IBD: From Diagnosis to Therapy

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Abstracts
Poster Abstracts
Abstracts of Invited Lectures
Poster Abstracts

Symposium 215

IBD: FROM DIAGNOSIS TO THERAPY

St. Petersburg, Russia
July 5 – 6, 2019

Scientific Organization:
W. Reinisch, Vienna (Austria)

Scientific Co-Organization:
H. Herfarth, Chapel Hill (USA)
Y. Shelygin, Moscow (Russia)
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* = Posters of Distinction
Session I

Epidemiology and translational science inform daily practice
Overview of current IBD epidemiologic and clinical features in Russia

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Moscow Regional Research Clinical Institute, Moscow, Russia

Aim: To study and compare inflammatory bowel disease (IBD) prevalence and incidence in some Russian regions and to present common Russian IBD demographic and clinical features.

Materials and methods: Ulcerative colitis (UC) and Crohn’s disease (CD) prevalence and incidence are presented according to IBD registers from six regions of RF: Moscow region, Irkutsk, Krasnoyarsk, Rostov-on-Don, Permsky region, Tatarstan. Demographic and clinical peculiarities were investigated in multicenter cross-sectional cohort study included 1797 patients (1254 UC and 543 CD), performed in 20 centers from 17 Russian regions 2010–2014.

Results: The incidence of UC over the past 10 years has increased by 2.5–6-fold and now ranges from 2,0 in Rostov and Krasnoyarsk to 5–6 per 100,000 in Irkutsk and the Moscow region. The CD incidence increased 2–4-fold in all regions during the same period. Now the maximum incidence is 2.5–3 per 100,000 in the Moscow region and Irkutsk. F:M ratio = 1:1 was similar in UC and CD. Median patient’s age was about 38 years in UC and 36 years in CD. The distribution of patients according to the age of disease onset demonstrated the highest incidence in 20–40 years in UC, whereas in CD it was shifted towards younger age (22.5% of the patients manifested before 20 years). Urban:rural ratio in UC and CD was 4:1. The proportion of current smokers in CD was 2-fold higher than in UC (15.6 and 8.8%, respectively). The median time from UC onset to diagnosis was 5 months, in CD -12 months). Mild UC was observed in 16%, moderate in 53%, severe in 31% of patients. The respective proportions among CD patients were 21, 44, and 35%. Proctitis was found in 33% of UC patients, left-side UC in 38%, pancolitis in 29%. In CD terminal ileitis was seen in 31.3% of patients, ileocolitis in 33.4%, colitis in 25.6%. The upper gastrointestinal CD was found in 4.4%, and mixed CD in 5.3%. Extraintestinal manifestations (particularly peripheral arthropathies and aphthous stomatitis) were more frequent in CD, than in UC (33.1% and 23%).
Novel immunologic pathways for future therapies in IBD

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The interplay of environmental triggers with genomic risk can cause pathological immune activation that manifests clinically as two phenotypically distinct diseases, Crohn’s disease and ulcerative colitis. While the distinctness is still not yet appropriately understood at a mechanistic, immunological level, several key themes have emerged. In addition to bona fide cells of the innate and adaptive immune system, other cell types such as intestinal epithelial cells and Paneth cells, and stromal cells are emerging as of key importance. Following on from NOD2 and ATG16L1, which have pointed to innate immune signalling and autophagy in Crohn’s disease, the in-depth investigation of major genetic risk factors has uncovered unexpected and intriguing new mechanisms. Genetic models allow investigating mechanisms and their functional interaction in detail. Such studies suggest the convergence towards a finite number of major pathways that play an important role in disease propagation. One major pathway relates to signalling through the IL23 receptor, which is targeted by anti-p19 antibodies already. This is intriguing since genetic variants of IL23R are amongst the strongest genetic risk factors of Crohn’s disease and ulcerative colitis. Another major pathway relates to endoplasmic reticulum stress in the intestinal epithelium, the threshold of which is determined by ATG16L1 genetic variants. ER stress has emerged as originator and driver of intestinal inflammation in intestinal epithelium and can orchestrate the activation of innate and adaptive immune cells, including NK cells and B cells. We will discuss these and other major emerging concepts in IBD pathogenesis.
Inflammatory bowel disease including Crohn’s disease and ulcerative colitis are complex polygenic disorders. There is an increasing understanding of environmental and genetic factors that determine that disease susceptibility but much less is known about the disease course and complications. A number of environmental factors confer risk or protection from inflammatory bowel disease (such as cigarette smoking, antibiotics, breastfeeding) but only a few affect disease course and complication rate (such as smoking). Some environmental factors such as CMV or EBV infection are associated with complications but confounded by treatment such as steroids or immunomodulators. Although over 200 genetic loci have been described that confer susceptibility to Crohn’s disease or ulcerative colitis, only a few are associated with disease course and complication rate. In addition to the polygenic disorders there are Mendelian forms of inflammatory bowel disease that present with extreme forms of inflammatory bowel disease and high complication rates. In those disorders, the genetic defects are associated with a number of unusual complications and treatments such as haematopoietic stem cell transplantation or disease specific biologics can prevent those complications.

This offers increasingly personalised medicine at the stage of diagnosis.
The role of the microbiome – What’s needed to successfully treat dysbiosis in IBD?

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Ever since instances of inflammatory bowel disease (IBD) were described, microbes were incriminated, firstly, as causal agents, secondly, as initiating or exacerbating factors and, finally, through unknown mechanisms, as components of the fecal stream that appeared essential for the development of IBD. While a search for a “causative” microbe in ulcerative colitis (UC) and Crohn’s disease has essentially come to naught, the roles of *Clostridium difficile* and cytomegalovirus, in precipitating relapses of IBD are now well recognized. However, it is the microbes in the fecal stream (the gut microbiota) that now garner most of the attention. While, using modern sequencing methods and advanced informatics, a variety of alterations in the composition of the microbiota have been demonstrated in IBD, their precise significance and relationships to disease pathogenesis remain to be defined. At the moment, the diagnostic and therapeutic potential of the microbiota in IBD is being actively pursued. Meanwhile, a variety of strategies that can modulate the microbiome are being employed, albeit on a somewhat empirical basis. Thus, antibiotics and probiotics are often used as adjunctive therapy in inflammatory bowel disease. However, data is limited and randomized controlled trials too inconsistent to provide generalized recommendations for their use in all patients with UC or Crohn’s disease. For now, antibiotics are best used in the management of infectious complications and fistulas in Crohn’s disease and, perhaps, in reducing the intensity of inflammation in luminal disease. Ciprofloxacin, metronidazole, and rifaximin have been most widely used and studied. On the other hand, there appears to be a limited role for antibiotics in UC. Probiotics are most effective in pouchitis, and may have a role in the initial therapy and maintenance of remission in mild UC; the probiotic cocktail VSL#3 has been the most widely studied. There is scant evidence of efficacy for probiotics in Crohn’s disease. Most recently, fecal microbiota transplantation has been studied; here again, data is limited.

For the future we should strive towards a more selective and perhaps personalized approach to microbiota modulation in IBD employing strategies addressed at abnormalities in a given patient’s resident microbiota.
Session II

Diagnostic approaches in IBD
Fecal and serologic markers – What do they help to diagnose and predict the course of IBD?

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The future of inflammatory bowel disease (IBD) care includes a goal of “personalized” medicine. The hope is that combinations of clinical phenotype, gene expression, serological, and microbiome data will ultimately guide risk stratification and individualized medication selection. Ultimately, if diagnostic accuracy is established, these markers could allow for earlier diagnosis of IBD and/or be applied to specific subgroups of IBD patients during disease course to guide treatment and prevent downstream complications of disease. However, at this time, data are limited as to the predictive value of non-invasive biomarkers. The accuracy of these markers for IBD diagnosis is impacted by the low prevalence of IBD. The pretest probability or prevalence of disease in any population strongly affects the positive and negative predictive ability of a test. For example, while serologies may have reasonable sensitivity and specificity, the diagnostic accuracy is limited when applied in low-prevalence populations. This results in a much lower positive predictive value. Accuracy is also limited for disease monitoring and/or prediction, with some preliminary data supporting a role for Anti-Saccharomyces cerevisiae antibodies (ASCA)-IgG and fecal calprotectin. This review includes a description of currently available fecal and serologic markers, current data on the diagnostic accuracy of these markers, limitations in the study designs, and a discussion of further prospective data that are needed prior to incorporation of these biomarkers into practice.

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Standardized endoscopic scores and their roles in clinical trials and daily practice

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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 for clinical practice and even more for clinical trials: European (EMA) and American (FDA) drug agencies set as a new standard the incorporation of endoscopic endpoints in clinical trials evaluating new therapeutic compounds for CD and UC.

Several endoscopic scores were developed and are currently used to objectively quantify the level of endoscopic severity. The most commonly scores used for UC are Mayo endoscopic score (MES) and UC endoscopic index of severity (UCEIS). The most commonly scores used for CD are Rutgeerts' score (for post-surgical recurrence), CD endoscopic index of severity (CDEIS) and the simple endoscopic score for CD (SES-CD) for luminal CD.

The use of endoscopic scores, however, is not a perfect tool. There is remarkable evidence exploring the magnitude of disagreement among different observers, with potential relevant effects on clinical trials results and on daily practice evaluations.

In order to reduce inter-observer variability in endoscopic scoring in clinical trials, off-site review of endoscopic features was advocated to reduce variability in scoring among different observers as well as the risks of overjudgement of basal severity and of post-treatment effects by local endoscopists. Nonetheless, central reading methodology is still undergoing a process of refinement, with different reading paradigms available which are still under evaluation (single reader scoring, multiple readers adjudication, head-to-head paired-reading) for their effectiveness.

All the mentioned scores may be used in clinical practice to support physicians in endoscopic reporting and in quantification of endoscopic severity, e.g. for precise evaluation of variation of the inflammatory disease burden before and after a given therapeutic intervention. Other means to reduce intra and interobserver variability (in daily practice and in clinical trials) might be common training paths and electronic-aided scoring systems.
Imaging in IBD by ultrasound – Current and future perspectives

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There are at least three main advantages of intestinal ultrasound (IUS) over other imaging modalities. The first advantages of IUS includes the rapid evaluation of bowel wall stratification, which directly mirrors the alterations in histopathology in Crohn’s disease as well as in ulcerative colitis. The immediate bedside assessment and possibility for unrestricted controls represent a big advantage for the treating physician compared to any time-consuming referral.

The second advantage is the direct visualization of vascularization of the bowel by color Doppler sonography, which reflects disease activity in ulcerative colitis and Crohn’s disease patients.

The third advantage is the visualization of motility. No other imaging modality can demonstrate particular small bowel motility more sensitive than intestinal ultrasound.

Intestinal ultrasound has been shown to be an easy to use, accurate, cost-effective and comfortable method for primary diagnosis as well as determination of extension of inflammatory bowel disease. IUS has also been shown to have high accuracy to detect small and large bowel Crohn’s disease and to determine intra- and extramural complications such as stenoses, fistulae and abscesses. In addition, IUS has also been demonstrated to be highly effective to determine postoperative disease recurrence in Crohn’s disease.

Beside Crohn’s disease, IUS is now more and more used in patients with ulcerative colitis as intestinal edema and mucosal inflammation in ulcerative colitis can directly be visualized by IUS.

Contrast-enhanced ultrasonography (CEUS) might be useful in some situations in Crohn’s disease patients and in particular for differentiation of abscesses from phlegmons. New methodology such as elastography may help to differentiate fibrotic from inflammatory components in strictures.

Sensitivity, accuracy and specificity of intestinal ultrasound is comparable to other cross sectional imaging modalities such as MRE and CT.

Recent studies have shown that IUS is a valuable tool in monitoring patients with Crohn’s disease as well as in patients with ulcerative colitis just by determining changes in bowel wall thickness and vascularization. Figure 1 shows a potential algorithm on how IUS may be used in follow up of patients with Crohn’s disease and ulcerative colitis in clinical practice.
In ulcerative colitis, normalization of bowel wall thickness as the most sensitive parameter of inflammation, can be determined as soon as 2 weeks after treatment initiation in a highly significant proportion of patients. Current trials evaluate the clinical long-term benefit of transmural response or remission in Crohn’s disease and in ulcerative colitis as determined by IUS. If it turns out that improvement of IUS parameters after treatment is associated with long-term clinical amelioration, IUS parameters may be used as new non-invasive markers in a Treat-to-Target concept in the future.

A variety of studies as well as a growing experience in daily clinical practice worldwide have clearly shown that bowel ultrasonography offers a variety of advantages in addition to other imaging modalities in IBD. IUS can already be used in daily clinical practice for clinical decision making and to optimize management of patients with IBD.
The problem of fibrosis in IBD – Are there diagnostic tools for early detection?

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Intestinal fibrosis, leading to stricture formation and intestinal obstruction is a common and serious complication of Crohn’s disease (CD), but can also be found in ulcerative colitis (UC). It can occur at any time during the disease course. Hence, it is crucial to identify patients at risk for stricturing disease by developing predictive or diagnostic tools. The aim is not only to understand the pathophysiology of fibrogenesis, but to be able to accurately inform subjects about their disease course, design future trials of potentially useful anti-fibrotic therapies and, most importantly, identify those CD patients at risk, with the promise for early, more aggressive, medical therapy. The role of endoscopy to diagnose the nature of strictures is limited by the superficial inspection of the intestinal mucosa, the lack of depth of mucosal biopsies, and by the risk of sampling error due to a heterogeneous distribution of inflammation and fibrosis within a stricturing lesion. These limitations may be in part overcome by cross-sectional imaging techniques such as ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI), allowing for a full thickness evaluation of the bowel wall and associated abnormalities. In the future, however, novel imaging techniques, genetic, serologic, transcriptomic and dynamic matrix turnover markers may open the door for early detection of fibrosis and an accurate patient stratification.
Session III

The essential guide to treatment of IBD
Guide to medical treatment of Crohn’s disease

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Medical treatment of Crohn’s disease (CD) needs correct diagnosis, assessment of disease activity, disease extension and presence of extraintestinal manifestations and knowledge about previous medical therapies including response and adverse events to medical therapy. In addition, knowledge about co-morbidities like previous or concomitant malignancies or the patients personal and social situation are important to develop an optimal treatment plan for the individual patient based on personal experience and current guidelines.

The management of CD has evolved significantly over the last decades. New steroid formulations as well as biologic therapies like anti-TNF blockers, anti-adhesion blockade and anti-IL23 blockers have been introduced. Surgery is still an important corner stone in the management of CD and surgical approaches have been improved and modified as well. New treatment strategies such as accelerated step-up, tight control and treat to target have emerged or are currently under evaluation. Our medical armamentarium has become broader and more complex. Conventional therapy with the locally acting steroid budesonide still represents the standard treatment for active mild to moderate ileocecal CD and with systemic steroids for acute moderate to severe CD of all locations, while treatment with thiopurine or methotrexate monotherapy have been challenged in the last decade. In contrast, anti-TNF blockade, anti-adhesion strategies and anti-IL23 blockade have gained more and more importance for the treatment of moderate to severe steroid-refractory or steroid-dependent CD. In refractory cases or in patients with adverse effects to medical therapy surgery still has an important role and close interaction between gastroenterologists and surgeons is mandatory.

Management of fistulizing CD is following different pathways: Treatment options and strategies depend on the location of disease and complexity of fistula. While simple perianal fistulas remain a primary surgical domain, complex fistulising disease is preferably targeted by medical strategies and often with a multidisciplinary approach. Medical therapies encompass antibiotics (metronidazole, ciprofloxacin), anti-TNF therapies (infliximab, adalimumab), thiopurines, calcineurin inhibitors (ciclosporin, tacrolimus), vedolizumab and ustekinumab. A recent new option is provided by mesenchymal stem cells derived from adipose tissues that have been used successfully in perianal CD.

While some of the topics are controversial and data are still limited, the guidance by ECCO guidelines, data from controlled trials, real world experience, and longitudinal observations and registries offer guidance in making evidence-based therapeutic decisions for the majority of our CD patients.
Guide to medical treatment of ulcerative colitis

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For a long time, there was limited innovation in the development of the drug for ulcerative colitis (UC) following the introduction of anti-TNF antibodies. This has changed since the approval of the first integrin inhibitor vedolizumab in 2014, and considerable momentum has been generated, which is also reflected in a number of therapy studies for various substance groups that are now hard to ignore.

The traditional pyramid of drug therapy – based on 5-aminosalicylic acid (5-ASA), topical steroids, systemic steroids, thiopurines and TNF inhibitors – is now increasingly questioned by the many innovations in therapy options and their positioning. Besides anti-integrins (of which besides vedolizumab more will be approved in the future), Janus Kinase (JAK) inhibitors have been developed for the treatment of UC and Tofacitinib is already approved by the regulators (e.g. FDA and EMA) in many countries.

However, the definitive place of the newer substances in the therapy algorithm has still to be determined more precisely and is currently not completely clear. Definitely, CU therapy is becoming more complex.

In the future different options for combination therapy must be examined, as it was shown to be meaningful in various other fields of medicine such as rheumatology. Looking more closely at these new substances, it is striking that there are various overlaps with other disciplines in the field of immune-mediated diseases, in particular rheumatology, dermatology, but also neurology and clinical immunology.

Since some of the new substances have already been approved for other indications in these disciplines, important information regarding side effects and safety can be found here. In contrast to the information on side effects, previous experience has shown that efficacy data, for example from rheumatology, can only be transferred to a limited extent to IBD.

In the presentation, the individual substance classes will be presented shortly. An overview of the usual dosages will be provided and a possible procedure for mild to moderate or moderate to severe CU will be given.
Important safety aspects of old and new IBD drugs

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Important safety aspects of IBD drugs are life-threatening drug class-specific complications, cancers and serious infections. Thiopurines promote EBV-related lymphomas, particularly in young EBV-seronegative young adults and in senior men. The use of anti-TNF agents is not associated with an overall excess risk of cancer, but is associated with a mild excess risk of melanoma and a still controversial excess risk of lymphoma. Whether methotrexate, vedolizumab, ustekinumab and tofacitinib promote some cancers is unknown. Based on concepts, we should primarily verify that vedolizumab does not facilitate carcinogenesis of digestive cancers and that tofacitinib does not promote virus-related cancers, including lymphomas. Serious viral infections are promoted by thiopurines, particularly in young patients. Fatal forms of varicella and primary EBV infection can be prevented by vaccination against VZV before starting thiopurines and limited use of thiopurines in EBV-seronegative patients, respectively. Anti-TNF agents promote all types of serious infections, particularly tuberculosis and bacterial, fungal and parasitic intracellular infections. Detection of latent tuberculosis, anti-pneumococcal vaccination, and physician reactivity to any clinical event suggestive of acute infection are important aspects of safety management in all patients, not only frail ones. Tofacitinib increases frankly the risk of herpes zoster, in an age-increasing manner. The risk of zoster is very high in older patients, and will be limited by the use of live or recombinant vaccine, according to time of vaccination (before or during immunosuppressive therapy, respectively). The risk of drug class-specific complications is roughly under control, proving the respect of contra-indications and specific drug monitoring measures, for thiopurines (bone-marrow suppression) and anti-TNF (multiple sclerosis, cardiac failure). Whether alterations of lipid profile associated with the use of tofacitinib have a clinical impact should be rapidly addressed. As a general conclusion, we should be cautious about easy/first-line use of new drugs, as far as major aspects of safety have not been clarified.
The evolution of therapies in IBD has reached enormous speed. After a decade of anti TNF therapy, vedolizumab introduced a novel principle with a focused inhibition of α4ß7 integrin. Surprisingly, a non-systemic immune modulation on the level of the gut mucosa delivered a strong clinical signal in UC as well as efficacy in CD. Shortly later, ustekinumab, an inhibitor against the p40 protein, which is shared by the cytokines IL12 and IL23 was introduced for the therapy of CD and lately showed efficacy in UC, too. The latest addition was an oral drug, the pan-JAK inhibitor tofacitinib, which delivers very fast efficacy in active UC.

With so many diverse therapeutic principles being effective, many companies in the immune area have speeded up developments in the field of IBD. Very soon new biologicals will be available with different specificities in the α4ß7 pathway, others with specific inhibitory capacity against IL23 and a further substance class directed against IL6 trans-signaling. In addition, we will see oral substances either delivering more specific inhibition of known targets (e.g. JAK pathway) or address novel MOA (e.g. S1P agonism).

