patients (39%) showed endoscopic and clinical remission. There was no statistically significant difference between disease extent and remission. Of these 22 patients, 17 patients were on the higher dose of 100 mg (p = 0.03). Three patients who were initially on 50 mg had their dose increased to 100 mg. They remain in remission. Of the 50% (n = 28) who switched biologic therapy, 23 were to vedolizumab, 1 to infliximab and 4 to adalimumab.

Discussion/Conclusion: Golimumab has not proven as effective in our real world data. Two important inferences were made from this study. Firstly, of those patients that went into remission, 75% were on the higher dose of golimumab. This may be secondary to higher trough levels; however therapeutic drug monitoring is currently unavailable in the UK for golimumab. Secondly, 5 patients who were switched to an alternative anti-TNF, where drug monitoring is available, had a good clinical response. This leads us to propose that drug monitoring is of clinical importance and should be available for golimumab in the UK to help maintain clinical remission.
Corticosteroid therapy and ursodeoxycholic acid therapy in patient with primary sclerosing cholangitis and psychosis – Case report

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Introduction: Corticosteroid therapy has several mechanisms of action such as anti-inflammatory, immunosuppressive and anti-proliferative activity. Unfortunately, there are numerous side effects, particular impact on the patient’s mental state. Budesonide has a strong but local limited activity in gastrointestinal tract; passes extensive biotransformation in the liver (about 90%) on the metabolites of poor glucocorticosteroid activity. But postmarketing reports include report about psychiatris disorders such are: psychosis, depression, aggressive reactions, irritability, nervousness, restlessness, anxiety, mood swings.

Results: 34-year-old male who has been treated for the last 10 years due to ulcerative colitis and psychosis, has received for hospital treatment because his family noticed yellow skin. Basic laboratory elaboration was performed including viral testing. Ultrasonography of liver were done, and showed discreet dilatation of ductus choledocus, so we performed endoscopic retrograde cholangiopancreatography, that showed a typical finding for sclerosing cholangitis so we made biliary stent implantation. We performed colonoscopy with multiple random biopsies accordingly to protocol for ulcerative colitis. Pathohistological diagnosis was in concordance with ulcerative colitis. Budesonid, azathioprine and mesalazin were introduced in therapy. Pre-transplantation tests were made and patient is on the transplant list. After 4 weeks, bilirubin level went down to normal. During therapy, there were no psychical problems. Patient is aware that liver transplantation will occur. He has no problem with accepting the operation. He is is regularly controlled by psychiatrist and gastroenterologists.

Discussion/Conclusion: Application of budesonide, with ursodeoxycholic acid and azathioprine caused remission of ulcerative colitis and primary sclerosing cholangitis without worsening of psychical status of patient.
Inhibition of Ras by farnesylthiosalicylic acid (FTS) is a potential target of treatment of experimental colitis

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²Schneider Children’s Medical Center, Petah Tikva, Israel

Introduction: Ras proteins have been shown to regulate cell growth, proliferation, and differentiation. Farnesylthiosalicylic acid (FTS) is a synthetic Ras antagonist that inhibits the binding of Ras to discrete membrane sites, thereby down-regulating several Ras-dependent signaling functions and accelerating Ras degradation. This study examines the role of Ras in the inflammatory process of colitis, and examines whether the Ras antagonist FTS can prevent it.

Methods: Colitis was induced in 26 Balb/c, 8–10 weeks old, female mice by adding 5% Dextran sodium sulfate (DSS) to their drinking water and allowing them to drink ad libitum for 7 days. Twelve mice were treated with FTS (5 mg/kg) 3 times a week, and 14 mice were treated with 0.9% normal saline 3 times a week. After 7 days the mice were sacrificed and the colon was removed. Colonic damage was assessed clinically by using a disease activity score which combines weight loss and rectal bleeding, and histologically by evaluating colonic segments stained with haemotoxylin and eosin. Mucosal myeloperoxidase activity, tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) levels were measured by ELISA. The expression of Ras and Ras downstream effectors such as P-ERK was determined by immunobloting assays.

Results: Mice treated with FTS had a significant lower disease activity score (p = 0.0001), and a lower histopathologic score (NS). A significant reduction was found in the inflammatory response in the FTS treated mice expressed by Myeloperoxidase activity (p = 0.007), The levels of TNF-α (p = 0.04) and the levels of interleukin-1 β (p = 0.01). The expression of activated Ras was found to be lower in the group treated with FTS (p = 0.004), opposing to the expression of P-ERK which was found to be higher in that group (p = 0.003).

Conclusion: Ras inhibition significantly ameliorates the severity of experimental colitis, and may offer a new therapeutic approach.
An investigation of taste preferences and attitudes towards long-term use of oral nutritional supplement drinks in adolescent and adult Crohn’s disease

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Introduction: The acceptability and palatability of ONS drinks are influenced by many factors including volume, taste, smell and duration of consumption. Studies mainly conducted in Japan have shown that when ONS drinks are used to replace 35–50% of food intake for one year or more they can prolong disease remission and increase drug effectiveness in CD. Our study aims to evaluate the feasibility of using ONS drinks as treatment in UK CD patients by assessing attitudes and taste preferences.

Methods: A cross sectional feasibility study was conducted over 12 weeks (July–September 2017). 30 CD patients were recruited from the gastroenterology outpatient clinic using convenience sampling. Patients were asked to rate 5 x 25 ml concealed samples of ONS drinks on appearance, smell, taste, aftertaste, consistency and overall impression using a 9 point hedonic rating scale. Based on the preferred ONS drink the perceived benefits and barriers relating to psychosocial and food related quality of life impact of long term consumption was assessed.

Results: Ensure plus milkshake was rated highest for taste and overall impression and Ensure plus juce lowest. Fortijuce was rated highest for consistency and Altraplen compact lowest. The main perceived benefits related to symptomatic relief from reduced food intake (70%), convenience (80%), weight (86%), and energy levels (79%). The main perceived barriers were taste fatigue (72%) and reduction in pleasure from eating and drinking (60%). 60% of patients were likely or very likely to consider using ONS drinks as a maintenance treatment option. However, only 26% of patients were confident that they could adhere to taking ONS drinks for 12 months.

Discussion/Conclusion: Despite high perceived benefits to long term use of ONS drinks, taste fatigue and the psychosocial impact at meal times may be potential barriers to their long term use.
Severe extensive ulcerative colitis: A case of good and fast response to treatment

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Learning Objectives:
• To recognize presentation of ulcerative colitis
• To review how to diagnose and treat pancolitis

Case description: A 33-year-old male with past medical of chronic diarrhea for 8 years, who was managed as ulcerative colitis for the last year with mesalazine, presents with with 4 weeks history of bloody, loose stools, up to 10 times/day, associated to diffuse abdominal pain, pallor, weakness and fatigue. On physical exam his vitals were significant for tachycardia (110 x'), marked pallor, and no abdominal tenderness.
Labs revealed: Hb 7.1 g/dl, WBC 8 x 10^9/l, Albumin 3.1 g/dl, C-reactive Protein (CRP) 3 mg/l. Normal liver function test and electrolytes.
Stool tests: Culture and C. difficile toxin A/B were negative. Ova and parasites were also negative.
He was initially started on hidrocortisone (100 mg/8h) and later prednisone (50 mg/day) plus azathioprine (125 mg/day), with partial response. It decided to start infliximab (300 mg ~ 5 mg/kg/dose), receiving first dose in house.
Patient was discharged on azathioprine. He got second and third dose of infliximab on week 2 and 6. On follow up he was doing well with complete resolution of his symptoms.

Fig. 1, 2: Colonoscopy on admission: Pancolitis. Mucosa – Mayo Score 2
Loss of vascular pattern, erythema, edema, erosion and multiple ulcerations without bleeding from rectum to cecum. Some pseudopolyps are also observed.
**Fig. 3:** Histopathology: Architectural distortion, chronic inflammation with lymphocytes, plasma cells, and eosinophils. Crypts with goblet cells depletion, metaplasia of paneth cells, cryptitis and crypt abscess. CMV: negative

**Discussion:** Ulcerative colitis (UC) is a chronic inflammatory bowel disease of unknown etiology mostly affecting the young and middle aged. Although more common in Europe, incidence is increasing in South America, including Peru. Symptoms of ulcerative colitis are dependent upon extent and severity of disease and include bloody diarrhea, rectal bleeding, tenesmus and fecal incontinence. A ‘gold standard’ for diagnosis of ulcerative colitis does not exist. It is established by clinical, laboratory, imaging, and endoscopic parameters, including histopathology. An infective cause should be excluded. CRP and calprotectin are useful for diagnosis and assessment of disease severity. Severe extensive colitis is an indication for hospital admission for intensive treatment. Several studies have assessed predictors of response to infliximab in patients with severe and/or corticosteroid-refractory disease. Our patient was started on biologics cause of young age, extension and severity of disease. He had a rapid and outstanding response to infliximab.

**Conclusion:** UC is more common in our area, lately. Biologics has to be considered in severe extensive colitis with a partial or lack of response to steroids. Management should be individualized.

**References:**


Malnutrition in Tunisian Crohn’s disease cohort

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Introduction: In the course of Crohn’s disease, protein-energy malnutrition is frequent and multifactorial. The purpose of our work was to assess the prevalence of undernutrition in patients with CD and to identify related risk factors.

Methods: We conducted a retrospective monocentric study including hospitalized patients with CD between January 2011 and January 2016. The patients were divided into 2 groups: Group 1: patients with normal body mass index (BMI) and Group 2: Malnourished patients. Undernutrition was defined as a BMI < 18.5 kg/m² and classified according to the WHO classification in deep (BMI < 15), severe (15 < BMI < 17) and moderate (17 < BMI < 18.5).

Results:

<table>
<thead>
<tr>
<th></th>
<th>Group 1 n = 37</th>
<th>Group 2 n = 7</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age (years)</td>
<td>37</td>
<td>34.43</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (H/F)</td>
<td>22/15</td>
<td>3/4</td>
<td>NS</td>
</tr>
<tr>
<td>Tobacco</td>
<td>54%</td>
<td>42.8%</td>
<td>NS</td>
</tr>
<tr>
<td>CD operated</td>
<td>18.9%</td>
<td>28.5%</td>
<td>NS</td>
</tr>
<tr>
<td>Seat of the disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ileal</td>
<td>35.2%</td>
<td>28.5%</td>
<td>NS</td>
</tr>
<tr>
<td>Ileo-colic</td>
<td>37.8%</td>
<td>71.5%</td>
<td>0.06</td>
</tr>
<tr>
<td>Colic</td>
<td>27%</td>
<td>0%</td>
<td>NS</td>
</tr>
<tr>
<td>Ano-perineal manifestations</td>
<td>21.1%</td>
<td>14.2%</td>
<td>NS</td>
</tr>
<tr>
<td>Extraintestinal manifestations</td>
<td>40.5%</td>
<td>42.8%</td>
<td>NS</td>
</tr>
<tr>
<td>Albuminemia &lt; 30 g/l</td>
<td>43.2%</td>
<td>42.8%</td>
<td>NS</td>
</tr>
<tr>
<td>Complications:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stenosis</td>
<td>62.1%</td>
<td>85.6%</td>
<td>NS</td>
</tr>
<tr>
<td>Abscess</td>
<td>16.2%</td>
<td>42.8%</td>
<td>NS</td>
</tr>
<tr>
<td>Fistula</td>
<td>16.2%</td>
<td>42.8%</td>
<td>NS</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>70.2%</td>
<td>42.8%</td>
<td>NS</td>
</tr>
<tr>
<td>Immunosuppressive therapy</td>
<td>62.1%</td>
<td>85.7%</td>
<td>NS</td>
</tr>
<tr>
<td>Surgery</td>
<td>24.3%</td>
<td>57.1%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Conclusion: In our series, malnutrition was observed in 16% of CD patients. No characteristic related to patients nor to the disease is significantly associated with undernutrition.
Intra-abdominal abscesses complicating Crohn’s disease: Clinical and therapeutic features

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Introduction: Intra-abdominal abscesses (IAA) complicating Crohn’s disease (CD) are still difficult to manage. This complication can be serious, especially as it may occur in malnourished and immunodepressive patients. The purpose of our study was to describe clinical features and management modalities of this complication in CD patients.

Methods: Retrospective study including patients with IAA complicating CD between January 2011 and July 2016. Postoperative abscesses were excluded.

Results: Among 49 patients followed for CD, 11 had spontaneous IAA (22.4%), 6 men and 5 women with a mean age of 30 years [extremes: 19–54]. IAA was inaugural in 5 patients. For the other cases, IAA complicated CD after a mean duration since the diagnosis of 1.8 years [1–4]. Four patients received immunosuppressive therapy for active CD. Location of the disease was ileocolic in 6 cases and ileal in 5 cases. IAA was associated with perforating ileocoecal CD in all patients. Diagnosis was made on radiological data provided by sectional imaging. IAA was single in 9 cases and multiples IAA were disclosed in 2 cases with a mean diameter of 37 mm [10–90]. Fistula was observed in all patients associated with stenosis in 9 patients. Intravenous antibiotic therapy was prescribed alone in 8 patients with small or undrivable IAA and associated with percutaneous radiological drainage in 2 patients. Only one patient required immediate surgery. Parenteral nutritional therapy was necessary in 5 patients. After successful medical treatment, patients with concomitant stenosis or persistent fistula required planned surgical treatment in localized CD. Patients with extensive ileal disease, anti-TNF therapy was prescribed. No recurrence of IAA was occurred during a mean follow-up of one year.

Conclusion: In our series IAA complicate 22.4% of CD patients. When feasible, percutaneous radiological drainage and antibiotics should be the treatment of choice of IAA in CD.
Severe disease activity in ulcerative colitis associated with mucosal hypoxia measured endoscopically

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Introduction: Tissue hypoxia has been shown to be a key microenvironmental regulator of mucosal barrier function and inflammation in pre-clinical models of colitis. However, the role of mucosal hypoxia in the pathogenesis of UC has yet to be extensively studied in IBD patients. Visible light spectroscopy can be utilised to measure the haemoglobin (Hb) oxygen saturations (%) of the colonic mucosa during endoscopy. Carbonic anhydrase IX (CA-9) is a hypoxia-inducible transmembrane protein and endogenous marker of hypoxia. The aim of this study was to compare mucosal oxygen saturations in normal and inflamed colonic mucosa of patients with UC and assess relationship with disease activity

Methods:
- Patients undergoing colonoscopy/sigmoidoscopy were prospectively recruited in a single academic medical centre, with over 3800 IBD patients. Endoscopies were performed using CO₂ insufflation.
- Measurements of colonic mucosal Hb saturations (%) were performed segmentally and from zones of transition from inflamed to normal mucosa, using an endoscopic probe (applied to intact colonic mucosa) and tissue oximeter (T-Stat System, Spectros). Endoscopic severity was graded using the endoscopic Mayo score.
- Mucosal biopsies were obtained to grade histologic activity and for protein analysis.

Results:
- 38 patients were included in this study; n = 7 controls, n = 31 UC; male = 25 (65.7%).
- The median age of UC patients was 39 years (IQR 34.6–55.9). n = 5 had Mayo 0, n = 9 Mayo 1, n = 11 Mayo 2 and n = 6 Mayo 3 activity.
- At the time of the procedure, 5 patients were on biologic therapy, 5 on immunomodulators and 6 on steroid therapy.
- The median rectal O₂ saturation in the control group was 76.2% (IQR 73.8–80.6) in the UC cohort (Mayo 0–3 inclusive) (p = 1.00). There was no significant difference across any colonic segment between these two cohorts.
- The median rectal mucosal O₂ saturation in Mayo 0 was 77.6% (77.4–81.2), Mayo 1: 80.6% (77–83.8), Mayo 2: 75.4% (73.5–79.2) and Mayo 3: 73.3% (68.7–74.8). (p = 0.02, Independent Samples Median Test) (Figure 1).
- CA9 protein expression was significantly higher in biopsies with Mayo 2–3 activity compared to Mayo 0–1 disease (Figure 2).
Figure 1: Mucosal Hb saturations (%) by disease severity

Figure 2: CA-9 protein expression in rectal biopsies

Discussion/Conclusion: Mucosal O₂ saturation is significantly decreased in severely active UC and oxygen signalling pathways are activated suggesting that mucosal hypoxia is an important determinant of disease severity in UC. These observations suggest the potential for oxygen signalling pathways as a potential novel therapeutic target.
Risk factors for ocular involvement during Crohn’s disease

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Introduction: Ocular involvement in Crohn’s disease is polymorphic. It is a multifactorial pathology which might worsen the prognosis of the disease. The study of risk factors allows the identification of high-risk population, and thereby to improve their management.

Aim: To study ocular manifestations during Crohn’s disease and to identify the main risk factors for ocular involvement.

Methods: We conducted a prospective study of 71 patients with Crohn’s disease, 142 eyes studied, collected in the Ophthalmology department of the Rabta Hospital of Tunisia between January 2010 and December 2010. These patients were distributed in two groups depending on the presence (group 1) or the absence (group 2) of ocular involvement. All patients had a complete ophthalmologic examination, and fluorescein angiography was indicated whenever uveitis was present.