With the enormous choice coming up the questions for the first choice and for the best sequencing of therapies become burning. A first head-to-head trial between biologics has recently been presented with many more coming in the next years. This may help to solve the quest for the best first choice but leaves the need for algorithm trials investigating synergisms through sequencing of targeted therapies.
Session IV

IBD and the interface of medical and surgical therapy
Surgical standards for Crohn’s disease and ulcerative colitis

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In modern IBD practice decision making is done in multidisciplinary team meetings. In the MDT discussion the best plan for the individual patient with IBD is developed. The surgical management of Crohn’s disease has evolved from last resort surgery failing medical therapy towards a valid alternative in the different treatment options. Surgery earlier in the treatment algorithm than before is indicated for limited ileocolic disease particularly in predominantly fibrotic stenosis, fistulizing disease and abscess formation that developed while on biologicals. Even in predominantly inflammatory stenosis limited resection showed to be at least as good alternative compared to biological therapy. This account probably for all limited segmental resection provided surgery is done laparoscopically and in an ERAS perioperative program. Crohn’s proctocolitis patients refractory to medical therapy can be counseled for pouch surgery provided the small bowel never has been affected and in the absence of perianal disease. If proctectomy is necessary, a TME type of proctectomy is best done with filling the pelvic cavity with omentum to prevent chronic pelvic abscesses. Enteric fistula generally require surgery if they are symptomatic.

In therapeutic refractory ulcerative colitis the line operation is always a subtotal colectomy with ileostomy. In a second stage a completions proctectomy and pouch is done. If old age or bad sphincters preclude pouch surgery, the rectum can stay in situ or if symptomatic removed.

Dysplasia and cancer will more and more indicate colectomy consisting of one stage proctocolectomy and pouch or colectomy with ileorectal anastomosis in the older and frail patient. In any case, if there is still large bowel or rectum in situ with longstanding IBD, the bowel must be carefully screened for the development of dysplasia.

A new kid on the block is the appendectomy for ulcerative colitis. There is emerging evidence that appendectomy prevents the development of ulcerative colitis, and if already present, modulates the disease in a positive way.
Treatment approaches for pouchitis

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Due to a refractory course of UC or histologically proven dysplasia approximately 20–35% of patients with ulcerative colitis (UC) eventually undergo colectomy, which is most often performed in conjunction with an ileal pouch-anal anastomosis (IPAA). The ileal pouch serves as a reservoir for the stool and improves functional outcomes following IPAA. Pouchitis is the most common long-term complication after IPAA in the setting of UC affecting up to 70% of patients. The clinical symptoms include diarrhea, crampy abdominal pain, fever, bloody bowel movements, dehydration as well as extra-intestinal manifestations such as joint pain. Pouchitis can be treated successfully with antibiotics (e.g. metronidazole, ciprofloxacin), but relapse of pouchitis is common. Antibiotic therapies, often in rotating therapeutic schedules are frequently required. A significant number of patients, who are in need and respond to recurrent antibiotic therapy to control their pouchitis symptoms, develop antibiotic dependent pouchitis (ADP). Since the therapeutic effect of antibiotics suggest a microbial dysbiosis as a key factor in the development of ADP, fecal microbial transplantation (FMT) appears to be a promising approach. However so far less than a handful of studies with small patient numbers could not demonstrate a convincing efficacy for FMT in this patient population.

Significant heterogeneity exists in the definition of CD of the pouch and the terminology used to describe an inflammatory Crohn's-like inflammatory presentation in a patient with an IPAA. The most commonly reported diagnostic criteria are 1) presence of a fistula/fistulae, 2) a stricture involving the pouch or pre-pouch ileum, and 3) presence of pre-pouch ileitis. A recent systematic analysis of all data suggest the prevalence of CD of the pouch in IPAA patients around 12%. Two recently published studies reported a relative high therapeutic efficacy for ustekinumab or vedolizumab in patients with CD like disease of the pouch.

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Therapy of perianal and entero-enteral fistulas: What’s standard and what’s the future?

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The indication for surgical inventions for perianal and entero-enteral fistula has shifted toward being restrictively used. Indications for surgery include complications like abscess, perianal and entero-enteral fistula and conditions insufficiently responsive to medical therapy. However in symptomatic patients with fistulating abdominal disease surgery should already be considered in an early stage as there is a risk that medical therapy will fail. Decision for early surgery should be weighted against risks of surgery subsequent to prolonged medical treatment. Entero-enteral fistula in asymptomatic patient are not considered an absolute indication for operation. Any abdominal operation should remain as restrictive as possible; organ preserving techniques should be preferred.

In perianal fistulas the distinction of simple and complex fistula is of clinical value, as these usually require different approaches. Common goals are local control of the septic complication and preservation of function. In selected simple, superficial fistulas fistulectomy and fistulotomy remain options as the risk of functional sequelae is low. Complex, high fistulas require a different, often staged approach. After control of the acute sepsis with surgical drainage of the abscess and non-cutting seton placement for drainage a combined surgical and medical approach has been found to be effective for the control and treatment of complex perianal Crohn’s disease. The timing of removal of the draining seton to achieve sustained symptom relief or fistula closure under medical therapy remains controversial, as does the timing of surgical re-intervention and choice of surgical procedure. Reparative surgical techniques include the use of fibrin glue, collagen paste, local application of anti-TNF-α infliximab and adalimumab, the use of an endoluminal mucosa flap, ligation of the fistula tract, the application of mesenchymal stem cells. Evidence for any technique is low. The choice of procedure should be tailored to the anatomy, direction of the fistula tracts and continence function.
Postoperative Crohn’s disease management

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The management of postoperative Crohn’s disease relies on stratification of high versus low risk for disease recurrence after surgery:

**Low Risk**
1. Older patient (> 50 years)
2. Non smoker
3. 1st surgery for short segment fibrostenotic disease (< 10–20 cm)
4. Disease duration > 20 years

**High Risk** Younger patient (< 30 years)
1. Smoker
2. More than 2 prior surgeries
3. Penetrating disease
4. Perianal disease

For those with high risk for recurrence, the recommendation is post-operative prophylaxis with an anti-TNF agent within 2–4 weeks of surgery. Low risk patients do not need prophylactic treatment, however these patients should undergo a fecal calprotectin at 3 months and colonoscopy at 6 months. If there is Crohn’s disease recurrence they should be started on treatment. All patients regardless of their risk factors undergo regular endoscopic surveillance at 6–12 months, depending on risk, to assess for POR at the pre-anastomotic area. In case there is worsening of disease on surveillance, there should be escalation of treatment with appropriate therapeutic drug monitoring. Fecal calprotectin can be used as a useful non-invasive tool to identify early recurrence. Biologics, especially anti-TNF alpha agents have the most data in the prevention of postoperative Crohn’s disease. Data on other biologics are currently lacking, but may be used in patients how have previously failed or are intolerant to anti-TNFs.
Session V

IBD: Special situations
Pregnancy in IBD: What the gastroenterologist needs to know

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In patients with inflammatory bowel diseases (IBD) a rising and early onset use of immunosuppressives and biologics is seen in order to control the disease. Most women carry the diagnosis of Crohn’s disease or ulcerative colitis during their reproductive years, hence many of them are exposed to these medications. Therefore, many questions arise in women already pregnant or wishing to conceive about continuation or discontinuation of these therapies, the risk for the newborn and the mother as well as about long-term safety. Consequently, family planning among women under immunosuppressive therapies has increasingly gained importance over the past years. Gastroenterologist should provide detailed preconceptional counseling for women with IBD who are under immunosuppressive and/ or biologic therapy and who wish to become pregnant. Such advice should contain information about the common risk factors for pregnancy, basic risks of neonates’ congenital health problems and “normal” miscarriage and malformation risks in the general population and in IBD. It seems substantial to create awareness that acute exacerbations of IBD during gestation harbor the highest risk for mothers and their unborn children and have to be adequately treated. Questions regarding breastfeeding and vaccinations should also be addressed in the preconceptional setting.

Substances such as 5-aminosalicylic acid, biologics or immunomodulator therapies may be continued during pregnancy and through delivery. Corticosteroids may be utilized as an adjunctive therapy for disease flares, but should be avoided in long-term. Caution is warranted with new drugs like vedolizumab, ustekinumab and especially tofacitinib because of insufficient data carrying out precise embryotoxicological risk assessment. Combination therapy utilizing biologics and thiopurines is discouraged due to increased risk of infection in the infant, methotrexate has to be stopped at least 3 months prior to conception. However, it should be noted that most immunosuppressive therapies in pregnancy are acceptable and that the probability of bearing a healthy child exceeds 90%. Deficient information concerning medical treatments for IBD during pregnancy must by no means indicate a risk-based termination of pregnancy.
Diagnosis and therapy of osteopenia and osteoporosis in inflammatory bowel disease

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Loss of bone mineral density (BMD) is a common feature in patients with chronic inflammatory bowel disease (IBD). In numerous publications from different parts of the world approximately 40–50% of patients show osteopenia (T-score < 1 and > 2.5). A T-score < 2.5, which is the definition of osteoporosis, was measured in 5–37% of IBD patients in several longitudinal studies when measured by dual x-ray absorptiometry (DEXA) in the lumbar spine [1].

IBD patients are predominantly young and premenopausal. There is a variety of reasons causing bone loss in patients with IBD like use of steroids, chronic inflammation itself, malnutrition, hypogonadism and deficits in calcium intake and vitamin D consumption and synthesis.

The diagnosis of osteoporosis is mainly made by dual x-ray absorptiometry (DEXA) which measures overall bone mineral density. Low mineral bone density leads to an increased vertebral fracture risk in these young patients [2].

In cross-sectional studies investigating prospectively cohorts of IBD patients a frequency of 15–22% mostly asymptomatic vertebral fractures have been reported [2]. But there is no linear association between BMD and fracture risk. By adding additional clinical variables the FRAX® score is used in postmenopausal osteoporosis to identify patients with a high risk for fractures. Again in IBD patients the FRAX score is not ideal to identify patients with a high risk of vertebral fracture.

Since bone strength depends not only on BMD but also on bone microarchitecture the measurement of trabecular bone score (TBS) has been used recently to define the risk for vertebral fracture in osteoporosis. In a recent study low TBS identifies patients with more severe forms of Crohn´s disease [3]. If this translates into a higher fracture risk for that special patient group is not clear yet.

IBD patients with decreased BMD should be supplemented with calcium and vitamin D. IBD patients with prevalent fractures and low BMD should be treated with bisphosphonates. Whether patients with osteoporosis and no prevalent fractures should get bisphosphonates is not clearly defined and needs to be determined individually. Very important to avoid bone loss is a consequent treatment of the underlying inflammatory bowel disease [4].

Recently the connection of the gut microbiome on bone health by influence on regulation of the immune system and translocation of bacterial products across the gut endothelial barrier has been increasingly investigated (5). These opens a new field for research into the pathophysiology and possible new therapies for osteoporosis in inflammatory bowel disease.
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**Frequency of inflammatory bowel diseases in patients with ankylosing spondylitis**

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**Background:** Ankylosing spondylitis (AS) is closely associated with inflammatory bowel disease (IBD). Patients with IBD can develop peripheral arthritis (10–20%), sacroiliitis (10–20%) and anterior uveitis (0.5–3%). 5–10% of patients with SpA develop IBD. Crohn’s disease (CD) is more common than ulcerative colitis (UC).

**Materials and methods:** In the analysis were included 36 patients with AS, among them men – 24 (67.7%), woman – 12(33.3%), mean age 37.7 ± 14.8 years, mean disease duration 11.4 ± 8.7 years. All patients were examined with ESR, CRP, esophagogastroduodenoscopy, colonoscopy and quantitative analysis of the FC level using the method of lateral immunochromatography with the BUHLMANN Quantum Blue rapid test. Standard range: 95–1800 µg/g.

**Results:** Most of the patients had a high disease activity, mean BASDAI was 5.6 ± 1.9, ASDAS CRP 4.8 ± 1.5. Thirty patients (83.3%) had FC level > 100 µg/g (15 patients [41.7%] – > 1800 µg/g, 15 patients [41.7%] from 100 µg/g to 1800 µg/g), 6 patients (16.7%) < 100 µg/g. In most cases patients with FC > 100 µg/g showed high CRP level (mean 17.6 mg/l). In 83.3% of patients with a FC level > 1800 µg/g, values of ESR was mean 38.6 mm/h, among them 12 patients (34%) were diagnosed IBD: 7 patients (19.4%) with CD and 5 patients (13.9%) – UC, in the remaining cases (66.7%) was no intestinal pathology.

**Conclusion:** Patients with FC levels > 100 µg/g had high disease activity. In most cases, inflammatory bowel disease was diagnosed in patients with high disease activity and FC levels more than 1800 µg/g.
Primary sclerosing cholangitis (PSC) is a chronic inflammatory, immune-mediated, fibro-obliterative bile duct disease affecting the large and – to a lesser degree – also small bile ducts which ultimately can lead to end stage liver disease requiring liver transplantation. In about 70% PSC is associated with inflammatory bowel disease (IBD) and carries a high risk for malignancy in the hepatobiliary tract and colorectum. Notably, the phenotype of IBD associated with PSC has specific clinical characteristics (‘PSC-IBD’) with a more quiescent or oligosymptomatic course, right-sided pre-dominance with rectal sparing, higher prevalence of backwash ileitis and high colon cancer risk, the latter emphasizing the importance of annual screening colonoscopies in PSC-IBD. In the past, PSC typically developed in patients with known IBD. Today, the sequence is frequently turned around, since clinically more silent PSC-IBD may be diagnosed after PSC. Therefore, work-up of de novo diagnosed PSC should always include an initial colonoscopy even in asymptomatic patients. Patients with PSC without IBD at index colonoscopy should have (3–)5-yearly repeat colonoscopies to detect the possible development of IBD after PSC diagnosis; as soon as PSC-IBD has been established yearly surveillance colonoscopies are indicated.

The close association with IBD supports the hypothesis that the “gut-liver-axis” could play an important role in the pathogenesis of PSC. Homing of gut-primed T-cells from the inflamed gut to the liver could result in immune-mediated bile duct damage. However, the association between PSC and IBD remains challenging with an often remarkable disassociation in timing and severity of their disease courses. On the one hand colectomy (before liver transplantation) does not protect against progression of PSC and IBD can manifest even after liver transplantation. Conversely, removal of the diseased colon before liver transplantation seems to protect against recurrence of PSC, while active IBD or pouchitis after colectomy appear to be risk factors for recurrence. Whether control of associated IBD prevents progression of PSC is still controversial. Experiences with corticosteroids, immunosuppressants and biologicals such as anti-TNF strategies and vedolizumab have so far been disappointing in PSC, with the exception of overlap syndromes with autoimmune hepatitis or IgG4-related disease responding to steroids.

Changes in microbiota (dysbiosis) in PSC are distinct from IBD without PSC (e.g. Veillonella, pore-forming Klebsiella pneumoniae) and may contribute to its pathogenesis together with changes in gut permeability. High levels levels of circulating markers of bacterial translocation are associated with poor prognosis, indicating that ongoing gut leakage of bacterial products could have clinical impact in PSC. In line, various absorbable/systemic and non-absorbable antibiotics have been tested in PSC and shown to improve liver biochemistry, with vancomycin being the most promising agent (particularly in kids), studies with rifaximin and probiotics have been disappointing, recently a FMT pilot study has been also completed. Sulfasalazine (combining a sulfonamide antibiotic with mesalazine) is again receiving attention in studies for treatment of PSC/PSC-IBD since it may not only alter intestinal inflammation and microbiota, but
may also have anti-apoptotic effects in the liver. Notably, microbiota may not only serve as a triggers of liver injury but may also have protective actions. As such the total elimination of intestinal microbiome in germfree mice has been shown to aggravate liver injury in mouse models of fibrosis and PSC. Moreover, alterations in bile composition in PSC could trigger IBD-associated dysbiosis. Since PSC is nowadays diagnosed frequently before IBD, this raises the intriguing question whether alterations in bile acid composition due to cholestatic disorders such as PSC may play a role in the pathogenesis of IBD, possibly turning around the “gut-liver-axis” into a “liver-gut axis”.

Elevated liver enzymes are commonly observed in patients with IBD. Besides PSC, drug-induced hepatotoxicity and non-alcoholic fatty liver disease (NAFLD), nodular regenerative hyperplasia and gallstones are other important hepatobiliary complications in IBD. NAFLD is an emerging epidemic affecting 25–30% of the general population and comprises a disease spectrum ranging from simple steatosis to steatohepatitis (NASH) with development of more advanced liver fibrosis, cirrhosis and cancer. Similar to PSC and IBD, specific changes in gut microbiota and permeability may play a role in its pathogenesis. While NAFLD is not uncommon in the IBD population (similar prevalences as in the general population, but fewer metabolic risk factors than non-IBD NAFLD patients), PSC (but not PBC) seems to be protective against NAFLD. The underlying mechanisms are still unclear, but could involve changes in microbiota and bile acid signaling. Interestingly, NAFLD is less common among patients who received anti-TNF-α therapy.

Ursodeoxycholic acid (UDCA) is the paradigm therapeutic bile acid and its role for medical therapy of PSC is still under debate. Promising novel bile acid-based therapeutic options for both PSC and NASH include 24-norursodeoxycholic acid (norUDCA), a side chain-shortened C23 homologue of UDCA, bile acid receptor/farnesoid X receptor (FXR) agonists (e.g., obeticholic acid, cilofexor, tropifexor) and intestinal FXR-regulated fibroblast growth factor 19 (FGF19) mimetics. Bile acids control intestinal inflammation, gut integrity and microbiota via FXR and part of the therapeutic actions of FXR agonists may also act through modification of gut microbiota. Other nuclear receptors such as fatty acid-activated peroxisome proliferator-activated receptors (PPARs) are also of potential interest and can be targeted by fibrates (PPARα) or elafibranor (PPARα/δ). Furthermore, drugs targeting the gut-liver axis (e.g. integrin blockers, MAdCAM inhibitors, antibiotics) hold some promise, most likely serveral other newer therapeutic options for IBD (e.g. ustekinumab, tofacitinib) will also be tested in PSC. Since PSC, IBD and NASH are complex diseases, combination/sequential therapies may be necessary to achieve full control of disease activity and progression. One of the major challenges will be earlier diagnosis of PSC, prevention of cancer and recognition/appreciation of disease heterogeneity. In this sense PSC become a prime example for personalized (‘P5’) medicine in the near future.
Recommended reading – recent references:

Session VI

Improving outcomes in IBD
Translation from trials into clinical practice: How to find the right patient

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Randomized clinical trials have benefited to IBD patients, who are treated with an increasing number of active drugs. Most clinical trials are funded and conceived by the industry. They compare drugs to placebo in the aim of drug labelling. There are some academic trials, in the field of IBD, but many of them are underfunded and, underpowered. Additionally, in Crohn’s disease (CD), there is only one randomized trial assessing efficacy and safety of surgical resection vs medical therapy (infliximab) whereas in clinical practice, surgery is a major therapeutic tool. There are several differences between randomized clinical trials and clinical practice (Table 1).

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
<th>Randomized trials</th>
<th>Clinical practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly patients, severe comorbidities, stoma, strictures, dysplasia</td>
<td>No exclusion criteria</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Randomized trials</th>
<th>Clinical practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 16 or 48 weeks Histological remission in some UC trials</td>
<td>Long-term Histological remission barely relevant</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Placebo arm</th>
<th>Randomized trials</th>
<th>Clinical practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Never</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Rerandomization of responders</th>
<th>Randomized trials</th>
<th>Clinical practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>In most trials</td>
<td>Never</td>
<td></td>
</tr>
</tbody>
</table>

How do the results obtained in randomized clinical trials apply to patients treated in clinical practice?

There are several strategic trials in IBD. Several of them have shown a better efficacy of combination of anti TNF and azathioprine over monotherapy of each of these drugs. One cluster-randomized trial suggests that late introduction of anti TNF is less efficient than an earlier one, in patients with CD. A recent controlled trial suggests that vedolizumab is more efficient than adalimumab in anti TNF-naïve patients with ulcerative colitis.