Results: We noted a significant male predominance. The average age was 38 years (range: 16–70). The ocular manifestations concerned 35 patients. Among ocular lesions observed, we noted the presence of anterior uveitis in 28.5% of cases, conjunctivitis in 22.8%, scleritis in 5.7%, episcleritis in 22.8%, and corneal infiltrates in 20%. Two patients had venous occlusion with oedematous capillaropathy on angiographic examination.

Independent risk factors for ocular involvement were: inflammatory relapse of his disease (AOR = 5.95; p = 0.0001), colonic or ileocolic localization (AOR = 4.31; p = 0, 0001). However, the ileal localization (odds ratio = 0.03, p < 0.0001) is characterized by a protective factor of ocular involvement.

Discussion/Conclusion: Ocular manifestations during Crohn’s disease are rare. They require regular monitoring and appropriate management mainly in relapse or in colonic or ileocolic localization.
Crohn’s disease or Behçet’s disease?

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Introduction: The distinction between Crohn’s disease (CD) with extra-digestive involvement and Behçet’s disease (BD) with digestive involvement is not always easy. There are indeed many extra-digestive manifestations in common. We report a series of 5 patients initially followed up for CD, and according to the type of ocular involvement, the diagnosis was corrected to a BD.

Methods: We analyzed retrospectively the records of 5 patients (10 eyes) followed up for CD and presenting with posterior uveitis and retinal vasculitis which leaded secondarily to establish Behçet’s disease diagnosis. The diagnosis of BD was based on the diagnostic criteria established by the international study group for BD. Each patient underwent a complete ophthalmologic examination and a retinal fluorescence angiography.

Results: The patients were 1 woman and 4 men with an average age of 31.6 years. The average interval between the diagnosis of CD and the onset of ocular involvement was of 16.3 months (range: 6–32 months). Ocular manifestations included: hypopyon in 4 eyes, panuveitis in 9 eyes, retinal periphlebitis in 10 eyes, and posterior segment inflammation in 2 eyes. Complications were observed in 3 eyes (pupillary seclusion 1 eye, retinal neovascularization 1 eye and macular hole 1 eye). The diagnosis of BD was established according to the international study group for BD, leading to the initiation of systemic corticosteroid therapy and the combination of Azathioprine in all cases.

Discussion/Conclusion: Ocular involvement is a major criterion for the diagnosis of BD. Posterior uveitis with retinal vasculitis is more characteristic of BD and it is seen very rarely during CD, and even if it exists it will be less severe.
Insights into mechanisms and new treatment options of ulcerative colitis in patients with latent autoimmune diabetes

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Introduction: The aim of the study was the search of molecular mechanism of UC in patients with latent autoimmune diabetes (LADA) and the development of new treatment.

Methods: The study included 62 adults with mild-moderate distal UC and LADA (32–38 years old, female – 28, male – 34). QoL measured by the IBDQ, UC activity – by the Mayo Score. Diagnosis based on symptoms of LADA and UC, laboratory tests for LADA (FPG, 2-h PG, FCP, PCP, HbA1c, HLA, autoAb ICA, IAAs, GAD) and for UC (pANCA, ASCA), colonoscopy with biopsy of intestinal mucosa. Proteomic analysis was made in serum and intestinal mucosa (2DE, MALDI-TOF-MS/MS, MASCOT Search). The randomization was performed in 2 groups: Group 1 (n = 30) – insulin detemir 6ED daily, mesalazine 1500/750 mg daily, budesonide MMX 9 mg daily for 12 weeks; Group 2 (n = 32) – standard therapy + Zacofalk NMX® 1.36 g 3 times a day +rosiglitazone 8 mg daily for 12 weeks. Control group-30 healthy persons. Statistics performed by “Statistica 10.0”.

Results: Clinical response achieved in 71.9% patients (Group 2), 43% patients (Group 1, p < 0.05), remission – in 28.1% patients (Group 2), 10% patients (Group 1, p < 0.01). Endoscopic remission was uncommon (10% Group 2 vs. 4% Group 1, p > 0.05). QoL was improved at week 8 in Group 2 (p < 0.01), at week 12 in Group 1 (p < 0.05). It has been registered the decrease of expression of TGFβ (93.7% vs. 50%), TNFα (68.7% vs. 36.7), IL-6 (87.5% vs. 56.7%), VCAM-1 (75% vs. 56.7%) and the increase of expression of PPARγ (61.2% vs. 43.3%), β-defensin (65.6% vs. 36.7%), RBP4 (71.8% vs. 36.7%) in serum and intestinal mucosa.

Discussion/Conclusion: Rosiglitazone combined with Zacofalk NMX® has the potential to downregulate inflammation and autoimmune response in patients with UC and LADA.
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.
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.
The development of a nurse-led inflammatory bowel disease outpatient clinic: Meeting the needs of adolescents with inflammatory bowel disease

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Introduction: Given the incidence of adolescents’ inflammatory bowel disease (AIBD) is increasing, it is important that the services provided to care for these patients meet their needs. With the development of IBD nurse-led clinics at our centre, the IBD nursing team aimed to understand the views and needs of their adolescent patients in order to help establish these clinics, whilst ensuring that the service is tailored to their needs.

Methods: A qualitative service evaluation study was conducted through semi-structured interviews with 7 adolescent service users, four of the participants were male and three were female. Participants were asked six open ended questions on the IBD nursing service they currently receive, their opinions on what they wanted to be included on the IBD nurse-led clinic and their thoughts and ideas on attending a shared medical appointment (SMA) with other adolescents with IBD.

Results: Data was analysed using thematic analysis. The study showed a general lack of knowledge regarding IBD, treatment involved and disease progressions. Adolescents felt that interaction with healthcare professionals (HCPs) was limited with most discussions around their disease being facilitated by their parents. The adolescents showed a desire for support from HCPs and their peers with IBD. Their knowledge of services available was limited, barriers contributing included their age, lack of knowledge of IBD and prominent parental involvement. There was a concern with confidentiality with SMAs, but most adolescents would attend.

Discussion/Conclusion: Our service evaluation study in these AIBD patients identified four themes: the general lack of knowledge; interactions with HCP; lack of knowledge of services; support needs. This supports the establishment of nurse-led AIBD outpatient clinics to facilitate the identified themes. It is hoped that SMA without parental involvement will help gap educational needs and facilitate peer support.
Biosimilar infliximab (CT-P13) is effective in induction of remission and mucosal healing in paediatric Crohn’s disease: A single-centre experience

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Background and objectives: Mucosal healing becomes a more and more widely accepted goal of therapy in Crohn’s disease (CD). Limited data are available on the effect of CT-P13, the first biosimilar infliximab, on mucosal healing (MH) in Crohn’s disease. Our aim was to evaluate the efficacy of CT-P13 therapy on remission rate and MH in a cohort of paediatric CD patients.

Methods: Biologic-naïve, 51 CD paediatric patients, who started CT-P13 therapy were consecutively enrolled into a prospective study. Demographic data, medical treatment, and laboratory results were documented. Weight Paediatric Crohn’s Disease Activity Index (wPCDAI) was used for evaluation of the clinical activity, and Simple Endoscopic Score (SES-CD) for mucosal healing, performed before CT-P13 therapy (T0) and after the 3rd dose at week 10. Clinical remission was defined as wPCDAI ≤ 12.5, MH as SES-CD ≤ 2, partial MH as a reduction of 50% in SES-CD from T0, and no endoscopic healing as no variation or worsening of the SES-CD.

Results: At the enrolment, 40/51 patients were diagnosed with luminal, 7/51 with complicated and 4/51 with perianal disease. All but one patients presented active disease by wPCDAI, 12/51 mild and 38/51 moderate to severe disease activity. Indications for therapy were: refractory severe exacerbation (5/51), chronic refractory activity (34/51), thiopurine intolerance (7/51), steroids dependency (3/51), complicated disease, and perianal disease (5/51). Clinical remission was achieved by 84% patients. At week 10, there was a significant decrease in mean wPCDAI (51.8 ± 9.4 to 9.0 ± 5.3; p < 0.01). One patient was considered as primary no responder. Complete and partial MH was achieved by 31% and 38% of patients, respectively, while 16% patients presented no or worsening of SES-CD. Median SES-CD was reduced from 13.6 ± 7.8 to 6.33 ± 5.55.

Conclusions: CT-P13 was effective for induction of remission and MH in paediatric biologic naïve CD patients. The rates was similar to the historical studies with reference infliximab.
Phenotypic variation in monogenic inflammatory bowel diseases – Glycogen storage disease 1B as an illustration

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Introduction: Glycogen storage disease (GSD) type 1B is considered one of the monogenic early onset inflammatory bowel diseases. Patients suffer from inflammatory bowel disease (IBD) and immunodeficiency in addition to a metabolic storage disorder. Treatment with granulocyte-colony stimulating factor (G-CSF) has been reported as being effective in controlling GSD 1B IBD disease, leading to several trials of G-CSF treatment of adults with ‘classic’ (non-monogenic) Crohn’s disease with varying success. Even though not effective in many monogenic IBD conditions, treatment with anti-TNF-alpha has also been found effective in GSD 1B.

Methods: Case report of two GSD 1B IBD patients and literature review.

Results: We report two disparate cases of GSD 1B IBD. Both cases were diagnosed in infancy with glycogen storage disease type 1B. Their metabolic phenotype has been stable under appropriate treatment, however both suffered from severe IBD. The first case is an 8-year-old boy who presented with progressive abdominal pain and bloody diarrhoea, requiring multiple blood transfusions despite azathioprine and G-CSF treatment. He was started on anti-TNF-alpha treatment with significant improvement and is stable on this treatment. The second case is a 13-year-old boy who had suffered from severe IBD while going through various treatments. Having failed 5-ASA, steroids, TPN, antibiotics, G-CSF and anti-TNF-alpha, he had suffered from progressive bloody diarrhoea and weight loss. Additionally, he developed a colonic stricture and eventually underwent hemicolecetomy and ileostomy. The colon was very inflamed and a neuroendocrine tumour was found in the appendix. Following hemicolecetomy and ileostomy he experienced prolonged remission. A literature review discovered similar phenotypic variance in GSD 1B IBD reported cases.

Discussion/Conclusion: Monogenic IBD, such as GSD 1B, can present with different phenotypes, a well-known phenomenon in ‘classic’, non-monogenic IBD.
Inflammatory bowel disease (IBD) in a patient with immunodeficiency – Is bone marrow transplant indicated?

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Introduction: Treatment of IBD with immunosuppressive medications, including corticosteroids, immunomodulators, anti-TNF-alpha and other biologics, carries documented risk of opportunistic infections. Anti-TNF-alpha, for example, is contraindicated in severe infections. Currently, no recommendations for prophylactic treatment exists for IBD patients commencing immunosuppressive treatment. However, greater caution should be carried out when treating patients with IBD who also have immunodeficiency.

Methods: We report a case of immunodeficiency and monogenic early-onset IBD who is on anti-TNF-alpha treatment.

Results: A 2-year-old girl presented with bloody diarrhoea and weight loss. Additionally, she suffered from multiple skin warts. Workup for early onset IBD included whole exome sequencing, which revealed homozygote mutations in TAOK2 gene. This is the first reported patient with TAOK2 related early onset IBD. The TAOK2 gene is a p38-MAPK regulator. P38-MAPK upregulates inflammatory responses and pro-inflammatory cytokine release (such as IL1 and TNF-alpha) and is hyperactive in IBD patients. Given that discovery, treatment with anti-TNF-alpha, infliximab, was started. After dose and interval adjustment the patient achieved deep clinical remission. However, other symptoms such as widespread skin warts, were proven to be of another cause – homozygote mutations in CARMIL2 gene were also discovered. Mutations in this gene are reported to cause several phenomena including immune deficiency. A case of near-fatal PCP-pneumonia in a family member harbouring the same CARMIL2 mutations prompted caution in using anti-TNF-alpha. The patient was started on PCP prophylaxis, and potential bone marrow transplant is under consideration.

Discussion/Conclusion: Prophylactic treatment against opportunistic infections, such as PCP, Is recommended in patients with primary immune deficiency and IBD.
Treatment of patients with Crohn’s disease and ulcerative colitis with manifestation arthritis and spondylitis

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Introduction: Regional or granulomatous ileitis is a chronic bowel disease (Crohn’s disease) that covers all the layers of the intestinal wall (transmural lesions), and sometimes spreads to the mesentery, regional lymph nodes affecting both the small and large intestines, but most often localized in the terminal section of a thin guts (regional, terminal ileitis).
These diseases can be accompanied by damage to the peripheral joints, spine, or joints and spine. The clinical manifestations of the joint syndrome in both processes are the same.
Arthritis, or joint inflammation, is the most common complication of ulcerative colitis. Twenty-five percent of people 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 (stiffness in the joint).
With ulcerative colitis, arthritis can manifest itself in two different forms: peripheral arthritis and spondyloarthritis. Spondylitis usually appears at the age of about 35–45 years.
In most cases, the symptoms of peripheral arthritis decrease with the disappearance of inflammation in the large intestine.

Methods: We study used for treatment of patients with Crohn’s disease and ulcerative colitis with manifestation arthritis and spondylitis in four groups.
In first group application for treatment Crohn’s disease and arthritis – budesonide (Budenofalk®) with non-steroidal anti-inflammatory drugs (NSAIDs); in second group – application budesonide (Budenofalk®) with of initial dose of infliximab (Remicade®); in third group application for treatment ulcerative colitis with spondylitis – prednisolone and mesalazine (Salofalk®) with non-steroidal anti-inflammatory drugs (NSAIDs); in fourth group – application mesalazine (Salofalk®) with of initial dose of infliximab (Remicade®).

Results: The results obtained in the second group are much better than in the first, while the results in the third group practically correspond to the results in the fourth group.

Discussion/Conclusion: This is most likely due to the severe course of ulcerative colitis with extraintestinal manifestations, which in these cases for effective treatment may require surgical treatment as an option for concrete of patients.
Systematic review: Psychosocial factors associated with pain in inflammatory bowel disease

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Introduction: Pain is a frequently reported symptom of inflammatory bowel disease (IBD) experienced by patients in active disease and in remission. Psychological factors play a significant role in pain but have not been systematically reviewed in IBD. The aim of this study was to review psychosocial factors associated with pain in adults diagnosed with IBD.

Methods: Electronic (PsycInfo, MEDLINE, EMBASE, Cochrane Library, CINAHL, Web of Science) and hand-searching were conducted February–May 2017. Two authors carried out screening, data extraction and quality appraisal.

Results: Fifteen studies including 5539 IBD patients were identified. Emotional, cognitive-behavioural and personality factors were associated with IBD-pain. Depression and anxiety were the most commonly explored constructs, followed by perceived stress and pain catastrophising. All were positively associated with greater pain. Greater abdominal pain was associated with a concurrent mood disorder over fivefold (OR = 5.75). Coping strategies and pain fear avoidance correlated with pain levels. Perceived social support (r = 0.26) and internal locus of control (r = 0.33) correlated with less pain. Patients reporting pain in IBD in remission more frequently had an existing diagnosis of a mood disorder, a chronic pain disorder and irritable bowel syndrome. Six studies controlled for disease activity, of which 4 found that psychosocial factors remained as significant predictors of pain. Ten studies were of high quality.

Discussion/Conclusion: Psychosocial factors appear to play a significant role in IBD-pain. Greater depressive symptoms, anxiety, perceived stress and pain catastrophising are associated with greater pain in IBD. Fear avoidance and coping strategies may modify pain levels. Positive psychology may be an important avenue to explore in relation to treatment for pain. Results from the review support the application of a psychosocial intervention, alongside IBD medication, for pain management. Further research is required to explore psychosocial constructs in relation to IBD-pain.
The role of different E. coli variants emphasizing opportunistic infection and colonic resistance in inflammatory bowel disease

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Introduction: Opportunistic infections (OI) in IBD pose challenging scenario for the clinician, they are often difficult to recognize and hard to manage. Although, there is increasing evidence of an aberrant immune response in IBD, further immunomodulation due to treatment raise the potential for OI making it a special concern for IBD patients. OI may be defined as an infection by a microorganism that has limited pathogenic capacity under ordinary circumstances, but which is able to cause serious disease because of the predisposing effect of another disease or its treatment. Several viral, fungal and bacterial agents are well studied forming existing ECCO Consensus. E. coli is one of the most diverse bacterial species with only 20% of the genes in a typical E. coli genome shared. Following this idea, we aimed on studying various variants of E. coli at inflamed colon as an pivoting point in changed colonic resistance and its failure as a background for opportunistic infection in IBD.

Methods: Totally 95 (mean 38.66 ± 3.11 years) individuals with different forms of chronic colonic inflammation (37 [38.95%] clinically proven IBD) and 58 healthy donors participate in the study. Colonic resistance studied in mucosal bioptates. Standard aerobic and anaerobic microbiology techniques with nosology identification and quantity composition of microbiota were used. Immunotyping (O, K, H antigens) and PCR (genomic study) were used for identification of E. coli variants.

Results: In 95 patients, 100 variants of E. coli of were found (1.05 per case). E. coli 055:K59 was found in 29.82%, E. coli 044:K74 in 12.28% and E. coli 026:K60/075:K95 – only in few cases. In IBD patients E. coli 0124:K72, 025:K1 and 028ac:K66 were observed in 75.68%. E. coli 0124:K72, 025:K1, 028ac:K66, 0144:K, 0124:K72, and 0144:K – in rest of samples. In addition to bifibacteria deficit by 46.65% and lactobacteria by 46.39%, microbiota included C. diversus, E. aerogenes, Proteus spp., Hafnia alvei, Candidae, with Bacteroide growth by 69.09%, and conditionally pathogenic Peptococci by 59.24%. Surprisingly, genomic study of hlyA and K1 genes showed insufficient correlation emphasizing IBD and colitis.