Several biomarkers of (non) response to anti TNF have been proposed: TREM, oncostatin M, expansion of IL23 receptor-bearing TNFR2 T cells, number of membrane-bound TNF immune cells. These biomarkers are not available for routine use. Yet, in clinical practice, there are clinical factors that help to find the right drug for the right patient (Table 2).
<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment of choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with strictures and fistula</td>
<td>Surgery</td>
</tr>
<tr>
<td>Patients with strictures and prestenotic dilatation</td>
<td>Surgery</td>
</tr>
<tr>
<td>Complex anoperineal lesions</td>
<td>Anti TNF + azathioprine</td>
</tr>
<tr>
<td>Acute steroid-refractory colitis</td>
<td>Infliximab + azathioprine</td>
</tr>
<tr>
<td>Spondylarthritis</td>
<td>Anti TNF monotherapy or combined with methotrexate, Jak inhibitors</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Anti TNF monotherapy, azathioprine monotherapy</td>
</tr>
<tr>
<td>TPMT deficiency</td>
<td>Avoid azathioprine</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>Avoid methotrexate</td>
</tr>
</tbody>
</table>
The clinical value of combination therapies in IBD

Stefan Schreiber
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Targeted therapies have fundamentally changed our ability to control inflammation in IBD. With introduction of anti-TNF therapies operation frequencies were reduced and many parameters that are synonymous with favorable outcome were positively influenced on a population level. However, in a substantial proportion of patients inflammation control cannot be reached although several targeted therapies are available now.

Combination therapy has been advocated to enhance the speed of induction, augment long-term efficacy or reduce side effects. The most frequently used combination is between anti TNF agents and the oral immune suppressive azathioprine. The use of azathioprine is a mainstay in the escalation of therapies in IBD and if continued while patients progress to the use of infliximab azathioprine can enhance efficacy and reduce immunogenicity of the biologic in CD. In both UC and CD several studies have subsequently documented that combination with azathioprine would reduce anti-drug antibody formation of therapies with infliximab or adalimumab, respectively. This effect is particularly strong in individuals who carry a risk HLA type.

The combination between targeted therapies has not been widely investigated, yet. Case reports of combination were triggered by the presence of different immune-mediated diseases that required both a local, gut specific therapy and systemic immune suppression (e.g. etanercept and vedolizumab in a case with ulcerative colitis and ankylosing spondylarthritis). These combinations were documented as successful and adequate in regards to side effects.

Presently it is unclear whether the next step is the investigation of combinations between targeted therapies or of programmed sequencing of biologics in prospective therapeutic trials. There are good arguments why the latter may be a more promising approach. The evolution of immune resistance can be seen by investigation of molecular markers (e.g. increased expression of IL23 under anti TNF therapies) and clinical events (e.g. manifestation of immune diseases like psoriasis and alopecia areata under anti-TNF therapy). This would advocate programmed sequencing of different, targeted therapeutic principles.
Treatment optimization in IBD

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The availability of biologics and small molecules poses an incisive improvement for the treatment of patients with inflammatory bowel disease (IBD). Nevertheless, treatment success rates defined by mucosal healing are still clearly below 50% highlighting a marked unmet need in the management of Crohn’s disease and ulcerative colitis. Various strategies have been explored recently aiming at the optimization of drugs with a focus on biologics. Clinically and biomarker driven monitoring has been shown to improve endoscopic outcome in ulcerative colitis and Crohn’s disease, respectively, with the CALM study impressively displaying the benefit of a biomarker guided treatment approach. Therapeutic drug monitoring (TDM) of biologics, in particular infliximab and adalimumab, is meanwhile ubiquitously implemented in the clinical routine management of patients with IBD, even though most of the supporting results are associative and not necessarily corroborated by prospective clinical trials. Models predicting serum concentrations of biologics might assist in the proactive utilization of TDM in near future in order to avoid rapid anti-drug antibody formation and loss-of-response. With the increasing number of drug treatments the aspiration of combing compounds with synergistic mode-of actions are arising. Despite the lack of sufficient translational data as rationale for combination treatment, the ground-breaking success from combination of biologics in oncology raises the appetite for similar approaches in patients with IBD. Similarly, the realization of precision medicine in oncology should pave the way for molecular medicine guided personalization of targeted therapies in IBD. First evidence from retrospective and prospective studies in this regard is available.
The dawn of omics: The future of IBD management

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The treatment of the two main forms of inflammatory bowel disease (IBD), Crohn’s disease (CD) and ulcerative colitis (UC), has undergone dramatic changes in the last two decades due to the introduction of biological agents, signaling molecule blockers, and leukocyte homing inhibitors. These new therapies have not only expanded the therapeutic armamentarium for IBD but also benefitted many patients with CD and UC. Notwithstanding these remarkable successes, a significant portion of patients still fail to respond to these new therapies or become refractory to them with the passage of time, requiring switching among the various agents, introducing immunosuppressive therapy or performing surgical interventions. This unsatisfactory situation indicates that we are still far from an optimal management of IBD and that additional progress is needed. Additional progress obviously means new research, but this alone will not be enough unless we also accept and adopt brand new ways of thinking about IBD in a far more comprehensive fashion. Both CD and UC are complex chronic conditions with multiple components, and targeting one cytokine, one receptor, one molecule or one set of microbes at a time will never control IBD in a global and permanent fashion. If so, progress must develop approaches that allow to functionally integrate most, if not all, components of IBD and identify the key molecules that control the so called “IBD interactome”. Integration of complex biological systems demands new thinking and new tools, primarily systems biology-based bioinformatics tools, where single “omics” are first analyzed in great depth, the individual results functionally integrated to create a unified biological picture of disease pathogenesis (the IBD interactome), define in it the “disease module” that controls pathogenesis, and identify the key controllers within the module, which then become the therapeutic targets. Once this is accomplished, these targets can be matched with existing drug databases to find new or known chemical compounds specific for each target (new drugs or repositioned drugs). This “omics”-based approach will not only improve target specificity to an unprecedented level, but will offer an opportunity to zero in and block the molecular mediators that are directly responsible for disease initiation or persistence. To be truly effective this approach will likely need to be applied at an individual level (personalized medicine) or to a group level among patients that share similar IBD systems pathogenesis.
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Poster Numbers 1 – 93
(* = Posters of Distinction)

Author Index to Poster Abstracts
Adherence to therapy inflammatory bowel disease observed in Moscow Clinical Scientific Center

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Introduction: Inflammatory bowel diseases (IBD) are chronic autoimmune inflammatory diseases with intestinal lesions and external manifestations. The concept of permanent life-long medication is the cornerstone in the treatment of IBD. Depending on the dosage regimen prescribed, the patient is injected with a dose and an interval between doses.

Objective: To assess adherence to the treatment of diseases in patients with Crohn’s disease (CD) and ulcerative colitis (UC), observed in the department of inflammatory bowel disease.

Materials and methods: The study included 55 (45.8%) men and 65 (54.2%) women older than 18 years, 70 (58.3%) patients with UC, 50 (41.7%) with CD, who attend treatment and examination in the department of inflammatory bowel diseases. Patient adherence to therapy is evaluated using the Moriska-Green test, the results of which all patients were divided into two groups: the first group – patients with low adherence treatment (LAT); the second group – patients with high adherence to treatment (HAT).

Results: It was shown that patients with high adherence to therapy were 78 (65.0%) versus 42 (35.0%), respectively (p < 0.001). In the group of patients with HAT, women predominate - 26 (61.9%) versus 16 (30.1%) men (p < 0.001). In the group of HAT, patients with CD 30 (71.4%) also prevail against 12 (28.6%) patients with UC (p < 0.001). It was established that in the group of HAT, patients receiving 5-aminosalicylic acid preparations (5-ASA) 23 (54.8%) and biological preparations (BP) – 15 (35.7%) predominate. In the LAT group, patients with the necessary immunosuppressors and glucocorticosteroids prevail – 54 (69.3%), against patients receiving 5-ASA and BP – 24 (30.7%) (p < 0.001). The frequency of exacerbations of diseases was higher in the LAT group – 52 (66.6%), versus 13 (30.9%) in the HAT group (p < 0.001). The frequency of surgical interventions in patients with CD was higher in the LAT group – 15 (75.0%) versus 5 (16.6%) in the HAT group (p < 0.001). A significant difference between the groups was noted when it was possible to obtain drugs in the preferential provision (38.5%) in the HAT group versus 40 (51.3%) LAT groups (p < 0.001). It was shown that the patient has no age, no educational and socio-economic status.

Conclusion: Among patients with IBD, examined in the department of inflammatory bowel diseases, 65% have a low commitment to taking prescribed medications. Low adherence of treatment is associated with factors such as the use of systemic immunosuppressants and glucocorticosteroids in therapy, complications during CD, the frequency of exacerbations of IBD. Female sex is reliably associated with high adherence to treatment, the presence of drugs in the preferential provision.
Small bowel adenocarcinoma as a rare complication of Crohn’s disease: A case report

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²Institute for Translational Medicine, University of Pécs, Medical School, 7624, Pécs, Hungary

Introduction: Inflammatory bowel diseases increase the risk of gastrointestinal malignancies. Colorectal carcinoma is a feared late complication of long-standing ulcerative colitis, similarly the risk of small bowel adenocarcinoma is higher in Crohn’s disease than in the general population.

Case report: We report here two cases of Crohn’s disease accompanied by small bowel malignancy. In the first case, small bowel adenocarcinoma developed after a 4-year history of perianal Crohn’s disease in a 51-year-old woman. When examining the whole gastrointestinal tract, no manifestations of Crohn’s disease were seen, except for perianal and rectosigmoid localisation. The abscess and fistula were successfully managed with surgical therapy, antibiotics, and local and systemic steroids. Three years later, she attended the clinic complaining of upper abdominal pain, bloating, and weight loss. Endoscopy revealed a deep penetrating ulcer in the proximal duodenum with stenosis, histology verified adenocarcinoma. The patient underwent a Whipple procedure and postoperative adjuvant chemotherapy. After 4 years of observation, the patient was symptom-free, the follow-up examinations did not show recurrence or the signs of an active Crohn’s disease.

The second case is a 41-year old male, who was diagnosed with ileal Crohn’s disease 10 years ago. He had been lost to follow-up for years and was not on medical therapy. Six months ago he presented the clinic with abdominal pain, vomiting, and weight loss. Intestinal obstruction was diagnosed, caused by a long, irregular small bowel wall thickening in the terminal ileum. Acute surgery (ileum resection and appendectomy) was required. The histology verified G2 adenocarcinoma (pT4 pN1 cM0). Although chemotherapy was indicated, the patient proved to be ineligible due to impaired wound healing and progressive jaundice caused by lymphoglandular metastasis.

Discussion/Conclusion: Small bowel adenocarcinoma is a rare complication in Crohn’s disease with a poor prognosis. Our cases underline the importance of effective disease management and regular surveillance in Crohn’s disease.
A 2-year follow-up study assessing bone status in children with inflammatory bowel disease using dual-energy X-ray absorptiometry

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²Clinical Hospital No. 1 Zabrze, Poland
³Student’s Scientific Society SUM in Katowice, Poland

Introduction: The purpose of this study was to assess the bone status in children with inflammatory bowel diseases (IBD) using dual-energy X-ray absorptiometry (DXA) at baseline and after two years of adequate treatment.

Methods: Sixteen children (six boys) with IBD, aged 13.4 ± 2.4 years, were examined at baseline and two years later. DXA was used to assess bone mineral density (BMD) and reference data were provided by the device’s manufacturer (Hologic Explorer, USA).

Results: Mean Z-scores for TB- and s-BMD were significantly below zero for both, baseline and follow-up (-2.61 ± 0.99 and -2.48 ± 0.88 for TB, and -1.83 ± 1.33 and -1.61 ± 1.19 for s-BMD, respectively), and did not differ significantly between the two time-points. The changes in time of TB Z-score and body weight Z-score correlated positively (r = 0.63; p < 0.01). There was a negative correlation between the baseline nutritional status and the activity of the disease.

Conclusions: BMD was found to be lowered in comparison to normative data both at baseline and follow-up, although no further deterioration was observed during 2-year follow-up period. Proper treatment and monitoring of IBD children may allow to keep a similar trend in the development of bone tissue as in healthy children.
Analysis of demographic and clinical features of IBD in Saint-Petersburg

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Introduction: The information about the prevalence, incidence and distribution of the IBD forms in world is limited and one of the tool is patients monitoring using registry. The main goal of our registry was to estimate the prevalence and types of IBD in St. Petersburg (Russia) and the secondary aim was to ascertain the outcome of IBD patients and predictors of outcome.

Methods: The registry of IBD patients is maintained electronically. The personal data and information about the disease are entered to the registry including CDAI or DAI, endoscopic data, lab tests and treatment regimens.

Results: Since 2017 Jan to 2018 Nov 973 patients with IBD were included to the registry: UC – 62.4% (n = 607) and CD – 7.6% (n = 366). The ratio of UC/CD was 1.7. The age of the patients with UC was from 20 to 75 y.o. and for CD - from 16 to 72 y.o. The average duration from the onset of symptoms to the verification of diagnosis for CD was 2 years and for UC – 0.95 years. For UC the analysis of distribution of the patients depending on the extent of inflammation detected the largest group – left-sided colitis – 60.5%, extensive colitis – 31.6% and proctitis – 7.9%. Distribution of the patients with CD depending on location of CD: the largest group was with terminal ileitis – 48.2%, ileocolitis – 29.9% and colitis – 21.8%. UC patients were in remission in 16.2%, with mild activity in 35.3%, moderate activity in 45.7% and with severe activity in 2.9% of cases. Patients with CD were in remission in 51.6%, moderate activity in – 39.2%, severe activity – in 9.2% of cases. Register is a dynamic process. Patients make regular visits every 3–6 months. In the cell of such a patient, new data on disease activity and information about laboratory tests are added. This makes it possible to assess the dynamics of the flow in an array of patients whom we observe in a specialized IBDs site. For example, in dynamics we can see a reduction in the number of patients with severe and moderate attacks of ulcerative colitis. Among patients with CD, the proportion of patients in remission and the mild form of the disease increased over the year. The number of patients with anemia among both CD and UC has decreased.

Discussion/Conclusion: The data of the registry allows to estimate the prevalence of IBD, the distribution depending on the extent of inflammation for UC and location of CD as well as the activity of the process in dynamics according to monitoring. Maintaining of the registry allows to estimate the efficacy and safety of different treatment regimens, the quality of medical care in various forms of IBD, depending on the severity of the disease, the presence of extraintestinal manifestations, complications, to assess outcome of IBD patients and to clarify predictors of outcome.
Efficacy and safety of thioguanine in IBD

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Introduction: Thioguanine (TG) is an effective treatment in inflammatory bowel disease (IBD), however, safety concerns have been risen due to reported (hepato) toxicity. We assessed the long-term efficacy and safety of TG in patients who were intolerant or resistant to conventional therapy.

Methods: Retrospective chart study of IBD patients who failed conventional thiopurine therapy, and were subsequently treated with TG between 2011 and 2018. Clinical remission was defined as Harvey-Bradshaw Index < 5 for CD and Simple Clinical Colitis Activity Index, without corticosteroids initiation during therapy. TG failure, withdrawal and adverse events were recorded. Biochemistry, liver biopsy, ultrasound and MRI data were followed up.

Results: 87 patients were included of whom 49 had Crohn’s disease, 36 had ulcerative colitis and 2 had IBD-unclassified. Median dose of TG was 40 mg/day, and median duration of follow-up was 37 months. Clinical response at 6 months was seen in 63/87 (72%). 36 (46%) patients were still using TG at final follow-up. Median survival time was 52.4 months. NRH was diagnosed in one (1.1%) patient on liver biopsy. Flares occurred in 10 (12%) patients and side-effects occurred in 23 patients (26%). Corticosteroids were initiated during TG use in 10 (11%) patients.

Discussion/Conclusion: TG is well-tolerated in IBD patients who failed conventional thiopurines therapy. Low dosage of TG is effective in IBD and patients remain on remission for a long time. NRH is not common in patients on low dose TG.
Risk factors for decreased bone mineral density in inflammatory bowel disease in a Tunisian cohort

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Introduction: Patients with inflammatory bowel disease [IBD] are at risk for metabolic bone disease. Many studies have identified various risk factors but most of them have involved western patients. The aim of this study was to investigate the prevalence and the risk factors for metabolic bone disease in Tunisian IBD patients.

Methods: Retrospective study including patients with IBD admitted in our department between January 2014 and December 2017. Demographic and clinical characteristics of patients were analyzed. Bone mineral density of the femoral neck, total femur and lumbar spine was quantified by dual-energy X-ray absorptiometry.

Results: Among 82 patients followed for IBD (70.7% with Crohn’s disease; 29.3% with ulcerative colitis), a bone densitometry was performed in 56% of cases (n = 46). 16 patients have osteopenia and 7 had osteoporosis, as assessed by T-score. Univariate analysis showed that Crohn’s disease in particular ileal disease, high steroid dose and the presence of extraintestinal manifestations were significantly associated with a low bone mineral density (for all p < 0.05). In the other hand, IBD duration since diagnosis, sexe, tabagism were not associated with bone loss. In multivariate regression analysis, risk factors for decreased bone mineral density were IBD duration since diagnosis, high steroid dose, ileal Crohn’s disease and extraintestinal manifestations.

Conclusion: In our Tunisian cohort of IBD patients, Crohn’s disease, high steroid dose and extraintestinal manifestations were associated with increased risk for metabolic bone disease. High risk patients should be identified and appropriate therapies should be started early to improve long-term quality of life.
Factors associated with non-adherence to medication for inflammatory bowel disease: A monocentric Tunisian study

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Introduction: Adherence is generally associated with improved treatment outcomes. Risk factors for non-adherence must be understood to improve adherence. The aim of our study is to determine which variables were consistently associated with non-adherence to treatment in inflammatory bowel disease (IBD).

Methods: Retrospective study including patients with IBD receiving maintenance medication and followed in our department between 2014 and 2018. We assessed a range of adherence behaviors. Demographic, clinical, and psychosocial characteristics were also assessed by chi 2 test. Adherence was considered as a continuous variable and then categorized as high or low adherence for logistic regression analysis to determine predictors of adherence behavior.

Results: Forty eight per cent of the patients reportedly adhered to their treatment. In univariate analysis, factors associated in dependently with low adherence in IBD patients were age younger than 30 [odds ratio: 2.519 (95% confidence interval: 0.837–7.576), p = 0.042], low socioeconomic condition [2.5 (0.813–8.134), p = 0.039], active smoking [0.148 (0.045–0.489); p = 0.001], male gender [0.148 (0.45–0.489); p = 0.001] and patients under immunosuppression [2.7 (0.768–8.136); p = 0.0123]. In multivariate analysis, factors associated independently with low adherence in the IBD population were age under 30 (p = 0.075), low socioeconomic condition (p = 0.049), active smoking (p = 0.000) and male gender (p = 0.001).

Conclusion: Approximately half of the IBD patients were low adherers. Predictors of low adherence were aged younger than 30 years, low socioeconomic condition, active smoking and male gender.
Abdominal ultrasonography in differential diagnosis of concurrent ulcerative colitis and diverticular disease

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Introduction: The percentage of patients with ulcerative colitis who develop colonic diverticulosis is still subject to debate. Currently, transabdominal ultrasonography (US) both with low-frequency convex probe and high-frequency linear probe is commonly used method for diagnosis and follow-up in patients with colonic inflammation.

Methods: We present two cases in female patients with known UC (62 years with history of UC pancolitis for more than 30 years and 35 years with history of left-sided UC for 8 years) and colonic diverticula of sigmoid colon, endoscopically diagnosed during routine follow-up colonoscopy with no endoscopic signs of diverticulitis and on maintenance therapy with 3.0 5ASA.
Both were manifested with episodes of left sided acute crampy abdominal pain, fever and elevated WBC and CRP.
Within 12 hours of the symptoms onset transabdominal ultrasonography was performed. The US findings in both patients included thickening of the bowel wall, hypoechoic diverticulum, echogenic stercolith with distal shadow, thickened mesenteric fat, but no free fluid.

Results: We concluded that those findings were associated with acute uncomplicated diverticulitis rather than UC flare.
The patients were treated with parenteral ciprofloxacin and metronidazole with favorable clinical outcome. Transabdominal ultrasonography and follow-up showed signs of reversal of inflammation and recovery.

Discussion/Conclusion: Diverticular disease and UC may concur, but they still represent separate risks for bowel inflammation.
Transabdominal bowel ultrasonography is noninvasive, safe and reliable diagnostic tool to distinguish possible causes of bowel inflammation and to avoid unnecessary endoscopy. Adequate treatment is a challenge due to difficult differential diagnosis.
Extraintestinal manifestations in inflammatory bowel disease – Results from a retrospective study

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Introduction: Patients with inflammatory bowel disease (IBD) often develop one or more extraintestinal manifestations (EIM). The most common EIM are manifestations at the level of musculoskeletal system, followed by skin involvement and ocular damage.

Methods: We performed a retrospective case-control study, which included 517 patients with IBD from Northeastern Romania. The Montreal classification was used to classify IBD by phenotype and to localize intestinal inflammation.

Results: In the study group, 51 cases with IBD and EIM were identified, having a prevalence of 9.9%. EIMs occurred with a higher frequency in patients diagnosed with CD than UC (52.9% vs. 47.1%) (p < 0.001). The most common EIM were musculoskeletal manifestations (7.4%), followed by renal manifestations (2.2%), cutaneous manifestations (1.2%), ocular (0.6%) and hepatobiliary manifestations (0.2%). Peripheral involvement – arthritis (n = 26; 68.42%) predominated, followed by axial damage – SI/AS (n = 12; 31.58%) (p = 0.001). All cases with ocular manifestations also showed peripheral articular manifestations – arthritis. Pyoderma gangrenosum was more common in CD patients than in UC cases and was associated with articular manifestations. PSC was highlighted in 1 patient with UC and did not associate other EIM. Renal manifestations occurred with a higher frequency in CD and were associated with the presence of other EIM.

Discussion/Conclusion: In the N-E region of Romania, the EIM prevalence in patients with IBD was 9.9%, being relatively low compared to other geographical areas. Compared with UC cases, patients with CD had a risk of over 3 times greater to develop EIM. Of all EIM, musculoskeletal manifestations proved to be the most frequent, also in CD patients. CD cases showed more frequently articular manifestations, pyoderma gangraenosum, uveitis and oxalic nephrolithiasis, while in patients with UC there was a higher ratio of PSC.
Non-invasive assessment of endoscopic activity in ulcerative colitis

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Introduction: Ulcerative colitis (UC) is a chronic, idiopathic and recurrent inflammatory bowel disease (IBD), characterized by periods of activity and remission whose monitoring requires invasive explorations associated with discomfort for the patient and important costs. Mucosal healing became one of the most important therapeutic targets in UC.

Methods: The aim of our study was to identify a score, made up of noninvasive, available, used in current clinical practice biochemical markers, which should correlate with endoscopic activity in UC. We conducted a prospective study on 114 patients with UC. All patients were assessed both for biological inflammatory markers: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fibrinogen, platelets, albumin, ferritine, fecal calprotectin (FC) and by colonoscopy to estimate the endoscopic activity using Mayo score. By linear regression, we tried to identify a biochemical score correlated with endoscopic activity.

Results: Out of the serological markers, ESR (p = 0.014), CRP (p = 0.021) and fibrinogen (p = 0.035) correlated with the endoscopic activity of the disease. The best sensitivity to determine the endoscopic activity was given by FC (96.05%) with a negative predictive value of 91.1% (p = 0.001). The score determined by linear regression: 1 (ESR > 15 mm/1 h) x 0.305 + 1 (fibrinogen > 340.5 mg/dl) x 0.309 + 1 (CRP > 5 mg/l) + 1 (calprotectin > 200 μg/g) had an increased positive predictive value compared to each and one biomarker, but with a sensitivity and specificity inferior to that of FC.

Discussion/Conclusion: Further studies are required, which should identify a non-invasive biomarker (or that combination of biomarkers), with high sensitivity and specificity, with reduced variability, replicable, that should be accessible for a proper evaluation of endoscopic activity in UC.
Anemia and iron deficiency in inflammatory bowel disease

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Background: Anemia is a complication commonly found in inflammatory bowel disease (IBD) with a great impact on the patient’s quality of life. The diagnosis and therapy of anemia has become one of the most challenging fields in the clinical IBD practice. The frequent cause of anemia is iron deficiency. Less common causes of anemia include deficiency of vitamin B12 and folic acid.

Materials and methods: We conducted a retrospective, observational study over a period of two years, in which we included 65 patients hospitalized in a tertiary center in North-Eastern Romania, between January 1st 2017–December 31st 2018. Each patient was evaluated clinically, endoscopically, histopathologically and blood tests were performed. We define anemia according with WHO criteria, hemoglobin level < 13 g/dl in male and < 12 g/dl in female. We analyzed the prevalence and main causes of anemia in patients with IBD in our geographical area.

Results: Ulcerative colitis (43 – 66.15%) was more frequent compared to Crohn’s disease (22 – 33.84%) in our study and males were mostly affected (29 – 67.44%). Anemia was found in 25 (38.46%) patients, more frequently in patients with Crohn’s disease (17 – 68.18%) versus patients with ulcerative colitis (20 – 46.51%) and was associated with high incidence of hospital admission. Iron deficiency anemia was present in 17 (68%) cases, followed by vitamin B12 deficiency in 5 (20%) cases and folic acid deficiency in 3 (12%) cases.

Conclusion: Anemia is an important extraintestinal manifestation that often is overlooked and decrease quality of life in IBD patients more than the disease itself. Therefore, special attention is needed to improve the quality of care, adequate treatment and proper follow-up to avoid consequences of iron deficiency anemia. Adequate treatment has a major impact on the patient and implicitly on society. To decrease the occurrence of anemia in patients, further studies are required to establish accurate treatment.

Keywords: inflammatory bowel disease, iron deficiency anemia
Clinical presentation of inflammatory bowel disease in hospitalized patients: A retrospective study in a tertiary center in Eastern Europe

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Introduction: Inflammatory bowel disease (IBD) is a global disease and an important socio-economic burden with great impact on quality of life in affected patients. Numerous studies provided a wealth of information regarding the clinical characteristics of IBD in European population. Our aim was to assess the demographic and clinical characteristics of IBD patients in a tertiary center in Eastern Europe.

Methods: We conducted a study between November 2017 and December 2018 in which we included patients with Crohn's disease (CD) and ulcerative colitis (UC) hospitalized in the department of Gastroenterology and Hepatology at St. Spiridon Hospital, Iasi. Clinical and demographic data were collected and analyzed.

Results: 70 patients were included in the study, 47 had UC, 23 had CD, out of which 40 female (57%), 30 male (43%), mean age 42.28 years (21–75 years). In UC, 7 (14.8%) had proctitis, 26 (55.1%) were diseased to the splenic flexure and 13 (27.6%) had extensive colitis. Three patients had articular manifestation; one (4.3%) had pyoderma gangrenosum. Out of 23 CD, 17 (73.9%) had affected ileum; 8 (11.4%) had colonic disease; 4 (17.3%) had ileocolonic disease. In the CD lot the behavior of the disease was different depending on the duration and progression in time, 16 (69%) patients with less than 5 years from the first onset of the CD had non-stricturing and non-penetrating form in comparison with those who had more than 10 years of disease progression 3 (13%) stricturing and one (4.3%) with penetrating form.

Discussion/Conclusion: Although this study included a small number of patients, it shows similar characteristics of IBD to that in the West of Europe but there are some differences regarding the extraintestinal manifestations. Our data contributes to the general understanding of ethnic and geographic distribution of IBD.
Prevalence and factors associated with impaired food-related quality of life: A cross-sectional survey of 1223 people with inflammatory bowel disease

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Introduction: Inflammatory bowel disease (IBD) patients often report that dietary intake and the enjoyment of food is affected by their condition. However, the prevalence of impaired food-related quality of life (FR-QoL) and associated factors have not been previously explored. This study aimed to determine the levels of FR-QoL and factors associated with it in a large, nationally representative sample of people with IBD.

Methods: A convenience sample of 1576 IBD outpatients ≥16 years old were recruited from seven UK centres. Patients consuming the majority of their intake as food completed previously validated questionnaires to capture demographic data, FRQoL-29, quality of life (IBDQ UK), IBD-distress (IBD-DS), IBD-fatigue (IBD-F), and anxiety and depression (HADS). A health professional recorded disease activity (HBI, SCCAI), disease classification (Montreal), blood results, body mass index and malnutrition risk (MUST). FR-QoL was regressed onto the explanatory variables (univariable/multivariable) using the Stata MI (20 imputed datasets) procedure.

Results: Data from 1223 patients were available (78% response, 65% CD and 51% female). FR-QoL mean score was 80.1 [SD 26.9] (minimum 29, maximum 145, higher score = better FR-QoL), considerably lower in comparison to previously measured healthy volunteers [123.0, SD 16.5]. The four items rated as the most severe (Strongly agree/Agree) were ‘avoiding food and drink I know does not agree with my IBD’ (71%), ‘being more aware of what I am eating due to my IBD’ (70%), ‘certain foods have triggered symptoms of my IBD’ (69%) and ‘enjoyment of a particular food or drink has been affected by the knowledge that it might trigger my IBD symptoms’ (67%). Twenty-six factors (demographic, clinical, drug-related, psycho-social) were significantly associated with impaired FR-QoL in univariate analysis. However, in the multivariable regression only lower educational level (p < 0.001), greater number of IBD flares in last two years (p < 0.001), more severe symptoms during last flare (p = 0.034), not taking immune suppressants (p = 0.026), greater distress (p < 0.001), greater fatigue impact on daily living (p = 0.025) and worse IBD QoL (p < 0.001) remained significantly associated with impaired FR-QoL.
**Discussion/Conclusion:** In this first large study reporting FR-QoL in IBD, many factors were identified as having a significant negative effect on patients with IBD. Understanding the relationship between IBD and FR-QoL may improve communication between health professionals and patients regarding its impact.
Clinical factors predictive of Crohn’s disease complications and surgery

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Introduction: The natural history of Crohn’s disease is one of progression over time to structural complications of the gastrointestinal tract (strictures and fistulae) requiring hospitalizations and surgeries. Given the difficulty in predicting which individuals will progress to complications, identifying risk factors for surgery would facilitate classification of patients and tailor therapy accordingly. The aim of this study is to identify risk factors predictive of surgery during Crohn’s disease.

Methods: We conducted a retrospective study including all patients followed for CD over a 5-year period. We included 93 patients.

Results: Sex ratio was 0.8 with a mean age of 42 years. Forty patients were smokers. Of the overall population of patients, 21 patients had an ileal involvement, 19 a colonic localization and the 53 remaining an ileocolon location. The behavior of the disease was inflammatory, structuring, penetrating and structuring and penetrating in respectively 48, 21, 14 and 10 patients. 49 patients were treated with azathioprine, 3 with 6-mercaptopurine and 21 with anti-tumour necrosis factor [TNF] agents. 20 patients were treated with no immunomodulator or biologic therapy over their disease course. 36 patients underwent surgery during follow-up. Risk factors for surgery were: smoking, ileal location, penetrating disease and an ileal involvement > 20 cm.

Discussion/Conclusion: In our study, risk factors for surgery were smoking, ileal location, penetrating disease and an ileal extensive CD. An identification of these factors would necessary for a better management by indicating an early use of immunosuppressants and biologic drugs altering the natural history of the disease.
Features of gut dysbiosis in ulcerative colitis patients

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Introduction: Recent studies indicate a significant role of gut microbiota in the pathogenesis of inflammatory bowel diseases. The aim of our study was to identify key markers of dysbiosis in ulcerative colitis (UC) patients.

Methods: Fecal samples obtained from 78 UC patients as well as 96 healthy volunteers (control group) were used for analysis. Whole-genome sequencing was performed using the SOLiD 5500 W platform (Life Technologies, Foster City, CA, USA).

Results: An increase in the representation of bacteria of Proteobacteria (3.84 ± 6.75)% and Bacteroidetes (37.84 ± 25.55)% phyla and decrease in the abundance of bacteria of Firmicutes (50.82 ± 21.80)% phylum compared to the control group – (1.85 ± 5.33)%, (24.29 ± 20.54)%, (65.22 ± 19.67)%, respectively (p = 0.0012, p = 0.0013, p = 0.000061) was found in UC patients. The second sign of dysbiosis is a lower alpha-diversity index both in acute stage – (2.11 ± 0.44) and remission of UC – (2.1 ± 0.35) compared to the control group – (2.79 ± 0.40), p = 0.028. The third sign is a decrease in the relative amount of Methanobrevibacter smithii and Methanobrevibacter unclassified in UC patients – (0.90 ± 3.33)%, (0.39 ± 1.71)% compared to the control group – (0.99 ± 2.33)%, p < 0.05. The fourth sign is a decrease in the representation of butyrate-producing – (17.61 ± 13.21)% and hydrogen-utilizing bacteria – (3.60 ± 6.48)% compared to the control group – (27.11 ± 15.96)%, (5.94 ± 7.57)%, respectively (p < 0.05). The fifth sign is metabolic dysbiosis with increased representation of 219 metabolic pathways in UC patients comparing to the control group (p < 0.05).

Discussion/Conclusion: The identified changes of gut microbiota composition can be the causal factor of inflammatory response and increased intestinal permeability in UC patients and should be taken into account in development of personalized UC treatment.
Ulcerative colitis in children: From diagnosis to treatment

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Introduction: The incidence of ulcerative colitis (UC) in pediatric population is rising and children often present with a more severe disease compared to adults. Early diagnosis and treatment of this disease could prevent late complications and improve the quality of life.

Methods: Retrospective study of children with UC was conducted at the University Hospital Split, Croatia.

Results: Twenty-seven children with UC were enrolled. Age of patients at time of diagnosis was 13.84 years. Only two children had early onset disease (younger than 10). Positive family history to autoimmune disease was found in 26%. For most children first symptom was bloody diarrhea (41%) and abdominal pain (22%). The mean time from onset to diagnosis was 2.23 months. According to PUCAI more than two thirds of children had moderate disease at time of diagnosis. More than half of these children had anemia, 80% of them had high CRP and 60% had high ESR, 41% had reactive thrombocytosis and only 13% had hypoalbuminemia. All analyzed children had fecal calprotectin level more than 50 µg/g (15/15) and 80% had vitamin D insufficiency. In only three children Clostridium difficile was isolated from stool. According to colonoscopy 52% children had pancolitis. There were no significant differences among children with pancolitis or distal or left sided UC according to anemia, reactive thrombocytosis, PUCAI or level of inflammatory markers. First line of treatment in most children was 5-aminosalicylic acid (45%) and combined with systemic corticosteroids (34%). Cyclosporine was added in 4 children (3 with moderate and 1 with severe disease).

Discussion/Conclusion: In all children with bloody diarrhea, abdominal pain, anemia and elevated inflammatory markers and calprotectin an inflammatory bowel disease should be excluded.
**Sustainability of biologic therapies is less in UC than CD patients independent of prior biologic experience**

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**Introduction:** Treatment of Inflammatory bowel disease (IBD) with biologics is usually effective but may be discontinued due to inadequate response or adverse effects. Few studies have examined what determines the sustainability of treatment in a real world setting.

**Methods:** To determine the factors which determine sustainability of biologics therapy we performed a single centre retrospective study of a prospectively maintained database of n = 4200 IBD patients. Patients were subdivided on whether they had ulcerative colitis (UC + IBD-U included) or Crohn’s disease (CD), whether they were biologic naïve versus experienced when they received a particular biologic therapy. Our primary end point was time to discontinuation of biologic (due to inadequate response or adverse effects) in biologic naïve patients (Group 1) and biologic experienced patients (Group 2) depending whether they were diagnosed with UC or CD. The impact of immunomodulator co-therapy and other disease characteristics was examined.

**Results:** A total of 765 patients were identified with complete data and included in our analysis. Median follow-up was 1.77 years.

**Group 1:** 539 patients were in our biologic naïve group. 117 (21.71%) were treated with infliximab (IFX), 375 (69.57%) with adalimumab (ADA). 15 (2.78%) were on vedolizumab (VD). 32 (5.94%) were on golimumab (GB). 32 (5.94%) had UC. 347 (64.4%) patients have CD. Median time to discontinuation was 2.84 years in UC which was significantly shorter than in CD patients with median time to discontinuation of 3.59 years (p = 0.000) (Table 1, Graph 1).

**Group 2:** 226 patients were in our biologic experienced group. 79 (35%) were treated with IFX, 53 (23.45%) with ADA, 28 (12.4%) with VD. 28 (12.4%) were treated with GB, 38 (16.81%) with ustekinumab (UST). 74 (32.74%) had UC. 149 (65.93%) had CD. Median time to discontinuation in UC was 2.58 years compared to 3.83 years in CD (p = 0.010) (Table 1, Graph 2). No significant differences in time to biologic discontinuation were observed between biologic naïve and biologic experienced treatments.

<table>
<thead>
<tr>
<th></th>
<th>UC</th>
<th>Median time to discontinuation</th>
<th>CD</th>
<th>Median time to discontinuation</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Total (n= 765)</td>
<td>269</td>
<td>2.68</td>
<td>496</td>
<td>3.504</td>
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</tr>
<tr>
<td>Biologic naïve (n= 539)</td>
<td>192</td>
<td>2.84</td>
<td>347</td>
<td>3.59</td>
<td>0.000</td>
</tr>
<tr>
<td>Biologic experienced (n= 226)</td>
<td>74</td>
<td>2.58</td>
<td>149</td>
<td>3.83</td>
<td>0.010</td>
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Table 1: Median time to discontinuation
Discussion/Conclusion: Our real world data indicate that the sustainability of biologic treatment is less in UC than in CD patients and is not strongly determined by prior biologic exposure. These findings are important in determining how biologic therapies are employed in both IBD subtypes and suggest the need for new non-biologic/small molecules to demonstrate their relative sustainability as IBD therapies.
Oral manifestation in inflammatory bowel disease

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Introduction: Crohn’s disease (CD) and ulcerative colitis (UC) belong to the group of chronic inflammatory bowel diseases (IBD). Although IBD primarily affects the intestinal tract, extraintestinal manifestations of the disease are often apparent, including in the oral cavity, especially in CD. Specific oral manifestations in patients with CD are as follows: indurate mucosal tags, cobblestoning and mucogingivitis, deep linear ulcerations and lip swelling with vertical fissures. The most common non-specific manifestations, such as aphthous stomatitis and angular cheilitis, occur in both diseases, while pyostomatitis vegetans is more pronounced in patients with UC. Non-specific lesions in the oral cavity can also be the result of malnutrition and drugs. Oral manifestations of CD patients may be present in 8–29%.

Case report: We report the case of 10 year boy with perianal Crohn’s disease who is treated in the Public Clinical Hospital in Gastroenterology Department from December 2017. Additionally patient presented symptoms of mucogingivitis from beginning of the disease. Because of this oral manifestation the patients was consulted by a dentist. The gingiva were edematous, granular, and hyperplastic without ulceration. The symptoms were so serious that they caused difficulty with drinking, eating and caused child’s suffering. In addition to infliximab (IFX) therapy that has been applied due to perianal Crohn’s disease we also administered the patients cinnamate- and benzoate-free diet and corticosteroid mouthwash. Despite the disappearance of intestinal symptoms after 6 months therapy, symptoms of mucogingivitis were still present. After the consultation with gastroenterologist, we jointly decided to include immunosuppressive treatment – methotrexate. After two months of therapy, we received clinical improvement.

Conclusion: Infliximab and methotrexate may be a promising treatment for the mucogingivitis associated with Crohn’s disease.
Ulcerative colitis: Age-related differences

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Introduction: The ulcerative colitis (UC) is a chronic disease with extremely varied clinical manifestations. The purpose of the study was to assess the impact of age on the phenotype and activity of UC.

Methods: It is a prospective study that included 105 patients hospitalized between January 2017–December 2018. We have noted: age, sex, area of origin, status smoker/nonsmoker, presenting symptoms, presence of inflammatory syndrome, the extension of lesions, severity, treatment, complications, need for surgery. All the patients were examined by colonoscopy and diagnosis of UC was confirmed histologically. The activity of the disease was quantified using Truelove and Witts clinical score of: mild, moderate and severe.