Discussion/Conclusion: E. coli plays an important role in modelling both colonic resistance and immune response in both healthy and inflammatory conditions. This study confirms the role of microbiota in development of IBD and forming the vicious background for OI. This study of selected genes cannot explain E. coli influence on the mucosal barrier and wider range of genomics and microbiomics must undergo further research.
Analysis of allele’s distribution and the association between the TGF-β1 gene’s polymorphism and IBD

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Introduction: IBD pathogenesis is multifactorial, resulting from tight interaction between genetic, environmental, and immunological factors. One of the candidate genes involved in IBD is the transforming growth factor-β1 (TGF-β1) gene, which polymorphisms may be responsible for the development of the disease through its fundamental role in maintaining the intestinal epithelial cell homeostasis, influence on modulating T-cell activity, dendritic cell function, and apoptosis. Moreover, this cytokine is an important player in intestinal fibrosis. The aim of the study was to analyse the allele’s distribution and the association between IBD and the TGF-β1 gene’s T/C (rs1800470) polymorphism.

Methods: Totally, 98 individuals participate in the study, among them 34 had proven IBD (27 – CD, 7 – UC), others (control) with at least three risk factors for IBD (family history, smoking, antibiotics, travel history, immune, etc.) but without the disease. Real-time PCR is used for genetic studies. Statistical data assessed with exact Fisher’s and χ² test.

Results: Wild T-allele was observed in 15 (44.12%) of IBD group patients and in 56 (87.50%) of control; C-allele found in 27 (79.41%) of IBD group and in 21 (32.81%) of control. The TGF-β1 gene’s C-allele showed reliable association with IBD (p = 0.004, OR = 1.76, 95.0% CI: 1.0–3.89). In addition, the CC-genotype was more frequent in IBD patients compared to the control group (p = 0.002, OR = 3.27, 95.0% CI: 2.01–9.37). All polymorphisms adhered to the Hardy-Weinberg equilibrium in both the IBD and control groups. We did not observe any association between TGF-β1 gene’s T/C (rs1800470) polymorphism and the IBD phenotypes including fibrosis.

Discussion/Conclusion: This study shows possible association between C-allele of the TGF-β1 gene and IBD, serving for both prognostic purpose and for customizable treatment developments. In contrast, several previous studies presented no significant associations between TGF-β1 polymorphisms and IBD, though its pathogenetic role is generally accepted. Moreover, the TGF-β1 gene has not been associated with IBD in genome-wide-association study. The possible explanations for these differences are selection of study groups and otherness of populations. Larger studies with larger cohorts and in different populations are needed to evaluate the reproducibility of our results.
Personalizing approach to IBD through pro-, anti-inflammatory cytokines and genetic polymorphisms

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Introduction: IBD is a polygenic disease for which over 200 risk loci in about 30 genes identified. Although the complex interactions among genetics have been long recognized among researchers, the understanding of its contribution to IBD pathogenesis continues to evolve. Genetic and epigenetic factors may not only determine personal predisposition to particular pathogenetic mechanism and prognosis, but also potentially predict therapeutic response and treatment efficacy. Taking into account known significance of several cytokines in IBD pathogenesis, we hypothesized that C-590T polymorphism of IL-4 gene and 35delG polymorphism of Gap junction β-2 protein/connexin (GJB2) gene, the one suspected to be responsible for L. van Beethoven's combination of IBD and deafness, may have pathogenetic significance in IBD.

Methods: Totally 102 (UC, CD) patients participated in the study. Diagnosis and management provided according to ECCO Guidelines. Female – 31 (30.4%), male – 71 (69.6%), control group – 40 practically healthy individuals (female – 17 (42.5%), χ² = 1.88, p > 0.05, male – 23 (57.5%), χ² = 1.38, p > 0.05). Levels of pro- and anti-inflammatory cytokines’ production (by ELISA) statistically calculated compared to control group quartiles. ‘Low’ (LQ) was L-1β < 23 pg/ml (lower quartile of control), TNF-α ≤ 15 pg/ml, IL-4 ≤ 4.95 pg/ml, IL-10 and IL-13 ≤ 15 pg/ml and ≤ 28 pg/ml, respectively. ‘High’ (HQ) was TNF-α > 32 pg/ml (upper quartile), IL-1β ≥ 60 pg/ml, IL-4 ≥ 45 pg/ml, IL-10 and IL-13 ≥ 25.96 pg/ml and ≥ 38 pg/ml, respectively. Allelic and genotypes distributions of GJB2 (rs80338939) and IL-4 (rs2243250) mutations analysed in PCR.

Results: All polymorphisms adhered to the Hardy-Weinberg equilibrium in both the IBD and control. Homozygous GJB2 gene mutation (35delG) in control has frequency of 5.0%, whereas among IBD patients in every second person, by 20.58% more often in male, χ² = 38.32, p < 0.001. The distribution of IL-4 (C-590T) genotypes between groups including gender stratification was similar. The presence of GJB2 mutation in haplotype, regardless of IL-4 (C-590T) genotypes, increases the likelihood of IBD (UC, CD) 7.5 and 15.0 fold (OR = 9.67, 95% CI: 2.13–43.9, p < 0.001 and OR = 19.67, 95% CI: 2.53–102.9, p < 0.001, respectively). Number of patients with LQ of TNF-α and IL-4 gene’s CC/CT genotypes dominate over TT-genotype: 22.06%/26.47% vs. 4.41% (χ² = 34.0, p < 0.001). The same trend registered for IL-1β. Lower IL-1β production found in 35delG genotype of CJB2 gene, compared to non-del-carriers by 30.35%: 63.16% vs. 32.81% (χ² = 8.91, p = 0.003).

Discussion/Conclusion: IL-4 gene’s C-allele (CC/CT) associates with lower TNF-α; high or normal IL-4, IL-10, IL-13 in 36delG-genotype of CJB2 gene. IL-4 hyper-production in TT-genotype of IL-4 gene, form conditions for chronic inflammatory
process. 35delG mutation of GJB2 gene is characterized by increased production of TNF-α, without significant growth of IL-1β and hyperproduction of IL-4 backed by activity of IL-10, IL-13. The obtained results may be used for prognostic as well as treatment customization purposes, including anti-cytokine therapies. However, more data must be collected and further wider studies are needed for clinical implementations.
Does drug level monitoring help us to understand the superiority of thiopurine and anti-TNF combination therapy in inflammatory bowel diseases?

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Introduction: Clinical data suggests a synergistic effect between thiopurine and anti-tumour necrosis factor (anti-TNF) therapy in IBD. In previous studies, azathioprine (AZA) metabolites and biological drug trough levels have not been investigated simultaneously to verify the mechanism behind the favourable outcomes.

Methods: Cross-sectional study aimed to evaluate the efficacy of azathioprine and anti-TNF (infliximab [IFX] and adalimumab [ADA]) combination. Consecutive IBD patients on maintenance AZA or anti-TNF monotherapy and on IFX/AZA or ADA/AZA combinations were enrolled. 6-TGN level was measured with high performance liquid chromatography, anti-TNF levels were assessed by ELISA method.

Results: Total of 98 (67 CD, 31 UC) patients were involved, average disease duration was 11.5 years. Average CDAI score for was 96, and average partial Mayo score was 1. Thirty patients were on maintenance AZA and 34–34 patients received concomitant biological therapy or anti-TNF monotherapy, respectively. Anti drug antibodies were detected in more patients in the anti-TNF monotherapy group compared to the combination therapy group (p = 0.008). Forty-five percent of the patients in the monotherapy group has therapeutic IFX levels and 85% in the combination therapy group (p = 0.019). Therapeutic ADA levels were found in 35.7% in monotherapy group and 78.6% among combination therapy group patients (p = 0.054).

6-TGN levels were lower in patients on combined IFX/AZA and ADA/AZA therapy (339 ± 126.2 pmol/8 x 10^8 RBC) compared to those on AZA monotherapy (412 ± 169.5 pmol/8 x 10^8 RBC, p = 0.04). Adalimumab levels were higher in patients on ADA/AZA combination therapy (p = 0.007). No correlation could be observed between 6-TGN levels and IFX or ADA levels in patients on combination therapy (r = 0.072 and r = -0.138 for IFX and ADA, respectively).