Results: Patients were divided into 3 groups according to age: group 1: 51 patients ≤ 40 years, group 2: 36 patients, 41–64 years and group 3: 18 patients ≥ 65 years. Characteristics of extreme groups were followed by age (young < 40 years and elderly > 65 years), to clarify whether there are significant differences between them on UC behavior. At the time of diagnosis 48.5% were younger than 40 years and 17.15% had more than 65 years. In both groups were predominantly men from urban area. The smoking status was more common in younger patients than elderly, but no statistically significant differences (18/51 vs. 6/18, p = 1). Regarding the symptoms of debut, in the young prevailed diarrhea (younger vs. older 41.8% 58.8%, p = 0.09), and in the elderly frankly bloody diarrhea (41.1% vs. 66.67% young, p = 0.089). Proctitis was met in 2.94% of the cases (only in the elderly), left-sided colitis as 71.1% – more frequently in young (52.17% vs. 18.8%) and pancolitis 26% of cases (29.4% vs. 16.66%, p = 0.36). As severity, there is a significantly large number of moderate-to-severe forms of the young versus elderly (60.8% vs. 13.04%, p = 0.028). In all patients had received aminosalicylates, 14.49% is the only therapy during follow-up, all elderly patients. The necessary of introducing the immunosuppressive therapies (corticosteroids) and biological therapy was increased in young people with moderately severe forms of disease (corticosteroids: 47.05% vs. 16.67%, p = 0.0270; biological agents: 23.52% vs. 5.55%, p = 0.0279).

Discussion/Conclusion: A more aggressive phenotype with extensive localization of lesions and more severe activity was seen in younger patients. They had an increased need for steroids and biological therapy. Elderly patients experienced mild forms, with limited extension of the lesions, and the majority were able to remain in remission only with salicylates.
The use of faecal calprotectin as a screening tool for referral of patients with possible inflammatory bowel disease

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Introduction: Faecal calprotectin (FC) has been shown to have high sensitivity and specificity for differentiating between Inflammatory Bowel Disease (IBD) and functional gastrointestinal disorders. However, there are different thresholds for interpreting FC results. The National Institute for Health and Care Excellence (NICE) therefore proposed the role of an intermediate range for values with Turvill et al. suggesting a cut off of > 100. At Chesterfield Royal Hospital, no intermediate range has been determined. The purpose of this study was thus to analyse FC results and referral outcomes to discover if using a cut off value of > 100 was adequate in diagnosing IBD.

Methods: A retrospective analysis was conducted for all patients in Chesterfield who had a FC requested by their GP between July and December 2017. The notes of those referred and seen in clinic were then analysed.

Results: 498 patients had a FC performed by their GP. 107 patients were seen in clinic with 9 diagnosed with IBD. If a cut off value for FC > 100 were used for these patients; 42 of them would have been referred with 6 being diagnosed with IBD. 65 would not have been referred but 3 would have IBD, giving a sensitivity of 66.67% (95% CI: 29.93–92.51%) and a specificity of 63.27% (CI: 52.93–72.78%).

Discussion/Conclusion: Our study has shown that using a cut off value of > 100 for FC will result in a lower sensitivity and specificity when compared to data from other groups. However, a larger cohort of patients will need to be retrospectively analysed to determine whether a cut off value for FC of > 100 should be used or if it should be lowered in order to improve sensitivity and specificity in diagnosing patients with IBD within our region.
Clinical characteristics of inflammatory bowel disease associated to Hidradenitis suppurativa

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Introduction: Hidradenitis suppurativa (HS) is a chronic inflammatory skin disorder of the hair follicle characterized by recurrent, painful nodules, abscesses, and sinus tracts. Small studies have linked bowel disease (IBD). We performed a retrospective study to further characterize IBD patients diagnosed with HS in a single center and to compare their clinical characteristics with published data.

Methods: A total of 23 patients with HS and IBD were identified in our center. Clinical and demographic relevant characteristics were obtained through extensive review of the health records.

Results: Twenty-three patients diagnosed with HS and IBD were identified (56.5% women, mean age 27.09 ± 11.17 years and 69.6% were diagnosed with Crohn’s disease). Montreal classification of Crohn’s disease patients was: L1: 31.3% and L2–L3 62.6%; B1 87.5%, B2 12.5% and B3 12.5%. A total of 11 patients had been operated related to IBD: 7 (63.6%) for perianal disease and 4 (36.6%) underwent bowel resection. The most common localizations affected by HS were axillary 11 (47.8%), inguinal 6 (26%), perianal 1 (4.3%), inguinal plus perianal 1 (4.3%), axillary plus inguinal 1 (4.3%), axillary plus perianal plus submammary 1 (4.3%) and scrotum 1 (4.3%). Patients were divided by Hurley’s classification into three categories: 10 (43.5%) as Hurley I, 11 (47.8%) Hurley II and 2 (8.7%) Hurley III. A total of 14 patients (60.9%) underwent surgery related to HS. Eleven patients (47.8%) were current smokers, 3 (13%) former smokers and 9 (39.1%) non-smokers. Thirty percent of the patients had overweight.

Discussion/Conclusion: Overweight and smoking, risks factors shared by patients with HS and IBD, are presented in 30–50% of our series of patients. HS is more frequent in Crohn’s disease patients with colonic involvement. This association should be taken into account in IBD patients with these clinical characteristics due to its implications in differential diagnosis of perianal Crohn’s disease and treatment.
Microbiota composition as a possible predictor of infliximab response in inflammatory bowel disease

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Introduction: Although the association of IBD pathogenesis with genetic factors has been established, the impact of intestinal microbiota is currently an emerging direction of research. Despite the efficacy of anti-TNF treatments, non-responders are frequent, and no predictive factors of patients’ outcomes have been identified. Our goal was to investigate patterns of intestinal microbiota composition in IBD patients before and after Infliximab treatment.

Methods: We performed 16S rDNA sequencing of colonic biopsies from Crohn’s disease (CD) and ulcerative colitis (UC) patients before and 30-weeks after Infliximab treatment and from healthy age-matched controls. Disease activity was evaluated endoscopically and defined using the Mayo and CDAI scores. Sequencing output has undergone quality control and closed OTU picking (greengenes 13.8, QIIME 1.9). To find associations between infliximab usage/response and microbial taxa, downstream analysis was performed for the top 3000 most abundant taxa using various individual and disease groupings before and after treatment. All diversity and statistical tests were performed using Calypso v8.84. α-diversity was calculated using the CHAO1 metric, β-diversity was calculated and visualized via Canonical Correspondence Analysis (CCA) and differential taxa abundance was performed using ANOVA and DESEQ2 (where applicable).

Results: CD and UC patients before treatment versus controls present different enterotypes. Overall a-diversity was reduced after treatment regardless of response, but non-responders showed additional loss of biodiversity. CCA showed clear distinction in the enterotypes of responders versus non-responders. At phylum level statistical (p < 0.05) taxonomical analysis shows increase of Acidobacteria and decrease of Bacteroidetes and Euryarchaeota in IBD non-responders, whereas, at genus level 65 taxa were found to be differentially abundant.

Discussion/Conclusion: Our findings suggest the existence of cross-influence between infliximab treatment and intestinal microbiota. Gut microbiome analysis can support the assessment of therapeutic response in IBD and microbiota composition can act as a potential biomarker.
Intestinal permeability in Crohn’s disease: Are there any age-related differences?

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Aim: To assess possible differences in intestinal permeability (IP) in patients with Crohn’s disease (CD) according to the age at diagnosis (Montreal classification).

Methods: Thirty-two patients with active CD were divided into two groups: the “younger” group (n = 18; 6 female, 12 male), diagnosed before 40 years of age (mean age 29.33 ± 8.76) and the “older” group (n = 14; 10 female, 4 male) – after 40 years of age (mean age 52.77 ± 8.15). The disease location and behavior, estimated using Montreal classification, were similar for both groups. Twenty-three age-matched healthy persons also divided in two groups were used as a control group. IP was assessed by using a contrast medium iohexol (Omnipaque), which was administrated orally (25 ml, 350 mg/ml) 2 hours after breakfast. Three and six hours later serum iohexol concentrations (SIC mg/l) were determined by a validated HPLC-UV technique.

Results: All permeability tests were well tolerated and no side effects were reported. The mean values of SIC for “younger” group of CD patients at 3 h (3.41 ± 0.75 mg/l) and at 6 h (3.66 ± 0.67 mg/l) post-ingestion were higher than those in the “older” group (2.73 ± 0.58 mg/l and 2.68 ± 0.67 mg/l, respectively) and then those in the age-matched control groups (1.43 ± 0.29 mg/l and 1.14 ± 0.19 mg/l, respectively), but the differences were significant only with the control groups.

Discussion/Conclusions: Our results indicate that the IP disturbances in patients with CD, assessed by iohexol test, were not influenced significantly according to the aging. Although our data have to be confirmed with large scale trials, they suggests similar morphological and immunological changes in the intestinal mucosa in patients of both age groups.
Latent tuberculosis infection in IBD patients receiving treatment with anti-TNF-α agents in an endemic region

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Introduction: Newly acquired or reactivated latent tuberculosis infection (LTBI) is a major impediment in initiating or maintaining biologic therapy in IBD patients. The aim of this study was to evaluate the effectiveness of the prophylactic treatment and the rate of reactivation of LTBI in an endemic region for TB.

Methods: We retrospectively reviewed all IBD patients of the Department 1 of Gastroenterology treated with anti-TNF-α between Dec 2017–Dec 2018. The anti-TNF-α agents of choice were infliximab (IFX) and adalimumab (ADA). The rate and type of adverse events, frequency of LTBI, rate and time to reactivation and time to anti-TNF-α reinitiation were noted. LTBI was diagnosed based on IGRA test and chest X-ray.

Results: A total number of 116 patients were included (70.68% with CD, 29.31% with UC). Ileocolonic location (48.78%) and inflammatory pattern (45.12%) were predominant in patients with CD, as pancolitis was predominant in patients with UC (58.82%). IFX was the anti-TNF of choice in 59.48% of cases. Adverse events occurred in 18 patients on anti-TNF-α (15.5%). The most frequently encountered were allergic reactions (50%), followed by infections, including newly acquired tuberculosis (27.7%). 21 patients (18.1%) were diagnosed with LTBI. All received prophylactic treatment with isoniazid 1 month prior to anti-TNF start dose that continued to a total time of 9 months. Reactivation of LTBI occurred in 4 patients (19.04%) previously diagnosed and treated completely (1 with ADA). The median time of follow-up for LTBI reactivation was 1.6 years. The mean time to reactivation was 10.2 months for IFX and 12.1 months for ADA. Anti-TNF was stopped and treatment for active TB was initiated in all patients. Anti-TNF was reinitiated in 80% of cases, after a median time of 8.5 months.

Discussion/Conclusion: Rate of LTBI is higher in endemic countries but reactivation of the disease can be efficiently reduced with a correctly made diagnosis and prophylactic treatment, leading to rates of reactivation that are only slightly higher than the ones reported in non-endemic regions.
Psychological distress and sleep disorders in IBD patients – Potential correlations with disease activity

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Introduction: Several clinical characteristics contributing to poor patient reported outcomes have been studied in IBD patients. The aim of this prospective observational study was to identify the impact of psychological symptoms and sleep quality on patients’ outcome and identify potential correlations with disease activity.

Methods: Patient reports on depression, anxiety and sleep quality were collected using the Hospital Anxiety and Depression Scale (HADS) and Pittsburgh Sleep Quality Index (PSQI), respectively. HADS scores of 8 or higher were considered abnormal and the considered cut-off for PSQI was 5. Patient demographics, anamnestic data and disease characteristics were also collected: age, sex, IBD phenotype. Disease activity and biochemical parameters (regarding the inflammatory syndrome, anemia, nutritional deficits) have also been evaluated.

Results: 42 IBD patients were enrolled. 47.6% were female, 40% had Crohn’s disease, 21.5% had active disease. 71.4% reported poor sleep quality based on PSQI score. Among patients with active disease, high PSQI scores were correlated with clinical disease activity (r = 0.86, p < 0.01), but not with biological parameters reflecting inflammatory syndrome (r = 0.29, p < 0.01). However, higher PSQI scores were not significantly associated with awakenings related to disease activity (pain, nocturnal stool emission). High depression and anxiety scores were present in 40.4% and 52.3% of the patients. Sleep impairment was associated with poorer outcomes regarding anxiety and depression scores in the study group (r = 0.68, p < 0.05). Psychological distress and poor sleep quality were associated with greater fatigue reported by patients as main complaint at patients’ interview.

Discussion/Conclusion: Sleep disorders are frequently associated in IBD patients, even during remission. Psychological symptoms are often unaddressed during patient evaluations, although early intervention should represent a potential target in managing IBD patients. Both improving sleep quality and addressing patients for psychological support and therapy are valuable resources for an integrative IBD patient care.
Epidemiology and clinical course of inflammatory bowel disease in Romania: A multicenter-based study

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Introduction: The incidence of IBD during the years in Romania was on the rise, but epidemiologic data is missing. The aim of this study was to define the characteristics of IBD, the phenotype among the patients from Romania.

Methods: We conducted a prospective study on a period of 12 years, from 2006 to 2017. All patients diagnose with IBD based on clinical, radiological, endoscopic and histological features were included. All data were collected from the IBD prospect database.

Results: A total of 2663 patients were included in this database, but only 2312 were included in the final analysis, with all data available. 959 had Crohn’s disease (CD), 1303 had ulcerative colitis (UC) and 50 IBD-undetermined. 1077 were female and 1235 were men. Mean age was 43.5 ± 15.9. Female to male ratios were 1.05:1 for CD, 1.08:1 for IBD-undetermined but 0.75:1 for UC. Mean age at diagnosis was 45.5, 41.6 and 42.9 years for UC, CD and IBD undetermined, respectively, p = 0.8. 43.6% of the CD patients have had moderately severe disease, 51.1% of the CD patients have had moderately severe disease and 50% of IBD-undetermined patients. Extraintestinal manifestations were present in 15%, 25% and 16% of CD and UC and IBD-undetermined patients, respectively, p = 0.78, in which peripheral arthralgia and arthritis being the commonest. 15.5% needed biologic therapy for remission in CD patients, 2.4% in UC patients and 0.6% in IBD-undetermined, p < 0.001.

Discussion/Conclusion: In Romania there is a predominance of UC and female gender among IBD. For age at diagnostic, disease severity and extraintestinal complications between the phenotypes there were no significant differences between phenotypes. CD needed more induction with biological therapy than UC and IBD-undetermined.
Regional differences in IBD in Romania

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Introduction: Inflammatory bowel disease (IBD) represents an inflammatory disorder of the gastrointestinal tract that includes ulcerative colitis (UC), Crohn’s disease (CD) and undetermined IBD. The aim of this study was to analyze the differences between the Romanian regions regarding the IBD.

Methods: The study was conducted in 10 University Centers from Romania. We included all patients diagnosed with IBD based on clinical, radiological, endoscopic and histological features. The population was demographically similar in all centers. Variables collected included age, gender, date of diagnosis, family history, smoking status. We divided the country into 8 regions: West, South-West, South, South-East, Center, Bucharest, North-West, North-East and analyzed the differences between them.

Results: Out of 2312 patients, we found 25% cases of IBD in North-East (408 UC, 152 CD, 10 UNDET), 21% cases in Bucharest (197 UC, 270 CD, 5 UNDET), 12% cases in West (133 UC, 151 CD, 5 UNDET), 11% cases in Center (183 UC, 73 CD, 7 UNDET), 10% in South (111 UC, 113 CD, 10 UNDET), 8% in South-East (78 UC, 105 CD, 3 UNDET), 8% in North-West (138 UC, 42 CD, 8 UNDET) and 5% in South-West (56 UC, 53 CD, 4 UNDET); p < 0.01. When we compared the IBD patients between the 8 regions of Romania we found that there are significant differences between them, regarding gender distribution (p < 0.01), number of cases (p < 0.01), IBD distribution (p = 0.03), complications (p = 0.01) and age (p < 0.001) and phenotypes (UC p < 0.001, CD p < 0.01).

Discussion/Conclusion: The region with the most IBD cases was North-East 25% and the region with the less IBD cases was South-West 5%. Regarding the phenotypes, the most UC patients were found in NE 31.3%, and the most CD patients were found in Bucharest 28.1%. There were significant differences regarding the IBD-undetermined patients between all regions.
Incidence, endoscopic features, risk factors and prognosis of Crohn’s disease involving upper gastrointestinal tract in China

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Background: At present, the clinical understanding of the upper gastrointestinal tract involvement of Crohn's disease (CD) is relatively unclear worldwide: (1.) The upper digestive tract involvement of CD is immensely different (2–75%), (2.) There is no unified endoscopic diagnostic or grading criteria for upper digestive tract involvement of CD, (3.) There are few large or case-control studies.

Objective: Retrospective cohort study was conducted to analyze CD’s upper digestive tract involvement rate, endoscopic features and severity of upper digestive tract involvement, and correlation factors and prognosis of upper digestive tract involvement in Crohn’s disease.

Methods: De novo CD patients in Shanghai Ruijin Hospital from 2014 to 2016 were continuously enrolled. The diagnostic criteria were in line with the consensus opinions on diagnosis and treatment of IBD in China. Patients should be consented to receive gastroscopic and upper gastrointestinal pathological examinations. Patients with Helicobacter pylori infection, NSAIDs administration or reflux esophagitis were excluded. The diagnostic criteria for CD in the upper digestive tract in this study were the endoscopic and pathological features of CD in the upper digestive tract proposed by Japanese scholar Atsushi in 2014. The severity scoring was determined by the Upper Gastrointestinal Simple Endoscopic Score for Crohn’s disease (UGI-SESCD), which was proposed by Ledder in 2012. According to the above diagnostic and scoring system, subjects were divided into upper gastrointestinal involvement group (UGI+) and non-upper gastrointestinal involvement group (UGI-). The incidence of upper digestive tract involvement, the endoscopic characteristics and severity of UGI+ group were first analyzed. Secondly, the risk factors of CD involvement in the upper digestive tract were obtained by Logistics multivariable analysis. Finally, Kaplan-Meier method was used to describe the survival curves and 3-year surgery free and complication free survival was analyzed between the UGI+ and UGI- group.

Results:
1. Baseline characteristics: 76 subjects were included in the study, and 50 were male, with the age range between 12 and 60 years old. Most of the patients were with moderate disease.
2. The incidence of upper gastrointestinal tract involvement and endoscopic characteristics: 46 patients had 68 positive endoscopic lesions (60.5%) during gastroscopy, involving the stomach, duodenum and esophagus. Endoscopic characteristics were diverse, including ulcers (45.6%), protruded lesion (25%), bamboo joint-like appearance (20.6%), stricture (5.8%) and fistula (2.9%). The gastric fundus bamboo joint-like appearance was the most common upper gastrointestinal endoscopic manifestation (20.6%), followed by duodenal bulbar ulcer (17.6%) and duodenal bulbar protruded lesion (14.7%). According to the UGI-SESCD score, the UGI+ group had a score ranging from 2 to 10, and most patients presented mild to moderate diseases.
3. Upper digestive tract involvement risk factors: univariate analysis indicated that male, age less than 25 years old, height > 170 cm, and ileocolonic lesions were risk factors of upper digestive tract involvement. Further multivariate analysis showed that male (p = 0.008, OR = 4.32, 95% CI: 1.45–12.84) and ileum involvement (p = 0.003, OR = 2.67, 95% CI: 1.41–5.09) were independent risk factors for CD upper gastrointestinal involvement. There was no correlation between the presence of upper gastrointestinal symptoms and CD involvement (p > 0.05).

4. Prognostic analysis: the median follow-up time was 38.5 months (27–60 months), there was no significant difference upon 3-year surgery free and complication free survival between the UGI+ and UGI- group. The 3-year complication free survival rate of UGI- group, UGI+ without duodenal bulb group and UGI+ with duodenal bulb group were 88.9%, 87.9% and 68.0%, respectively (p = 0.013). Among them, the 3-year complication free survival rate of UGI+ with duodenal bulb involvement was significantly lower than that of UGI- and UGI+ CD upper digestive tract involvement in non-duodenal bulb group (p = 0.015).

**Conclusion:** Upper digestive tract involvement is not rare in CD patients at first diagnosis. Endoscopic manifestations are various, some of which are characteristic, such as protruded lesion and bamboo joint-like appearance manifestations, while others are non-specific ulcers. Although the endoscopic manifestations of CD involvement in the upper gastrointestinal tract are common, the severity is mainly mild to moderate. Gastroscopy should be performed for all newly diagnosed CD patients regardless of the symptoms of upper gastrointestinal tract, especially for male and patients with ileocolonic diseases. In general, there was no significant difference between UGI+ and UGI- patients in terms of prognosis, but when the duodenal bulb was involved, the surgical and complication rates were significantly increased. Therefore, aggressive treatment should be given to these patients as soon as possible to improve the prognosis.
Patient perception and approval of fecal microbiota transplantation (FMT) as an alternative treatment option for ulcerative colitis

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

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

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

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

Conclusion: For the majority of the UC patients surveyed FMT represents a feasible, already high profile treatment option. Approximately half of the questions would consider FMT as an alternative treatment option, even in spite of a satisfactory disease response to current standard therapies. Unsurprisingly there are concerns in regard to the transmission of possible infectious agents as well as to the hygienic implementation of FMT itself.
Evaluation of CD83 with correlation between anti-apoptotic markers in Crohn’s disease

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Introduction: CD83 is a marker of mature dendritic cell. The dendritic cells play an important role with response for immune system. Bcl-xl is a transmembrane molecule in the mitochondria. It is one of several anti-apoptotic proteins which are members of the Bcl-2 family of proteins. Bcl-xl overexpression contributes to carcinogenesis by protecting tumor cells from death. The study objective was the immunohistochemical assessment of the expression of the apoptosis-regulating proteins Bcl-xL and CD83 expression in Crohn’s disease.

Material and method: Our study was performed on 35 patients with Crohn’s disease. Standard immunohistochemical technique was adopted to detect the expression of CD83 and Bcl-xL. The protein expression was evaluated by two independent pathologies.

Results: CD83 expression was found in 90% patients with Crohn’s disease. The increasing of number of dendritic cells (CD83) was observed especially in inflamed tissue. The expression of Bcl-xL protein was observes in cytoplasm of epithelium cells. Increased expression of Bcl-xL were found in dysplastic crypts.

Conclusion: In our study we observed response from immune system by increasing expression of CD83 in mucinous of lamina propria in Crohn’s disease with dysplastic cells Bcl-xL positive.
Crohn’s and Colitis Pregnancy Knowledge score (CCPKnow score) evaluation in women with inflammatory bowel disease: Preliminary results of a Tunisian study

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Introduction/Objectives: Inflammatory bowel disease (IBD) usually develops at a young age, and many women experience marriage, pregnancy and delivery during the disease course. The management of such a chronic pathology can be improved by a better patients understanding of their disease.

The aim of our study is to evaluate the pregnancy-related knowledge of women with IBD in Tunisia, and to investigate the associated factors.

Material and methods: Women followed for IBD in consultation were administered a questionnaire comprising 17 questions from the validated Crohn's and Colitis Pregnancy Knowledge Score (CCPKnow) which assess knowledge level about pregnancy and childbirth among these patients. Demographic and epidemiological data were collected as well as the CCPKnow score. Factors associated with CCP knowledge (poor vs. adequate) were determined using non-parametric tests. Data analysis was performed using SPSS software.

Results: Twenty women were included with a mean age of 42 [23–72]. Half of patients had Crohn's disease. The average CCPKnow score of the twenty patients was 3.55. Most of the patients exhibited a poor knowledge level: it was poor (0–7) in 85% of cases and adequate (8–10) in 15% of cases. The main lack of knowledge concerned disease transmission questions: 85% of women answered incorrectly to all points. The majority of patients (80%) answered incorrectly to the questions about: drugs effect on pregnancy, breastfeeding and the question about ano-perineal disease. Among surveyed patients, 55% answered correctly at least one question about disease impact on pregnancy. There was no correlation between a good CCPKnow score and education level (p = 0.59), nor IBD type (p = 0.5). A statistically significant link has been found between the duration of disease progression (> 6 years) and a CCPKnow score adequate (p = 0.031). Higher household income was significantly associated with an appropriate level of pregnancy-related knowledge (p = 0.04).

Conclusion: Preliminary results of our study show that more than three-quarters of women with IBD had a poor level of pregnancy-related knowledge. A general education program should be conducted by gastroenterologists in order to raise patients awareness about this matter and thus improve IBD management during pregnancy.
Withdrawal of thiopurines in Crohn’s disease treated with scheduled adalimumab maintenance: A prospective randomized clinical trial (DIAMOND2)

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Background: The risk:benefit ratio of concomitant use of thiopurines with scheduled adalimumab (ADA) maintenance therapy for Crohn’s disease is controversial.

Aim: To study the influence of withdrawal of thiopurines in patients in remission with combination therapy in an open-label, randomized, controlled trial (DIAMOND2; UMIN UMIN000009596).

Methods: Patients in corticosteroid-free clinical remission (CFCR) for ≥ 6 months with ADA (40 mg, s.c., every other week [e.o.w.]) scheduled maintenance combined with thiopurines were randomized to continue (Con) or discontinue (Dis) thiopurines, whereas all patients received scheduled ADA maintenance therapy for 52 weeks. The primary endpoint was the proportion of patients who had CFCR at week 52. Secondary endpoints were mucosal healing, trough levels of ADA in serum, and safety.

Results: Fifty patients were randomized to Con or Dis groups. The Crohn’s disease Activity Index (p = 0.866), Simple Endoscopic Score for Crohn’s Disease score (p = 0.450), and serum C-reactive protein (CRP) level (p = 0.694) at baseline were not significantly different between groups. CFCR prevalence at week 52 was not significantly different between groups (log-rank, p = 0.704). Prevalence of endoscopic remission at week 52 was not significantly different between groups (p = 1.000). Trough levels of ADA in serum were not significantly different between groups (p = 0.515). The proportion of patients with AAA positivity at week 52 was not significantly different (p = 0.437). No serious adverse effects were observed in either group.
**Conclusion:** Continuation of thiopurines > 6 months offers no clear benefit over scheduled ADA monotherapy. CFCR, endoscopic activity, and ADA trough level at week 52 were not significantly different between groups (UMIN000009596).

**Key words:** Crohn’s disease, adalimumab, thiopurines
Therapy experiences among patients with inflammatory bowel disease-related iron deficiency anemia – A real life study

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Background: The leading cause of anemia in patients with inflammatory bowel disease (IBD) is iron deficiency. The aim of our study was to evaluate the therapeutic approach of iron deficiency and delivery either intravenously for iron ferric carboxymaltose (FCM) and iron-sucrose complex (IS) or oral preparations for iron deficiency anemia associated with IBD.

Methods: We retrospectively analyzed patients with IBD-related iron deficiency anemia, hospitalized in a tertiary center in North-Eastern Romania between January 1, 2018 through December 31, 2018. Diagnosis of IBD was established based on endoscopic and histological findings, with biologically documented anemic syndrome (Hb < 13 g/dl for males and < 12 g/dl for females, MCV < 78/fl, MCH < 27/pg, iron status – sideremia < 50 mcg/dl).

Results: The study included 42 patients with IBD-related iron deficiency anemia, mainly males (29 – 69%), with mean age 44.8 ± 12.8 years. Twenty (47.61%) patients had severe anemia (Hb < 8 g/dl) and received i.v. iron preparations in the form of iron-sucrose complex (13 – 65%) or ferric carboxymaltose (7 – 35%), and the remaining 22 (52.38%) patients received oral iron preparations. For all patients, the mean value of hemoglobin at admission was 8.2 ± 1.1 g/dl, with lower value in patients requiring i.v. iron preparations. Nine (40.9%) patients with oral iron administration had adverse effects (headache – 3, nausea – 5, constipation – 1) while 6 (30%) patients with i.v. preparations had headache (4 – 66.6%) and injection site reactions (2 – 33.3%). Mean hemoglobin value at discharge was 12.4 ± 1.3 g%, with no significant differences (p = 0.063) between patients receiving either i.v. or oral preparations.

Conclusion: Most patients with IBD-related iron deficiency anemia required parenteral iron preparations. Intravenous administration represented a more rapid achievement of Hb with significantly lesser adverse effects compared to oral administration.

Keywords: inflammatory bowel disease, iron deficiency anemia
Correlation of fecal calprotectin with clinical and endoscopic findings in patients with ulcerative colitis (UC)

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Introduction: Fecal calprotectin (FC) has been shown in many studies as a good biomarker in the diagnosis and monitoring of patients with UC. The aim of our study is to correlate the FC values with the clinical index of the Truelove-Witts and Mayo endoscopic activity score (MES) before and after 6 months of initiating therapy with mesalazine preparations.

Methods: At the Department of Gastroenterology with Endoscopy Hospital Prijedor from May to December 2018, we conducted a retrospective study that included 20 patients with UC (12 men and 8 women average age of 41.16 years). We have all assigned a MES and FC that we repeated after treatment with mesalazine preparations for 6 months.

Results: According to Truelove-Witts clinical index, 10 patients (50%) had mild disease, 7 patients (35%) with moderate difficulty, and 3 patients (15%) with severe disease.
According to Mayo endoscopic scores: Ei0: 0 patients, Ei1: 9 patients (45%), Ei2: 9 patients (45%), Ei3: 2 patients (10%).
Fecal calprotectin (ELISA) ranged from 74 micrg/g to 595 micrg/g.

At the control for 6 months there is a reduction of FC from 35.6% to 43.2%.
12 patients achieved clinical remission (60%), 6 with mild disease (30%), 2 with medium difficulty (10%) and 0 patients with severe form.
Mayo score in 15 patients (5 patients rejected the colonoscopy) Ei0: 4 patients (26.6%), Ei1: 7 patients (46.6%), Ei2: 4 patients (26.6%), Ei3: 0 patients.

Discussion/Conclusion: Significant clinical and endoscopic improvement was noted in all patients with significant reductions in FC. Fecal calprotectin correlates well with the clinical activity of the disease as well as endoscopic findings and can be recommended for monitoring disease activity and response to therapy.
The effectiveness of combination therapy mesenchymal stromal cells and certolizumab pegol in perianal lesions in Crohn’s disease

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Introduction: Perianal fistulas are common types of fistulas in Crohn’s disease (CD). They are difficult to treat, worsen the quality of life of the patient and increase the risk of intestinal resection. Despite the significant effect of anticytokine therapy of fistula form of CD, treatment of this category of patients remains a difficult task, with a high risk of relapse of CD. Mesenchymal stromal cells (MSC), which have immunomodulatory properties and high regenerative potential, are currently also used for the treatment of fistula CD and perianal fistulas of other etiology.

Objective: To compare the effectiveness of combined therapy (local and systemic administration) of bone marrow MSC, the effectiveness of combined therapy of MSC (local administration) and certolizumab pegol (CZP) according to the scheme and monotherapy of CZP according to the scheme of the frequency of healing of simple perianal fistulas in CD.

Materials and methods: 54 patients with CD with perianal lesions were divided into three groups depending on the method of therapy. The 1st group of patients aged 19 to 58 years (Me-29) (n = 18) received the culture of MSC systematically according to the scheme and locally: 40 million MSC – 4 injection points of 1 ml of physiological solution containing 10 million MSC were administered along the perimeter of the fistula. Then, after 4 and 8 weeks, 40 million MSC were re-introduced into the fistula area. The second group of patients with CD (n = 18) aged 20–68 years (Me-36) received MSC locally and anticytokine therapy with CP according to the scheme. The third group of patients with CD (n = 18) aged 20 to 62 years (Me-28) received anticytokine therapy for CZP according to the scheme. The dynamics evaluated the complete closure of the external opening of the fistula. Ano-and rectosigmoscopy was performed 2, 6 and 12 months after the start of therapy.

Results: After 2 months in the 1st group of patients the healing of simple fistulas was observed in 7/18 (38.9%), in the 2nd group the healing of simple fistulas in 14/18 (77.8%) (OR = 5.5; 95% CI: 1.28–23.7; p = 0.043 in comparison with the 1st group). In the 3rd group – 6/18 patients (33.3%) (OR = 0.26; 95% CI: 0.07–0.97; p = 0.019 in comparison with the 1st group).

After 6 months in the 1st group receiving MSC, the healing of simple fistulas persisted in 6/18 (33.3%), in group 2nd 14/18 (77.8%) (OR = 7.0; 95% CI: 1.59–30.8; p = 0.019 in comparison with the 1st group). In the 3rd group - in 5/18 patients (27.8%) (OR = 9.1; 95% CI: 1.99–41.45; p=0.008 in comparison with the second group).

After 12 months in the 1st group receiving MSCS, the healing of simple fistulas persisted in 8/18 (44.4%), in the 2nd group – in 15/18 (83.3%) (OR = 6.2; 95% CI:
1.33–29.43; p = 0.038 in comparison with the 1st group). In the 3rd group – in 7/18 patients (38.9%) (OR = 7.857; 95% CI: 1.65–37.4; p = 0.017 in comparison with the 1st group).

**Conclusion:** Combined cell and anti-cytokine therapy of CD with perianal lesions promotes more frequent and prolonged closure of simple fistulas, compared to MSC monotherapy and CZP monotherapy.
In-hospital profile of patients with inflammatory bowel diseases

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The aim of the research was to evaluate the IBD patients' response to therapy in a referral center in Kazakhstan.

Introduction: The main types of treatment, including biologicals are partially covered by the Kazakhstan’s government. Since anti-TNFs were available only in the hospital, all patients ought to be hospitalized (not only with relapse, but those who need to receive maintain treatment).

Methods: In a cross-sectional setting, we evaluated 202 patients with the IBD diagnosis during the period of 2015 to 2018. The related probable treatment outcomes were tested.

Results: During the capture period, 148 with UC and 54 with CD were admitted. The median age was 38.5 years. Overall, mesalazine received 99.3% UC and 92.6% CD patients. With immunosuppressants were 44% of all patients. Corticosteroids were recommended in 68.2% UC and 61.1% CD. The number of steroids complications (refractory or dependency) was 18.8%. Anti-TNFs had prescribed in 28.7% in UC and 12.3% in CD. During 4 years period non-medical switch was in 8.1% UC and 5.6% CD cases with following loss of response (Fisher's exact test, FET, p = 0.040). Partial response was evaluated in patients received infliximab original (FET, p = 0.009), infliximab biosimilar (FET, p = 0.044), golimumab (FET, p = 0.044). Tuberculosis in anti-TNFs had been reported in 0.99% (both CD patients). The all-cause mortality was 1.98% and associated with high level of CRP (likelihood ratio test = 8.98, df = 2; p = 0.011). Two patients had fulminant UC, in cases of CD patients were overlapped with end-stage of liver cirrhosis due to primary biliary cholangitis or autoimmune hepatitis.

Discussion/Conclusion: The result of switch due to non-medical reasons was poor outcome. The most serious complication of treatment with anti-TNFs is tuberculosis in our region. In same time, delayed access to early aggressive therapy had increased mortality rate.
Efficacy of vaccination against hepatitis A in inflammatory bowel disease patients: A single-center cohort study

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Introduction: Inflammatory bowel disease (IBD) patients are vulnerable to viral infections. The aim of the present study was to investigate the efficacy of vaccination against hepatitis A virus (HAV) in a single center cohort of IBD patients.

Methods: Consecutive IBD patients were screened for HAV status and those not immunized with an age < 60 years received the respective vaccine (Havrix, GlaxoSmithKline®, Brentford, UK, 1 ml, two doses, one at baseline and the second 6–12 months after the first dose). Immune response was defined as a positive anti-HAV IgG measured at least 3 months after the 2nd dose.

Results: 356 IBD patients (females: 40.2%, Crohn’s disease [CD]: 52.2%, median [IQR] age at diagnosis: 42.2 [27.8–56.2] and age: 50.0 [33.5–63.1] and disease duration: 2.7 [0.4–9.1] years at study entry) have been prospectively examined as of January 2010. In total, 115/356 (32.3%) were eligible for anti-HAV vaccination with the rest being either actively or passively immunized before IBD diagnosis. So far, 82/90 (90.1%) have adequately responded to vaccination. Interestingly, anti-HAV IgG turned out positive in 12/21 patients (57.1%) already after the first dose. Ulcerative colitis was associated with a greater success of anti-HAV vaccination (OR = 1.8 [1.5–2.2], p = 0.01, all patients with a negative post-vaccination anti-HAV IgG titre had CD). Patients receiving anti-TNF alpha agents responded less to vaccination (OR = 0.04 [0.00–0.24], p < 0.0001) and those not receiving any kind of immunosuppressive therapy responded better (OR = 9.7 [1.1–81.3], p = 0.015).

Conclusion: Two thirds of our IBD patients are already immunized against HAV before diagnosis. Response rate to vaccination is strikingly high in the rest and especially in UC patients. One dose can provoke immunization, a critical condition in selected cases where rapid introduction of immunosuppressants is warranted. Anti-TNF alpha agents seem to influence vaccination success rate. These results need to be verified in other cohorts.
Feasibility of laparoscopic surgery and minimal invasive radiologic technics in the treatment of complications of Crohn’s disease

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Introduction: 70–90% of Crohn’s disease patients require surgical intervention during their lifetime. 10–15% of the operations are urgent, only 6–8% are laparoscopic. The goal is to choose the most optimal surgical treatment. With help of CT scan and minimal invasive radiologic techniques, maybe we could raise the rate of laparoscopic procedures. Based on our experiences we have analyzed feasibility, role and results of minimal invasive techniques.

Methods: We have analyzed data of our department’s 78 patients operated for complications of Crohn’s disease, from 2009 to 2018, retrospectively. The ten years period was divided for two 5 years to compare. Feasibility, technique, role, results of the minimal invasive radiologic and laparoscopic technique and open procedures were examined on the basis of our surgical treatment of Crohn’s disease.

Results: Our operations were mostly emergency cases, in septic condition and the diagnosis in 20% were unknown. Mostly, the intraoperative finding were multivisceral inflammation or abscess. Two third of patients were medically treated, even so complication occcured. Important for diagnosing the fast CT scanning. Often two steps operations were only feasible, with temporarily stoma. In most cases, we are unable to carry out invasive radiologic or laparoscopic surgical intervention. Evolution of radiologic interventions and laparoscopic techniques resulted raising the number of laparoscopic operations (11) and US-guided abscess drainages (4), in last years. Laparoscopic operations were done: in stenosis (6) stenosis and fistula (2) stenosis and abscess (1). We have performed: laparoscopic hemicolectomies /right (8), left (1)/, and 2 laparoscopic appendectomies – in which histologic examinations showed Crohn’s disease. The laparoscopic operations have better results and quicker recovery for patients then open surgery.

Discussion/Conclusion: In our practice, prevalence of Crohn’s disease and rate of surgical treatment of complications are not decreased, rather increased. The radiologic intervention and laparoscopic surgical techniques were feasible only in selected cases, but increasingly and with good results. In stenotic cases elective laparoscopic operations are recommended with good results and quicker recovery then open surgery.
Perceived acceptability towards long-term use of oral nutritional supplements (ONS) in adolescent and adult Crohn’s disease

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Introduction: Evidence mainly from Japan suggests replacing 35–50% of food intake with enteral nutrition “partial enteral nutrition” (PEN) can prolong disease remission and increase drug effectiveness in CD. This study explored the acceptability of PEN by looking at perceived ease of use, benefits and barriers and organoleptic ratings of ONS.

Methods: A cross sectional feasibility study was conducted over 16 weeks. Patients with confirmed CD were recruited from a gastroenterology outpatient clinic using convenience sampling. Full ethical approval and informed consent was obtained. Five ONS samples were rated using a hedonic rating scale followed by completion of a questionnaire based on the preferred ONS. All questions except barriers rated good (> 0.7) for internal consistency using Cronbach equation (Bland, 1997)

Results: 60 patients 37.4 years (± 17.2) 33 males were recruited. There was little or no correlation between overall impression and demographic, nutritional status and PTC score respectively. Ensure plus milkshake rated highest for all organoleptic qualities (p < 0.05) and was the preferred ONS in 46.7% of patients. Main perceived benefits of PEN were assurance of nutrient intake (86.4%), convenience (76.7%), weight maintenance (84.5%) and improved energy levels (71.4%). Perceived barriers related to taste fatigue (74.1%) and reduced pleasure from eating and drinking (63.8%). Liking and perceived ease of use significantly correlated to confidence to consume ONS for ≥ 12 months (p < 0.01). Confidence of ONS consumption was 73.4% at 3 months which dropped to 51.6% and 28.4% at 6 and 12 months respectively. 56.7% of patients would consider PEN as a treatment option which didn't highly correlate to predicted length or volume of consumption.