Discussion/Conclusion: According to our data the possible synergistic effect of combination therapy is based on the decreased antibody formation against the anti-TNF drug among infliximab treated patients. In patients receiving adalimumab and immunosuppressive therapy the possible explanation could be the increased anti-TNF drug level.
Dietary patterns in patients with inflammatory bowel disease

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Introduction: Dietary patterns have been recognized as one of the environmental triggers for inflammatory bowel diseases. Dietary antigens, alteration of the gut microbiome and changes in gastrointestinal permeability can influence intestinal inflammation. However, evidence based dietary guidelines for patients with inflammatory bowel disease have not been available to patients. Previous studies have shown that patients are aware of the effects that diet can have on relieving symptoms or inducing remission. Therefore, the aim of our study was to evaluate dietary patterns of patients with inflammatory bowel disease (IBD).

Methods: A cross-sectional survey based study was carried out at the University Hospital of Split. In total, 30 patients with ulcerative colitis and 30 patients with Crohn’s disease were included in the present study. Survey gathered socio-demographic data, questioned patients’ dietary patterns as well as their attitudes about diet with reference to their disease.

Results: Almost all of the patients considered diet important in life in general (98.3%), while 86.7% of patients considered diet important with reference to their disease (96.7% with ulcerative colitis vs. 76.7% with Crohn’s disease, p = 0.052). Furthermore, 81.7% patients considered that their symptoms can be reduced with proper diet. Patients rated the importance of diet with an average grade of 4.2 ± 1.0 on a 5-point scale. As many as 91.7% of patients reported getting advice about diet from their physician, while only 16.7% of patients consulted a nutritionist. Internet was a source of information about diet for 86.7% of our patients. All of patients with ulcerative colitis agreed that educational programs about diet would be useful to them, while 80% of patients with Crohn’s disease agreed with this statement (p = 0.024). Overall, 85% of patients would visit such programs.

Discussion/Conclusion: Results of this study suggest that patients with IBD consider diet important in their disease management and should be provided with evidence based counseling.
Isolated appendiceal orifice inflammation associated with distal ulcerative colitis – A case report

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Introduction: Ulcerative colitis is by definition an inflammatory process involving the recto-colonic mucosa in an ascending and continuous fashion. Isolated appendiceal involvement is not a usual finding in this disease.

Methods: We describe the case of a Peruvian patient with a left-sided ulcerative colitis exacerbation associated with concomitant isolated appendiceal orifice area inflammation.

Results: Our patient is a 45-year-old female, allergic to salycilates with an 18 month diagnosis of ulcerative colitis circumscribed to the distal 35 cm, presenting at that time with rectal bleeding and tenesmus. Endoscopic aspect and biopsies confirmed the diagnosis of ulcerative colitis and prednisone 40 mg qd + azathoprine 2 mg/kg/day were started and three weeks later she was in complete clinical remission. However, she became steroid-dependent so infliximab 5 mg/kg was started at 5 mg/kg/day as induction 0, 2 and 6 weeks and maintenance every 8 weeks thereafter. Steroids were withdrawn after 3 months of therapy. Despite this, 5 months after steroid discontinuation she had severe arthralgias on shoulders, elbows, knees and concomitant exacerbation of her colitis presenting 2 to 3 bloody diarrheal stools/day. An ileo-colonoscopy was performed, showing a normal terminal ileum, moderate inflammation of the recto-sigmoid mucosa, similar to her presentation 5 months ago. The rest of the colonic mucosa was normal, except for the appendiceal orifice area, with an endoscopic aspect identical to the recto-sigmoid inflammation. The histologic aspect of the biopsies taken from the recto-sigmoid and the appendiceal orifice was also identical.

Discussion/Conclusion: Colonoscopists evaluating ulcerative colitis should be aware of this peculiar presentation of isolated appendiceal orifice presentation. The literature quotes a frequency of 27% of appendiceal orifice involvement in this disease.
Position for vedolizumab in the treatment of ulcerative colitis, rescue therapy. Our modestly experiences

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Introduction: Vedolizumab, an α4β7 integrin monoclonal antibody inhibiting gut lymphocyte trafficking, is an effective treatment for ulcerative colitis (UC). In this paper, we want to show our modest experience with the use of vedolizumab as a rescue therapy when other medical therapies have failed.

Methods: We report three patients with severaly active ulcerative colitis with previously use tumour necrosis factor (TNF) antagonist therapy. Disease activity indices and blood tests were assessed over a time period of one year in those three patients.

Results: Our data suggest a significant correlation between vedolizumab and response to therapy in IBD patients and was effective and safe in induction of clinical remission and steroid-free clinical remission. Vedolizumab demonstrated real-world effectiveness in our three patients after one year.

Discussion/Conclusion: Vedolizumab alone or in combination with immuno-modulators or steroids may be used as a rescue therapy in patients with medically refractory UC. Our experience indicates that be a cost-effective treatment option compared with conventional therapy for both anti-TNF-naïve and anti-TNF-failure patients with moderately-to-severely active UC.
TLR 2, 4, 6 as a tool for prediction of the risk of early relapse of ulcerative colitis

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Introduction: Success was made in the study of TLR in congenital and adaptive immunity, which determined a new look at immune processes at ulcerative colitis (UC).

Methods: The study included 86 patients with UC, an average age of 39.0 ± 1.4 years. Groups: 1 – 15 (17.4%) patients with distal form of UC, 2 – 42 (48%) left-sided form, 3 – 29 (33.7%) patients with total UC. The expression of TLR on peripheral blood monocytes was determined in the immunofluorescence test. Surface staining of the cells with monoclonal antibodies (MA) conjugated with phycoerythrin-PE to a CD14 monocyte marker (Beckman Coulter, USA) and murine MA to TLR2 (CD282) HM2064F, TLR4 (CD284) HM2068F and TLR6 (CD286) HM2221F conjugated to FITC (Hycult biotechnology, Holland). The corresponding isotypic controls were used. Two-color analysis was performed on a flow-through laser cytofluorimeter (Cytomics FC500, Beckman Coulte). The percentage of monocytes (CD14 + cells) carrying TLR2, TLR4, TLR6 on their surface was assessed.

Results: The direct average relationship was established between the number of monocytes expressing CD14+ CD282+, CD14+ CD284+, CD14+ CD286+ and the area of inflammation (r = 0.49, r = 0.55, r = 0.42, p < 0.05). The nonlinear regression equation was used. Calculation example: the risk of recurrence development is \( NAK = \exp (-26.1 + (0.4) \times TLR2)/(1 + \exp (-26.1 + (0.4) \times TLR2)) \), \( \chi^2 = 130,59, p < 0.0001 \). When translating the nonlinear regression equation into a nomogram, the risk tables for recurrence developed. Thus, when the number of monocytes expressing TLR2 is not more than 60%, the risk of recurrence of the YaK is not more than 11%, with values above 70%, the probability of recurrence exceeds 80%. Analysis of the total effect of the expression of CD14+ CD282+ and CD14+ CD286+ on these events allowed us to formulate the following equation: \( HK = \exp (-16.5 + (0.2) \times TLR2 + (0.4) \times TLR6)/(1 + \exp (-16.5 + (0.2) \times x + (0.4) \times y)) \), \( \chi^2 = 86.9, p < 0.001 \). With the highest expression of CD14+ CD282+ and CD14+ CD286+, the risk of early recurrence approaches 100%.

Discussion/Conclusion: Expression of TLR 2, 4, 6 on blood monocytes can be used as a tool for prediction of recurrence of UC.
The role of stool genetic testing (SGT) for differential diagnosis of early stage IBD and IBS

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Introduction: Clinical differentiation of mild forms of inflammatory bowel disease (IBD) from irritable bowel syndrome (IBS) is often difficult but important for early diagnosis and adequate immunosuppression. Pathomechanisms of both diseases are under intense research but IBD seems to be associated with genetically predisposed disruption of intestinal barriers and dysregulation of the innate immune system. Recent data suggest that IBS is associated with disruption of the intestinal microbiome with significant dysbiosis.

Aims: Retrospective analysis of stool microbiome samples of IBD and IBS patients to determine distinct patterns to guide differential diagnostics.

Methods: We have determined the stool microbiome patterns of 54 patients (14 IBD and 40 IBS) by the standard 16S RNA sequencing and determined diversity index as well as relative ratios of distinct taxonomy classes.

Results: Clostridiaceae, Prevotellaceae, Verrucomicrobiaceae, Rhodospirillaceae Family of bacteria were by far less abundant in the IBD group (40%, 59%, 72%, 71% respectively), whereas Desulfovibrionaceae, Enterobacteriaceae, Sutterellaceae, Veillonellaceae, Acidaminococcaceae, Erysipelotrichaceae were less abundant in the IBS group (105%, 194%, 76%, 79%, 53%, 51%) respectively. There was no clinically significant difference in the microbiome diversity (Simpson’s Score).