Discussion/Conclusion: Despite high perceived benefits of PEN confidence in long term consumption is low with high perceived taste fatigue. Research looking at actual rather than perceived ONS usage would further validate these findings.
The role of microRNAs in S1P-dependend signaling axis in a different phenotypic presentation of ulcerative colitis in patients with primary sclerosing cholangitis (PSC)

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Introduction/Aim: A sphingosine-1-phosphate (S1P), a product of sphingosine kinases (SphKs) which act via S1P receptors 1 (S1PR1) is involved in immunomodulation and cell survival. MicroRNAs (miR), short non-coding RNAs, epigenetically silence gene expressions. MicroRNA-155 modulates the egress of T cells from lymph nodes by targeting S1PR1, whereas miR-506 negatively regulates SphK1 expression. The aim was to investigate whether either of these miRNAs is involved in modulation of colonic inflammation by tuning the S1P/S1PR1 signaling axis in patients with primary sclerosing cholangitis (PSC) in comparison to patients with ulcerative colitis (UC).

Methods: Ascending and sigmoid colon biopsies were obtained from patients with PSC, PSC and UC (PSC-UC), UC, and healthy controls (n = 10 in each group). The relative levels of miR-506, miR-155, and gene expression of SphK1 and S1PR1 were determined by real-time PCR.

Results: In the presence of miR-506 over-expression in the ascending colon in both PSC and PSC-UC patients (5-fold and 6-fold increase, p = 0.04 and p = 0.03, respectively) there was no changes in SphK1 mRNA levels. In contrast, the substantial downregulation of this miRNA in UC (90% reduction, p = 0.006 vs. controls; p = 0.007 vs. PSC-UC) was accompanied by up-regulation of SphK1 expression. Furthermore, the expression of miRNA-155 in both parts of colon of PSC patients was significantly increased (2.7-fold in ascending colon, and 5.5-fold in sigmoid colon, p = 0.006 and p = 0.004, respectively), however, S1PR1 mRNA levels remained at the control values. In UC patients, in the absence of miRNA-155 induction the level of S1PR1 mRNA was enormously increased (p = 0.004 vs. control; p = 0.003 vs. PSC-UC).

Discussion/Conclusion: This study shows a distinctive pattern of miR-155 and miR-506 expressions in the group of patients with PSC-UC in comparison to patients with UC, which was associated with different modulation of S1P/S1PR1 axis. A selective modulation of these miRNAs may be a potential target for future pharmacological interventions.
Surgical treatment of Crohn’s disease complications 2009–2018

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Introduction: The etiology of Crohn’s disease is unknown. It is a chronic autoimmune bowel disease. The incidence and prevalence of Crohn’s disease has shown an increasing tendency recently. 70–90% of Crohn’s patients need to undergo surgery during their lives, and 10–15% of these operations are urgent.

Methods: 78 patients operated for Crohn’s disease complications have been examined retrospectively between 2009 and 2018. The observed period was divided into two 5-year parts.

Results: The epidemiological data are similar to the literature. Most of the patients were operated urgently in severe septic condition. In 20% of the cases the diagnosis of Crohn’s disease was unknown before the operation. In many cases the abdominal inflammation and abscess was spread to multiple organs. More than two third of the patients were under gastroenterological control and treated with combined therapy, however, in spite of all that complications appeared. CT is very important in establishing the correct diagnosis. In numerous cases two-step procedure could only be performed with temporary deviating stoma. Due to the spread of laparoscopy and interventional radiology the rate of laparoscopic operations (11) and one-step procedures (51) have increased. The number of postoperative complications has decreased but not significantly in these two five-year periods. 1 severe septic old patient died. The perioperative nutrition status was assessed. Malnutrition cases were corrected. As a result of this the final results were better, and the operations were safer. In 10% of the operated patients only the histological examination showed the presence of Crohn’s disease.

Discussion/Conclusion: Although modern therapies have been available for years, both the frequency and the complications of the Crohn’s disease have shown an increasing tendency. As a result of modern diagnostic possibilities, the rate of one-step operations has increased. In some cases the interventional radiological and minimal invasive procedures can be applied. They result in a decreased operational stress and faster recovery.
Association between chronic non-bacterial osteomyelitis and inflammatory bowel disease in children, result from a national survey of the SIGENP IBD Group

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Introduction: Chronic non-bacterial osteomyelitis (CNO) is an autoinflammatory disorder characterized by sterile bone osteolytic lesions usually multifocal. Sometimes patients have skin manifestations and in these cases the condition is called SAPHO (Synovitis, Acne, Pustulosis, Hyperostosis and Osteitis). It can be associated with other inflammatory conditions and few cases have been described in the literature associated with inflammatory bowel diseases (IBD).

Aim of our study was to investigate the prevalence and characteristic of CNO/SAPHO associated with IBD in Italy.

Methods: A questionnaire was sent to all pediatric IBD centers in order to collect clinical and therapeutic informations of patients with CNO/SAPHO and IBD.

Results: 11 patients with CNO/SAPHO and IBD were identified among all the patients followed by the 5 pediatric IBD centers that responded to the survey (0.8% over a total of 1364 patients); Nine patients had CNO, 2 SAPHO. 3 females (F), 8 males (M); mean age at CNO diagnosis 10 years (range 5–17), at IBD diagnosis 9 years (range 5–17); 1 had ulcerative colitis (UC), 7 Crohn’s disease (CD), 3 IBD unclassified (IBDU). Five patients presented with CNO, 4 with IBD and 2 with both diseases.

Of the 5 patients that presented with CNO, 4 were initially treated with non-steroidal anti-inflammatory drugs, 1 with methotrexate, when IBD was diagnosed 2 patients started adalimumab, 1 budesonide and methotrexate, in 1 salazopyrine was added to methotrexate and in one salazopyrine and steroids were started, they all went into remission with control of both CNO and IBD.

Of the 4 patients that presented with IBD one was initially treated with azathioprine, one with enteral nutrition and the other two with infliximab, they all were switched to adalimumab at the CNO diagnosis with remission of both diseases; the 2 patients on infliximab developed SAPHO while on treatment but went into remission on adalimumab. The last 2 patients that presented simultaneously with both CNO and IBD responded to adalimumab.

Discussion/Conclusion: This is the largest case series so far of CNO and IBD. It shows that CNO/SAPHO can be a rare extraintestinal manifestation of IBD and could precede or follow the IBD presentation. In our experience it was more common in CD than in UC or IBDU and in male than in female. Remission of both diseases was obtained when treatment was implemented especially using adalimumab.
Gene expression signature in Crohn’s disease: Novel in silico approaches for drug repositioning and drug-disease interactions

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Introduction: Contemporary therapeutic interventions for Crohn’s Disease (CD) have been gravitating towards biologics in combination with the more classical approaches. Furthermore, drugs used in everyday clinical practice have not been extensively evaluated for their effects on CD. In this work, using a drug repositioning bioinformatics pipeline based on differential gene expression, we report on compounds which positively and negatively perturb a de novo CD gene signature.

Methods: Expression data were obtained from eight publicly available CD datasets via Gene Expression Omnibus. Each dataset was analysed independently via GEO2R for differentially expressed genes (DEGs) vs. healthy controls to avoid experimental bias. The statistically significant genes (p < 0.05) of each dataset were split into two up-regulated and downregulated categories. We combined these categories from all datasets using the SuperExactTest R package to find their intersection and create a de novo CD gene signature. This signature was used as input for a) REACTOME to identify etiopathogenetic mechanisms of CD and b) CLUE.IO to identify compounds, which reverse or amplify it.

Results: Among the CD datasets several thousand DEGs were identified. Their intersection highlighted 39 upregulated and 12 downregulated DEGs. These, respectively, were implicated in 26 and 52 inflammatory and immunological signalling pathways. In total, 22 compounds were found to reverse the gene signature, that could be examined for drug repositioning, and 33 to amplify it, that might be involved in pathogenetic pathways of CD. Interestingly, no significant correlation was found between the common clinical practice drugs and the IBD DEG signature, which could indicate a possible interaction.

Discussion/Conclusion: These results suggest that bioinformatics pipelines could provide drugs for repositioning in CD therapy and novel gene signatures implicated as biomarkers or in pathogenetic pathways of CD. In addition, they could explore drug-disease interactions in CD.
Short-term and long-term outcomes of endoscopic dilatation for Crohn’s disease strictures

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

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

Design: This was a retrospective study based on chart review of an electronic medical chart system using OPS (5-489.b, 5-469.b3, 5-469.h3, 5-469.j3, 5-489.2, 5-499.0) and ICD-codes (ICD K50.0-K50.9) including 169 dilatations.

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

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

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

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

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

Fig. 1. All patients (Bogenhausen Academic Teaching Hospital and Klinik und Poliklinik für Innere Medizin II, Technical University of Munich, Munich, Germany)
Pathogenetic and diagnostic significance of the antibodies to lipopolysaccharide of gut microbiota in ulcerative colitis

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The aim of this study was to assess the pathogenetic and diagnostic value of serum concentrations of antibodies to lipopolysaccharides of gut microbiota (ALM) and overall antiendotoxin antibodies (AEA) in ulcerative colitis (UC).

**Material and methods:** 59 UC patients (32 with mild and 27 with severe forms) and 50 healthy donors (HD) were included in the investigation. The ALM to E. coli, Proteus, Bacteroides, Streptococcus, Klebsiella and AEA level in blood serum were assessed by the ELISA method.

**Results:** In healthy donors the range of ALM was as follows: for E. coli – 14.1 ± 0.42 µg/ml, Proteus – 11.53 ± 0.56 µg/ml, Streptococcus – 13.5 ± 0.58 µg/ml, Klebsiella – 24.9 ± 0.876 µg/ml, Bacteroides – 14.4 ± 0.61 µg/ml, AEA – 8.0 ± 0.38 µg/ml. In patients with UC the concentration ALM was: for E. coli – 26.1 ± 4.1 mg/ml, Proteus – 15.2 ± 4.6 µg/ml, Streptococcus - 11.4 ± 3.4 µg/ml, Klebsiella – 21.6 ± 4.5 µg/ml, Bacteroides – 9.1 ± 2.4 µg/ml, AEA – 15.4 ± 2.31 µg/ml. The increase of the level of ALM to E. coli and AEA was significantly shown in patients with UC. In patients with severe UC, there was the significant increase of ALM to E. coli and AEA levels in comparison with mild UC. The concentration of the ALM in other studied microorganisms in patients with UC did not differ from HD.

**Conclusion:** Anti-endotoxic activity was increased in UC. The high level of antibodies to the lipopolysaccharide of E. coli and AEA indicates their role in pathogenesis of UC. This finding give prove for the usage of antibiotics with significant modulatory effects on the gut microbiota, pro-and prebiotics in the treatment of UC.
Changes in the hemostatic system in patients with ulcerative colitis depending on the degree of activity of the disease

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Patients with inflammatory bowel disease (IBD) showed more frequent development of thromboembolic complications, compared with the General population.

Objective: To identify changes in the hemostatic system in patients with ulcerative colitis, depending on the degree of activity of the disease.

Materials and methods: The study included 15 patients with total lesions, who were divided into three groups, depending on the degree of activity of the disease on the meio scale. The 1st group of patients was in remission, the 2nd group of patients with UC had moderate activity of the disease, the 3rd group-high. The state of the blood coagulation system of the patients was assessed by the method of extended coagulogram (INR, ACTV, prothrombin by Kvik, antithrombin III, protein S, factors VII and VIII) and using the method of thromboelastography (TEG). Patients were excluded hereditary coagulopathy.

Results: In all three groups of patients with UC, according to the extended coagulogram, no changes in the indicators typical for the disorders of the blood coagulation system were revealed. According to the TEG data in group 1, the time from the beginning of clot formation to the achievement of a fixed level of clot strength (amplitude = 20 mm) (K) was on average 3.7 minutes, an increase in the angle built tangentially to the thromboelastogram from the point of clot formation (Angle) to 48.9, the maximum amplitude characterizing the maximum dynamic properties of the fibrin and platelets compound by GPIIb/IIa receptors (MA) to 57.9 mm. In the 2nd group, the time from the beginning of clot formation to the achievement of a fixed level of clot strength (amplitude = 20 mm) (K) was on average 2.45 min, an increase in the angle built tangentially to the thromboelastogram from the point of clot formation (Angle) to 58.9, the maximum amplitude characterizing the maximum dynamic properties of the fibrin and platelet compounds by GPIIb/IIa receptors (MA) to 63.05 mm. In group 3, the time from the beginning of clot formation to the achievement of a fixed level of clot strength (amplitude = 20 mm) (K) was on average 2.92 min, an increase in the angle built tangentially to the thromboelastogram from the point of clot formation (Angle) to 63.9, the maximum amplitude characterizing the maximum dynamic properties of the fibrin and platelets compound by GPIIb/IIa receptors (MA) to 71.24 mm.

Summary: The method of thromboelastography is a more sensitive method for detecting hemostatic disorders in patients with ulcerative colitis, compared with a standard coagulogram. According to thromboelastography in patients with ulcerative colitis there is a hypercoagulation state of the blood system, regardless of the activity of the inflammatory process. The degree of hypercoagulation increases with the activity of the disease.
The incidence of cancer and mortality in pediatric onset inflammatory bowel disease in Denmark and Finland during a 23-year period: A population-based study

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Introduction: Recent studies report increased risks of both cancer and mortality in pediatric onset inflammatory bowel disease (pIBD) but the reproducibility of this is unknown. In this population-based study we aim to estimate the incidence of cancer and mortality in the Danish and Finnish pIBD population in a 23-year period.

Methods: The pIBD population was defined as individuals registered in the national patient registries with a diagnosis of Crohn's disease, ulcerative colitis or IBD-unclassified before their 18th birthday from 1992 to 2014. This cohort was cross referenced with the national cancer and mortality registries identifying all pIBD patients who subsequently developed cancer and/or died and followed up to the end of 2014. Risk estimates are presented as standardized incidence ratios calculated based on incidence figures from the populations.

Results: 6689 patients with pIBD were identified. Of these, 72 subsequently developed cancer and 65 died. The standardized incidence ratio of cancer in general was 2.5 (95% confidence interval [CI]: 2.0–3.2). The cancer specific standardized incidence ratios were: colorectal cancer: 15.3 (CI: 8.7–24.8), liver cancer: 42.8 (CI: 19.5–81.3), skin cancer: 4.2 (CI: 2.4–6.7), and lymphomas: 2.9 (CI: 1.4–5.3). The standardized mortality ratio was 3.0 (CI: 2.4–3.9) with the main causes of mortality being cancer, infections and suicides.

Discussion/Conclusion: We found an increased risk of cancer and mortality in pIBD. These findings are in line with recently published data. These present study underlines the importance of cancer surveillance programs being implanted in the standard of care in adolescent pIBD patients.
Anemia in inflammatory bowel disease: Is it underestimated?

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Introduction: Anemia has been recognized as a key symptom of IBD. Although efficient therapeutic options have been developed for the treatment of IBD associated anemia, treating anemia often has a low priority for gastroenterologists. Iron deficiency is the most important cause of anemia in Crohn’s disease and ulcerative colitis patients. Iron deficiency even without anemia may impact the quality of life of our IBD patients. Thrombocytosis and iron deficiency anemia are frequent complications of inflammatory bowel disease (IBD).

Aim: To evaluate prevalence of anemia and to investigate the correlation between iron deficiency anemia and thrombocytosis in IBD patients.

Methods: Total of 36 patients were recruited and 30 healthy subject controls. All patients with histopathological verification of IBD were divided into three groups, according to CDAl (Chronic Disease Activity Index). Biochemical parameters were recorded: full blood count, platelets (PLT) hemoglobin, hematocrit, RBC, WBC, proteinogram, fibrinogen. Thrombocytosis was defined as an absolute number of PLT greater than 400 k/μl. Disease activity indices (Crohn’s Disease Activity Index for Crohn’s disease and Simple Clinical Colitis Activity Index for ulcerative colitis) as well as C-reactive protein (CRP) were also correlated with the study parameters.

Results: The IBD patients demonstrated decreased HCT levels, Hb levels, MCV, mean platelet volume, and ferritin levels and an increased absolute PLT count (p < 0.001) compared with healthy controls. Eight patients exhibited thrombocytosis (22.2%). The median value for PLT (interquartile range) was 299 (228–355) k/μl, for Hb levels was 13.5 (12.1–14.6) g/dl, for ferritin levels was 35.6 (18.7–80.3) ng/ml. The PLT in IBD patients correlated with HCT levels, Hb levels, MCV, RDW, Fe levels, ferritin levels, CRP levels, Simple Clinical Colitis Activity Index, and Crohn’s Disease Activity Index (Spearman’s ρ correlation). In the multivariate analysis, only Hb levels, CRP levels, ferritin levels remained significant (p < 0.05).

Discussion/Conclusion: Anemia could be the most common systemic complication of acute IBD. The PLT count correlate with iron deficiency anemia parameters and disease activity in IBD patients. Managing iron deficiency and controlling the inflammation could lead to reversal of thrombocytosis in IBD patients.
Intestinal microbial signature in inflammatory bowel disease

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Introduction: Intestinal microbiota is considered to be an organ in another organ having its own functions. Currently, gut microbiota composition is well known, but its functions have not been fully elucidated. Inflammatory bowel disease (IBD) can be considered the result of the interaction between genetic and environmental factors.

Methods: We conducted a prospective case-control study that enrolled 79 patients distributed as follows: 20 cases – Crohn’s disease (CD), 27 cases – ulcerative colitis (UC) and 32 control cases. Intestinal microbiota analysis was performed by polymerase chain reaction (PCR) in patient's feces.

Results: The diversity of intestinal microbiota was decreased in all cases compared to control group. There was a numerical increase in Bacteroides, E. coli adherent/invasive, Bifidobacterium and Lactobacillus versus control group (p < 0.005). Bacterial species such as Clostridium leptum, F. prausnitzii and Clostridium coccoides showed a significant decrease (p < 0.005). The more extensive Crohn’s disease was, the more accentuated intestinal dysbiosis became. In patients with UC a more pronounced dysbiosis was observed in left-side colitis. Significant correlations were demonstrated between CDAI and Mayo scores and the degree of intestinal dysbiosis. Treatment improved intestinal dysbiosis in all studied groups.

Discussion/Conclusion: Intestinal dysbiosis in patients with CD and UC is quite similar, being more pronounced compared to the control arm. Intestinal dysbiosis in CD patients has been shown to be the most significant. Cases with UC presented a particular intestinal dysbiosis, different from that of the control group, but less pronounced compared to CD. Our results support the presence of a link between intestinal microbial composition and IBD.
Introduction: The most commonly used scores in determining inflammatory bowel disease (IBD) severity are the CDAI score in Crohn’s disease (CD) and UCDAI in ulcerative colitis (UC). Although they are time-tested scoring methods, their use should be re-evaluated in the context of changing therapeutic targets in the management of IBD.

Methods: The aim of the study was to correlate the CDAI and UCDAI scores with biological parameters in patients with IBD. 196 patients (48 with CD and 148 with UC) were prospectively admitted to a tertiary IBD center. The following parameters were correlated with severity scores: full blood count, erythrocyte sedimentation rate (ESR), fibrinogen, C-reactive protein (CRP), serum iron, ferritin, total protein, albumin. Fecal calprotectin was assayed using a semiquantitative method (CalDetect, Sofar) and categorized as follows: T1 < 15 μg/g, T2 15–60 μg/g, T3 > 60 μg/g.

Results: The CDAI score positively correlated with abnormal levels of hemoglobin (p = 0.007), platelets (p = 0.005), iron (p = 0.05), ferritin (p = 0.029), fibrinogen (p = 0.000), CRP (p = 0.000) and fecal calprotectin (p = 0.001). The UCDAI score correlated positive with abnormal platelets (p = 0.000), white cells (p = 0.007), iron levels (p = 0.003), ferritin (p = 0.011), fibrinogen (0.014) and fecal calprotectin (p = 0.000).

Discussion/Conclusion: Our study demonstrated that is a good correlation between serologic inflammatory markers (platelets, fibrinogen and ferritin, not ESR and albumin) and severity of IBD. CRP is a good marker in CD but not in UC. FC is the best inflammatory biomarker, which correlates with activity both in UC and CD. Further studies are needed in order to find the ideal biomarker to estimate severity, disease course and response to treatment among individualized patients with IBD.
Association between the IL23R gene polymorphism and Serbian patients with inflammatory bowel disease

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Introduction: Inflammatory bowel diseases (IBD), Crohn’s disease (CD) and ulcerative colitis (UC) result from the combined effects of susceptibility genes and environmental factors. Polymorphisms in genes regulating inflammation may explain the part of the genetic heritage. Genome-wide association studies have identified several genes associated with IBD, including interleukin-23 receptor (IL23R), while investigations in Serbian IBD patients have not been done so far. We investigated the relationship between IL23R rs 11209026 (G1142A) and Serbian IBD patients.