Discussion/Conclusion: Stool Genetic Testing for determining changes in the microbiome is a potentially new and non-invasive method to help differentiating early/mild forms of IBD requiring early introduction of 5ASA therapy in adequate doses that can help restoring the gut mucosa barrier function. Detection of lower abundance of Prevotellaceae and Clostridiaceae family of bacteria in these patients as well as higher abundance of Enterobacteriaceae and Veillonellaceae may prove valuable tools for differentiation as shown already in recent publications also supported in our small pilot cohort. Furthermore SGT results can help establishing personalized diet and probiotic recommendation for both patient group. Prospective clinical trials are needed to prove the role of SGT in this respect but given its non-invasive nature, easy-to-repeat format and decreasing costs in the future make it a very appealing tool for the daily clinical setting.
Immunohistochemical expression of proliferation markers in colitis ulcerosa

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**Introduction:** Ki-67 and PCNA are proteins involved in cell cycle. The aim of this study was comparison of expression of these two proteins as markers of cell proliferation in Crohn’s disease.

**Methods:** The study was conducted in a group of 32 patients with Crohn’s disease. Dysplastic changes was present in 10 cases. Immunohistochemical investigations were carried out using antibody against Ki-67 and PCNA. PCNA and Ki-67 expression were determined using the semiquantitative method. Expression for PCNA was absent (lack of reaction or reaction in < 30% cells), weak (reaction in 31–50% cells), average (reaction in 51–80% cells) or strong (reaction in 81–100% cells). Expression for Ki-67 was absent (lack of reaction or reaction in < 15% cells), weak (reaction in 16–35% cells), average (reaction in 36–70% cells) or strong (reaction in 71–100% cells).

**Results:** Cells without dysplasia in Crohn’s disease showed a lack of protein expression of Ki-67 in 5/32 cases and poor in 5/32 cases, while the PCNA protein showed only weak expression in 100% (10/10) of cases. The dysplastic cells expressing Ki-67 was on average 3/32 cases and strong in 3/32 cases, while the protein showed strong PCNA expression in 100% (5/5) cases.

**Conclusion:** Dysplastic cells show a greater expression of Ki-67 protein and PCNA than nondysplastic cells. PCNA protein appears to be a better marker to distinguish dysplastic epithelium from nondysplastic.
The expression of caspase-8 in inflammatory bowel diseases

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Introduction: Caspase-8 is one of the proteins that initiate apoptosis, a physiological process of the programmed cell death. Moreover, it participates in the lymphocytes activation. Its deficiency or disturbance in the functioning can result in the extension of the inflammatory process. In tumors, the lack of this enzyme contributes to the prolongation of cancer cells life and tumor development. Therefore, the purpose of the research was to evaluate the expression of caspase-8 in inflammatory bowel diseases that are threatened with the development of colorectal cancer.

Material and method: The study included a group of 10 patients diagnosed with Crohn’s disease and 31 patients with ulcerative colitis. The expression of caspase-8 in tissue material was evaluated and determined by the immunohistochemical technique. The staining reaction was observed in details in the surface epithelium, normal and dysplastic glands and in inflammatory cells. The score of immunohistochemistry expression was 4-step: the reaction to caspase-8 was absent, weak, medium and strong.

Results: In patients with ulcerative colitis it was observed: the weak and the medium expression of caspase-8 in the surface epithelium (38.7% and 38.7%), the absence and the weak expression in normal glands (41.9% and 32.3%), predominant weak and medium reactions in dysplastic glands (33.3% and 50%), and weak in the inflammatory cells (58%). In turn, the patients diagnosed with Crohn’s disease had a strong expression of caspase-8 located in the surface epithelium in 80% of cases. Moreover, in the normal glands the expression defined as weak, medium and strong (30%, 40% and 20%, respectively) was noted. Only one patient was found with a dysplastic glands where the strong expression of caspase-8 was observed. The strong reaction of inflammatory cells to caspase-8 was observed in up to 90% of patients with Crohn’s. Statistical analysis showed a correlation between the increase in caspase-8 expression in normal glands with its growth in the surface epithelium (\(p = 0.035\)) and in inflammatory cells (\(p = 0.033\)).

Conclusion: A stronger expression of caspase-8 in Crohn’s disease than in ulcerative colitis was the evidence of the increased induction of apoptosis in this disease process. Whereas, in our opinion, the increased expression of caspase-8 in inflammatory cells in Crohn’s disease may be associated with the increase in the number of lymph nodules as a response to chronic inflammation.
Virtual biologics clinic for IBD in a district general hospital

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Introduction: Biological drugs are costly and long term use carries risk of potential side effects. Annual review of IBD patients is recommended to ensure biological treatment is continued appropriately. A virtual biologics clinic (VBC) was therefore set up in 2016.

Methods: Clinics were held monthly during 2016/2017 and attended by both Consultant Gastroenterologists and the Clinical Nurse Specialist. A proforma was used to document the patient’s IBD history, previous treatments, surgery and investigations. The outcome of discussions in the VBC was added to the proforma with one copy in the medical notes and another sent to the GP. We reviewed the notes of all IBD patients on biological therapy to ensure that appropriate assessments were made and decision for continuing or stopping treatment was documented.

Results: There were 46 IBD patients on biological treatment (1 Remicade®, 16 Inflectra®, 21 Humira®, 8 vedolizumab). 11 had been on treatment for less than 12 months. The remaining 35 patients had all been reviewed in the virtual biologics clinic. Biologics were stopped in 4 patients (1 poor response, 2 loss of response, 1 deep remission); 1 patient had the biological drug switched. The decision to continue treatment was documented for the remaining 30 patients; 4 had a decision to reduce or stop immunomodulators and 9 required additional investigations. 4/35 patients had no imaging/colonoscopy in the previous 12 months compared to 10/29 patients during 2015 before the VBC was set up.

Discussion/Conclusion: Implementation of the VBC ensures compliance with annual assessment and documentation of the need to continue biologics. Use of our proforma has facilitated decisions on further management. The VBC will be extended in future to include patients receiving immunomodulator drugs for more than 5 years.
Primary immunodeficiency and ulcerative colitis: Are there any points of interaction?

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The aim of the research is a comprehensive study of the structure of gut microbiota and protein protease profile (PPP) in the mucosa of the colon in patients with primary immunodeficiency (PID) and ulcerative colitis (UC) in different phases of the disease course.

Introduction: In a few studies, changes in the intestinal microbiota in patients with PID and UC are shown, but the effect of these disorders on the course of the disease is not determined.

Methods: The research included 18 patients with PID with an autoimmune type and 26 patients with UC. Estimation of gut microbiota was performed by bacteriological seeding faeces, and hydrogen breath test (HBT) with lactulose. Content of short-chain fatty acids (SCFA) and microbial lipid markers (MLM) in feces and colon mucosa was determined by gas-liquid chromatographic and gas chromatography-mass spectrometry (GC-MS).

Results: In 31 (70.5%) cases of microbiological study of stool a decrease in titers of bifido- and lactobacilli, bacteroids on average 4.6 ± 0.8 Lg, an increase in the titers of hemolytic strains of Escherichia coli, Klebsiella spp. and Candida fungi in titers > 10⁶ was revealed. MLM GS-MS results showed a 4.5 and 5-fold increase in the total bacterial load represented by: streptococcus mutants, clostridium difficile, candida glabrata. HBT revealed 8 and 11-fold increase in hydrogen production of 120th and 150th minutes of the study. SCFA showed a 7 and 10-fold decrease in propionic and butyric acids: 0.14 ± 0.03 mg/g and 0.04 ± 0.02 mg/g (p < 0.05), respectively. 29 (66%) patients (12 with PID and 17 with UC) received treatment: rifaximin 1.2 g/day – 15 days followed by multi-strain probiotics and prebiotic with inulin for 8 weeks. A repeated complex examination after 12 weeks showed that in 18 (62%) cases the production of hydrogen decreased, in 22 (75.9%) a 3-fold decrease in the total bacterial load by anaerobic microflora, in 17 (58.6%) cases, the increase in production of propionic and butyric acids to subnormal level.

Discussion/Conclusion: In patients with PID and UC, markers of colon excess growth with an increase in resident anaerobic flora and significant decrease in SCFA production is note are recorded during the relapse period. The therapy with rifaximin with prolonged intake of pro- and prebiotics with inulin is accompanied by normalization of the structure of the intestinal flora, production of SCFA, a decrease in calprotectin and lactoferrin.
Acute severe colitis in pregnancy: A case report

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Introduction: A 24-year-old female with known ulcerative colitis developed a fare of her colitis early in pregnancy. She was initially managed with oral steroids with good response. Unfortunately she clinically relapsed after the course of steroids. She was commenced on infliximab 5 mg/kg after a limited flexible sigmoidoscopy demonstrating severe disease but was a primary non responder and was switched to adalimumab. Unfortunately she failed to respond to adalimumab. At 28 weeks gestation, the patient was offered and declined vedolizumab due to the lack of safety data at the time.

Discussion/Conclusion: The management of inflammatory bowel disease in pregnancy can be fraught with emotion both on the side of the clinicians and the patient. Activity of disease pre pregnancy is linked to activity of IBD through pregnancy and also outcomes for the foetus. Pre-pregnancy counselling is of utmost importance in this situation. Management of severe disease in pregnancy is difficult with concerns regarding effects on the foetus of both the active disease and the drugs used in an attempt to control it. In our case, the patient was admitted to the gastroenterology ward at 28 weeks as she was no longer responding to oral steroids. She was managed with iv hydrocortisone and after some discussion about options, including surgery, cyclosporine was commenced, given the fact she had failed to respond to biologics. With the inception of cyclosporine, her symptoms and blood parameters started to improve. And she was discharged at 32 weeks. She went into spontaneous labour at 33 weeks and delivered a healthy baby. Swiftly after delivery her clinical stated deteriorated and she required semi-emergency colectomy.
**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.
Serum MMP-9 – A novel biomarker for prediction of clinical relapse in patients with quiescent small bowel Crohn’s disease

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Introduction: Matrix metalloproteinase-9 (MMP-9) is a relatively new and promising marker of intestinal inflammation. We aimed to assess, for the first time, whether serum MMP-9 levels can predict clinical relapse in CD patients with quiescent small bowel disease.

Methods: This was a post-hoc analysis of patients with quiescent small bowel CD who were included in a prospective observational study and followed until clinical relapse or the end of the 24 months study. Clinical relapse was defined as an increase in CDAI score of at least 70 points from baseline, or an intensification of therapy, as per physician global assessment based decision. The patients were followed with serial MREs and capsule endoscopies (CEs). Small bowel inflammation was quantified by Lewis score (LS) for CE. MaRIA score was calculated for MRE. CRP and fecal calprotectin (FC) were obtained at baseline and at each follow-up visit. Serum MMP-9 levels in baseline blood samples were quantified by ELISA and the correlation of MMP-9 levels with subsequent clinical flare was investigated.

Results: Sixty one patients were enrolled. After exclusion of three blood samples due to technical causes, there were 58 analyzable samples from 58 CD patients (median age 29.5 years, 43% female), of whom 16 have relapsed. Baseline MMP-9 was higher in patients who developed symptomatic relapse [median 661 ng/ml, 25–75 IQR (478.2–1441.3) vs. 525.5 ng/ml, (339–662.7), in relapsers versus non-relapsers, respectively, p = 0.01]. Patients with baseline serum MMP-9 levels above 945 ng/ml were significantly at higher risk of relapse within 24 months with hazard ratio (HR) of 8.13 (95% CI: 3.0–21.9, p < 0.001). ROC analysis of serum MMP-9 levels showed a fair discriminatory accuracy with an AUC of 0.72 (95% CI: 0.56–0.88). MMP-9 concentrations displayed a moderate and low correlation with baseline FC and LS respectively (r = 0.46, p < 0.0001; r = 0.31, p < 0.05).

Discussion/Conclusion: Serum MMP-9 may be a novel biomarker for prediction of relapse in CD patients with quiescent disease.
Profound loss of neprilysin accompanied by decreased levels of neuropeptides and increased CRP in ulcerative colitis

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Introduction: Neprilysin (NEP, CD10) acts to limit excessive inflammation partly by hydrolyzing neuropeptides. Although deletion of NEP exacerbates intestinal inflammation in animal models, its role in ulcerative colitis (UC) is not well explored. Herein, we aimed to demonstrate changes in NEP and associated neuropeptides at the same time in colonic tissue.

Methods: 72 patients with UC and 27 control patients were included. Patients’ demographic data and laboratory findings, five biopsy samples from active colitis sites and five samples from uninvolved mucosa were collected. Substance P (SP), calcitonin gene related peptide (CGRP) and vasoactive intestinal peptide (VIP) were extracted from freshly frozen tissues and measured using ELISA. Levels of NEP expression were determined using immunohistochemistry and immunoreactivity scores were calculated. GEBOES grading system was also used.

Results: We demonstrated a profound loss (69.4%) of NEP expression in UC, whereas all healthy controls had NEP expression. Patients with UC had lower neuronal SP; however non-neuronal SP remained similar. UC patients had also lower neuronal and non-neuronal VIP levels. CGRP were low in general and no significant changes were observed. Additionally, CRP positive patients with UC had higher rates of NEP loss (80% vs. 51.9%) and lower SP levels when compared with CRP negative patients with UC.

Discussion/Conclusion: Concurrent decreases in SP and VIP with profound loss of NEP expression observed in UC is likely to be one of the factors in pathogenesis. Further studies are required to define the role of neuropeptides and NEP in UC.
Significance of metalloproteinase 9 (MMP-9) expression in ulcerative colitis

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Introduction: The extracellular matrix (ECM) is a specific matrix participating in the migration, cell adhesion, differentiation, and inter-cell interactions. Remodeling of the ECM is important in the development of many disease processes. A key mechanism is metalloproteinases activity (MMPs) which has the capacity to its degradation and remodeling. One of the proteins belonging to the MMPs is matrix metalloproteinase 9 (MMP-9) whose overexpression was observed in inflammatory and neoplastic processes. Therefore, the aim of our study was to evaluate the expression of metalloproteinatease 9 and to analyse the correlation of MMP-9 with chosen clinicopathological parameters in patients with ulcerative colitis.

Methods: The study consisted of 30 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. According to Geboes classification, an analysis of the severity changes (architectural changes, the assessment of crypt destruction, erosions an ulcers, infiltration of inflammatory cells) was performed. The expression of metalloproteinatease 9 in tissue sections was assessed by immunohistochemical methods. The staining reaction in a 4-point scale was assessed as absent – 0, weak – 1, medium – 2 and strong – 3.

Results: The expression of MMP-9 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. The expression of MMP-9 was higher in 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. Statistical analysis showed that increased expression of MMP-9 protein in epithelial cells in patients with ulcerative colitis was associated also with remodeling of tissue architecture (p = 0.046).

Discussion/Conclusion: Overexpression of metalloproteinase 9 is associated with the inflammatory reaction in patients with ulcerative colitis. Moreover, MMP-9 likely to contribute to the tissue damage and remodeling seen in inflammatory bowel disease.
Impairment of cognitive and psychomotor performance in patients with inflammatory bowel disease

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Introduction: Patients with chronic diseases often experience cognitive deficits. Several risk factors for developing cognitive and psychomotor impairment are identified in patients with inflammatory bowel diseases (IBD). Although there is a growing evidence that cognitive impairments are found in different chronic illnesses, there is a limited research concerning IBD patients. Therefore, the aim of this study was to investigate cognitive and psychomotor performance in IBD patients and compare it to healthy controls.

Methods: This study included 60 patients with IBD (30 Crohn’s disease and 30 ulcerative colitis) and compared them with age/gender matched controls. Participants were tested on three different tests of cognitive and psychomotor performance measuring reaction times of light stimulus perception, solving simple arithmetic operations, and complex psychomotor limb coordination using the computer-based system Complex Reactionmeter Drenovac (CRD-series). Three parameters were analysed; total test solving time (TTST), minimum single task solving time (MinT) and total number of errors during test (TE). TTST and MinT were descriptors of speed, accuracy and mental endurance, while TE was a descriptor of attention and alertness.

Results: In light signal position discrimination test (CRD311) patients with IBD had significantly longer TTST (36.75 ± 6.5 vs. 33.28 ± 7.5 s; p = 0.008) and MinT (0.46 ± 0.08 vs. 0.41 ± 0.08 s; p = 0.002), while there was no difference in TE (p = 0.991). Patients with IBD had significantly longer TTST (151.40 ± 62.90 vs. 122.78 ± 38.46 s; p = 0.003) and MinT (2.33 ± 0.72 vs. 1.96 ± 0.55 s; p = 0.002) in simple arithmetic test (CRD11), while there was no difference in TE (p = 0.318). In complex motor coordination test (CRD411) patients with IBD had significantly longer TTST (48.99 ± 19.64 vs. 37.49 ± 11.29 s; p < 0.001) and MinT (0.58 ± 0.15 vs. 0.51 ± 0.12 s; p = 0.006) and higher TE (12 ± 9 vs. 7 ± 5; p < 0.001).

Discussion/Conclusion: Results of this study indicate that patients with IBD have impaired cognitive and psychomotor performance when compared to healthy controls. Further research is needed to clarify the significance of these findings.
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October 5–6, 2018
Milan Marriott Hotel
Milan, Italy