Methods: A total of 206 IBD patients, 107 CD and 99 UC, and 255 healthy controls were included in the study. All subjects were genotyped using TaqMan SNP genotyping assay.

Results: G allele of rs 11209026 IL23R was more frequent in IBD, CD and UC group (OR = 5.08; p = 0.0002; OR = 6.62; p = 0.003 and OR = 4.06; p = 0.013). Moreover, GG genotype of rs 11209026 IL23R was more frequent in IBD, CD and UC group (OR = 5.36; p = 0.0007; OR = 7.00; p = 0.0085 and OR = 4.26; p = 0.02 respectively). G allele and GG genotype could be recognized as a potential predisposing factors, while significantly lower frequencies of GA genotype and A carriers were observed in all IBD groups, suggesting protective role of A allele in IBD pathogenesis. Genotype AA was not detected in all IBD groups and healthy controls.

Discussion/Conclusion: In this study we investigated the association of IL23R rs 11209026 (G1142A) with Serbian IBD patients. Our results, together with the previous findings, suggest that the IL23R gene is associated with susceptibility of CD and UC in Serbian IBD patients.
Fertility, conception and delivery in IBD patients: A retrospective study in a Greek center

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Background: Patients with IBD are concern about fertility, conception and relapse of disease during pregnancy. Moreover, birth weight and pregnancy outcome seems to be related with surgical procedures and medical treatment.

Aim: To evaluate the above mentioned parameters in a retrospective analysis of Greek IBD patients.

Methods: In total, 95 patients were registered; 52 males (mean age: 33 ± 14), 32 with Crohn’s disease (CD) and 20 with ulcerative colitis (UC) and 43 females (mean age: 33.1 ± 14.5), 29 with CD and 14 with UC.

Results: No children have been reported by 41.2% of the patients: 46.7% of the males and 33.9% of the females (p = 0.005). The rest 59.8% of them had at least one child (average 1.92 kids per patient). Patients with children are statistically older than those without (39 ± 13.8 vs. 24.3 ± 9.7, p < 0.001). Almost 1/3 of the patients (29.2%) had their first child after the IBD diagnosis, while 70.8% of them before. There were positive correlation between duration of disease and age of first conception in women that conceive after IBD diagnosis. Between women that conceive after IBD diagnosis 44.2% were treated with azathioprine, 41.9% with biologics, 2.3% with combination of biologics and azathioprine and 7% with 5ASA, while 41.9% of them were not receiving any treatment. Preterm delivery between women conceive in clinical remission (6%), were statistically inferior (p = 0.022) to them that conceive with active disease (61%). Women with active disease at conception had clinical relapse during pregnancy more often than these with quiescent disease (37.5% vs. 4.8%, p = 0.005). Cesarean section was performed in 16% of deliveries.

Conclusion: Fertility, conception and outcome of pregnancies in Greek IBD patients do not differ from these published in other populations.
Atypical cutaneous manifestation of Crohn’s disease

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Introduction: Erythema nodosum, sweet syndrome and pyoderma gangraenosum are common cutaneous manifestations during Crohn's disease. Spontaneous skin necrosis has been rarely reported in Crohn’s disease.

Methods: We report a case of Spontaneous skin necrosis revealing Protein S deficiency in Crohn’s disease.

Results: A 35-year-old woman presented with acute pelvic pain, bloody diarrhea and abdominal ecchymotic lesions rapidly extensive. This patient is followed for Crohn’s disease treated by azathioprine. Examination in the emergency department found fever, acute circulatory insufficiency and multiple ecchymotic and necrotic placards at almost the entire trunk and pelvis. The biologic assessment showed a leukocytosis at PNN, a normochromic normocytic anemia, a thrombocytopenia, an elevated CRP (C-reactive protein) and a low prothrombin level at 41%. A colonoscopy revealed aphthoid ulcerations scattered all over the colon. Cutaneous biopsies concluded at multiple thrombosis of the dermal blood capillaries and the vaginal wall, without vasculitis lesions, with C3 and IgM deposits in the vascular wall. The immunological assay including ANA, APL and cryoglobulinemia was negative. A thrombophilia assessment has demonstrated a deep deficit in Protein S at 1%. The patient received vascular filling with fresh frozen plasma, curative anticoagulation with low molecular weight heparin, antibiotic therapy, as well as high-dose corticosteroid therapy. Then, the patient was treated by anti-vitamin K indicated for life. The evolution was favorable: healing of skin lesions under local care and disappearance of bloody diarrhea.

Discussion/Conclusion: Spontaneous skin necrosis is a serious and rare manifestation of protein S deficiency. This condition has been rarely reported in Crohn’s disease. We report this case to emphasize the importance of considering skin necrosis as a possible cutaneous manifestation of Crohn’s disease.
Predicting factors of sexual dysfunction among Crohn’s disease patients

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Introduction: Sexual dysfunction can affect Crohn’s disease patients (CD) and decrease their quality of life. Sexual dysfunction among CD patients is poorly studied in Tunisia, probably because the subject remains taboo and patients may be reluctant to talk about intimate aspects of their life.

The primary aim of our study was to determine predictors of occurrence of sexual dysfunction among CD patients.

Methods: A prospective cross sectional study including all consecutive CD followed in the Gastroenterology Department of Habib Thameur Hospital (Tunisia) from January to June 2018 was conducted. Patients included were invited to fulfil a validated questionnaire on their sexual function: Female Sexual Index Function (FSIF) for women and International Index of Erectile Function (IIEF) for men. Psychological functioning was evaluated by the Hospital Anxiety and Depression Scale (HAD) and the Fatigue Scale Score (FSS). Predictors of sexual disorders were identified through univariate than logistic regression analysis (SPSS software, p value significant if lower than 0.05).

Results: Thirty patients were included. Mean age was 45 years (range 18–65 years) and sex ratio was 0.875 (M/F = 14/16). Sexual dysfunction was identified in 7 men (50%) and all women (n = 16). In univariate analysis, five predictors of occurrence of sexual dysfunction were objectified: female gender (p = 0.008), surgery (p = 0.05), corticosteroid therapy (p = 0.026), the Fatigue Severity Scale (p = 0.017) and the depression Scale (p = 0.045). In multivariate analysis, only sex was independently associated with sexual dysfunction (odds ratio of 2.75 for women).

Conclusion: Sexuality is often disturbed in CD patients, particularly among women. Global support both medical and psychological is needed in these young patients in full sexual activity to prevent the occurrence of these troubles.
A case of unusual cutaneous side effect during TNF-alpha inhibitor treatment of IBD?

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Introduction: Patients treated with the TNF-alpha inhibitors may develop an autoimmune condition, presumably as a result of therapy. The majority of cases have been vasculitic syndromes, most often cutaneous vasculitis, lupus-like syndromes or psoriatic skin changes. In most of these patients the condition resolves with discontinuation of the offending drug.

Methods: 46-year-old female patient has been suffering from ASCA (IgG and IgA) positive Crohn’s disease of terminal ileum since 1998. After the failure of conventional therapy, we started treating her with infliximab in 2012. Deep remission was achieved. In March of 2017 the patient reported skin changes below the knees. Leukocytoclastic vasculitis was diagnosed by dermatologists. Rheumatologists excluded systemic vasculitis. She was treated with topical corticosteroids and compression bandages. We assumed the vasculitis was due to TNF-alpha inhibitors, therefore in June 2017 we switched to vedolizumab, a gut selective antagonist of α4β7 integrin.

Results: Vasculitic skin lesions gradually disappeared. However, in the autumn of 2017 the patient complained about three thick reddish nodules (above the Achilles tendon). Firstly, we excluded tuberculosis. Also, there were no signs of either pulmonary or systemic sarcoidosis. Histological analysis confirmed a rare type of vasculitis called erythema elevatum diutinum. We continued with vedolizumab treatment. Dapsone treatment of erythema elevatum diutinum has been started under dermatological surveillance and some regression of skin changes has already been noticed.

Discussion/Conclusion: Erythema elevatum diutinum (EED) is a chronic form of leukocytoclastic vasculitis. It may occur in association with infections, hematologic abnormalities, and autoimmune diseases. There were three case reports of EED as extraintestinal manifestation of Crohn’s disease. Also, a connection between treatment with TNF-alpha inhibitors and leukocytoclastic vasculitis is well-established. Ninety-two percent of the cases of vasculitis are resolved following the discontinuation of TNF inhibitors. Our patients suffered from leukocytoclastic vasculitis during TNF-alpha inhibitor treatment and later on, erythema elevatum diutinum, which is a morphological distinction of leukocytoclastic vasculitis.
Regional survey on psychosocial aspects of living with inflammatory bowel disease: Patients’ perspective

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Introduction: Inflammatory bowel diseases (IBD) are chronic and lifelong conditions that can have a major impact on patients’ lives. Our aim was to survey IBD patients’ opinion on the impact of the disease on psychosocial aspects and quality of life.

Methods: We created an anonymous questionnaire and posted it to the web-based IBD patient group that gather patients from our geographical region (Croatia, Bosnia and Hercegovina, and Serbia). Besides general information, such as gender, age and diagnosis, we gathered patients’ opinion about their disease activity, quality of life, impact of the disease on their mood, and concerns about the disease. We received 387 responses between November 2017 and November 2018, and analyzed them by descriptive statistics.

Results: A total of 193 patients with Crohn’s disease and 194 patients with ulcerative colitis filled the questionnaire, of which 268 (69.3%) were female. Median age was 35 years (min. 13, max. 70 years) and median disease duration was 6 years (min. 0, max. 42 years). About half of the patients (n = 199, 51.4%) consider their disease as a large or very large burden in their lives. Also, 51.7% of patients (n = 200) think that disease has a large or very large impact on their mood, with 37.7% of patients (n = 146) feeling depressed or anxious because of their disease often or very often. Despite of that, only 16% of patients consider their quality of life poor or very poor. Greatest concerns that patients have about their disease were not being able to enter or sustain remission (n = 217), surgery (n = 192), disability (n = 127), colonoscopy (n = 110), and difficulties in social (n = 79) and sexual life (n = 75).

Discussion/Conclusion: IBD presents a great psychosocial burden for patients. Patients have multiple concerns considering their disease. This implicates that psychological help should be mandatory in multidisciplinary approach to treatment of these patients.
Stoma-related complications after ileal pouch-anal anastomosis in ulcerative colitis

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Background: The formation of a diverting ileostomy in ulcerative colitis (UC) patients undergoing restorative proctocolectomy with J-shaped ileal pouch-anal anastomosis (IPAA) is preferred by many surgeons. Our aim is to present the stoma-related complications in UC patients operated in our surgical department.

Methods: This is a retrospective observational study of 79 consecutive UC patients who underwent IPAA in our department between 2010 and 2017. A defunctioning loop ileostomy was created in every patient and was reversed at least 3 months later. Stoma-related complications were recorded, whereas possible risk factors were evaluated using the demographic and clinical characteristics of our sample.

Results: Of the 79 patients (52 males/27 females), with mean age of 39.3 ± 17.3 years and follow-up of 3.64 ± 2.01 years, 19 (24.1%) underwent a three-stage procedure and the remaining a two-stage procedure. 16 patients (20.3%) developed high-output ileostomy, whereas after ileostomy closure 6 patients (7.5%) presented wound infection and 5 patients (6.3%) small bowel obstruction [of which 4 (80%) required surgical intervention]. Anastomotic leakage after reversal occurred in one patient (1.3%). Incisional hernia at stoma site was developed in one patient too. Demographic and clinical features were inserted in univariate analysis as potential risk factors, but statistical significance was not reached.

Conclusions: High-output ileostomy was the most common complication of defunctioning ileostomy in our study. Risk factors could not be identified, probably due to small sample size.
Cardiovascular assessment in patients with inflammatory bowel disease

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Introduction: Inflammatory bowel diseases (IBD), largely represented by Crohn’s disease (CD) and ulcerative colitis (UC), alter gastrointestinal physiology and mucosal immunity through a complex inflammatory process. The extensive inflammation may lead to significant arterial endothelial dysfunction, as well as modification of cardiac structure and function.

Methods: Patients with CD or UC before pharmaceutical or surgical intervention were included in the study. Patients with a history of established cardiovascular risk factors were excluded. All patients underwent extended baseline cardiovascular assessment including vascular endothelial function [flow mediated dilatation (FMD), intima-media thickness (IMT), pulse wave velocity (PWV), endothelial glycocalyx] and echocardiographic myocardial function (systolic and diastolic parameters, deformation indices, coronary flow reserve estimation). IBD severity was quantified using Mayo score and Harvey-Bradshaw Index (HBI) for UC and CD respectively, and correlated with the cardiovascular disease markers, as above mentioned, using non-parametric bivariate correlations.

Results: 27 IBD patients (19 CD and 8 UC) were included in the study. The mean age of the population was 36 ± 11 years, while 63% were male. The mean Mayo score and HBI was 5.63 ± 1.77 and 5.21 ± 1.62 respectively and the mean C-reactive protein (CRP) was 10.9 ± 13.4 mg/l. Disease severity score was significantly associated with PWV (r = 0.389, p = 0.05), central carotid-femoral augmentation index (r = 0.360, p = 0.06) and markers of diastolic dysfunction (r = -0.435, p = 0.038 for E velocity, r = -0.413, p = 0.06 for lateral E’ velocity, r = 0.484, p = 0.017 for E untwist velocity and r = 0.458, p = 0.019 for peak untwist velocity).

UC patients had worse central carotid-femoral PWV (19.06 m/s vs. 11.87 m/s, p = 0.031) and worse global longitudinal (9.3% vs. 15.4%, p = 0.05) and circumferential strain (8.1% vs. 15.9%, p = 0.017) than CD patients.

Conclusion: IBD severity is correlated with vascular and diastolic dysfunction. Vascular endothelial function and myocardial deformity are more compromised in UC patients than in CD patients.
Comparative frequency of Clostridial infection in patients with ulcerative colitis receiving mesenchymal stromal cells and biological preparations

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Patients with inflammatory bowel disease (IBD) experienced more frequent development of Clostridial infection (CI) and much higher rates of morbidity and mortality compared to patients without IBD. Risk factors are immunosuppressive therapy.

The aim is to compare the frequency of CI in patients with ulcerative colitis (UC) receiving bone marrow mesenchymal stromal cells (MSC) and biological therapy.

Materials and methods: The patients were divided into three groups: the first group (n = 23) received the MSCs culture according to the scheme (0-1-2 weeks, then every 26 weeks); the second group of patients with UC (n = 21) received infliximab (IFX) in combination with azathioprine (AZA) according to the recommended scheme, the third group received only IFX according to the scheme. The toxins A and B of Clostridium difficile were determined by the enzyme immunoassay in the stool. The comparative analysis was carried out using the method of four-field tables using nonparametric statistical criteria.

Results: In patients of the 1st group, toxin A was detected in 1/23 patients (4.3%), in the 2nd group – in 2/21 (9.5%) (RR = 0.45, 95% CI: 0.04–4.6, x^2 = 0.46, p > 0.05), in the third – in 2/18 (11.1%) (RR = 0.4, 95% CI: 0.04–3.98, x^2 = 0.7, p > 0.05). In patients of the 1st group, toxin B was detected in 2/23 patients (8.6%), in the 2nd group in 3/21 (14.3%) patients (RR = 0.6, 95% CI: 0.1–3.3, x^2 = 0.3, p > 0.05), in the 3rd – in 2/18 (11.1%) (RR = 0.8, 95% CI: 0.12–5.03; x^2 = 0.07; p > 0.05). In patients of the 1st group toxins A and B were not detected – 0/23 (0.0%), in the 2nd group toxins A and B were detected in 7/21 (33.3%) patients (x^2 = 9.5, p < 0.05), in the third – in 5/18 (27.8%) (x^2 = 7.3, p < 0.05). Totally in patients of the 1st group, Clostridium difficile toxin A and B was detected in 3/23 patients (13.1%), in the 2nd group – in 12/21 (57.1%) patients with UC (RR = 0.23, 95% CI: 0.075–0.7, x^2 = 9.5, p < 0.05), in the 3rd – in 9/18 (50.0%) (RR = 0.26, 95% CI: 0.08–0.82, x^2 = 6.6, p < 0.05).

Conclusions: The frequency of Clostridial infection in patients with ulcerative colitis receiving mesenchymal stromal cells is significantly lower than in patients with ulcerative colitis receiving biological immunosuppressive preparations.
Azathioprine as a monotherapy or in combination with 5-amino-salicylates in patients with inflammatory bowel disease in achieving better therapeutic response

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Introduction: Immunomodulators are widely used in inflammatory bowel disease (IBD) patients, especially in countries where biological treatment is very expensive treatment option. But still it is uncertain whether concurrent therapy with 5-amino-salicylic acid (5-ASA) is needed for disease control. The aim of this study was to assess whether azathioprine (AZA) treatment as a monotherapy is sufficient to achieve remission in patients with IBD, or a combination therapy with 5-ASA is needed for better therapeutic outcome.

Methods: A total of 63 IBD patients treated either with AZA as a monotherapy or concomitant therapy of AZA + 5-ASA in a period of more than 3 months were included in this retrospective study. Patients were followed-up in a period of 3 years. Treatment outcome in both groups of patients was estimated on the basis of necessity for corticosteroids, surgery and hospitalization after initiation of AZA + 5-ASA therapy or AZA as a monotherapy.

Results: Twenty-seven patients (42.86%) have used AZA + 5-ASA and thirty-six patients (57.14%) have used AZA as a monotherapy. There was no significant difference between the two groups regarding the age, gender, clinical type of the disease and time duration of AZA treatment. 15% of the AZA + 5-ASA group and 8% of the AZA monotherapy group, additionally received corticosteroids (p > 0.05). Disease-related hospitalization between the two groups were not significantly different (AZA + 5-ASA [11.1%] vs. AZA monotherapy group [13.9%]). Crohn’s disease patients had more intestinal surgery operations when compared with Ulcerative colitis patients (p < 0.05).

Discussion/Conclusion: AZA treatment is effective therapeutic option in IBD patients, regardless it is administered as a monotherapy or as a concomitant therapy with 5-ASA. More prospective studies are needed, with longer follow-up of patients, taking into account more informations that might have influence on therapeutic outcome, when patients are treated with AZA monotherapy or concomitant AZA + 5-ASA therapy.
Arthropathies in ulcerative colitis: Various clinical types

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Introduction: The extra-intestinal manifestations of the intestinal bowel diseases have been acknowledged and studied for a long time. Their emergence mechanisms are connected to a number of pathogenetic directions. The affecting of the joints occurs under several forms and evolves in different ways.

Aim: The present study investigates the presence and variety of arthopathies in a group of 52 patients diagnosed with ulcerative colitis who were subjected to a follow-up from September 2015 to September 2018. We have analyzed the predominant articular clinical manifestations, the type and number of affected joints, the relation with the evolution of the intestinal disease and the exclusion of other independent arthopathies.

Results: Out of the 52 patients, 10 (19.2%) had an affecting of several weight-bearing joints, while in 8 (15.3%) patients the manifestations occurred at the level of the small joints of the hands. The patients with oligoarticular affection manifested pain and inflammatory signs at the level of the large joints, self-limited, with a duration of 1–3 weeks and present during the activity periods of the inflammatory bowel disease. The patients with affection of the small joints of the hands had symmetrical affecting, pain more frequently than obvious inflammatory signs and symptoms that were not related to the activity periods of ulcerative colitis, spanning over longer periods of time.

Conclusions: The two types of non-axial arthropathy have different patterns in patients with ulcerative colitis, but their connection with the inflammatory bowel disease must be well documented, both by a clear delineation from other articular diseases and by excluding their being part of the side effects of the treatment of the inflammatory bowel disease.
Urolithiasis as an extraintestinal manifestation of inflammatory bowel disease in a tertiary referral center

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**Introduction**: Extraintestinal manifestations (EIMs) of inflammatory bowel disease (IBD) are common in both ulcerative colitis (UC) and Crohn’s disease (CD). The association of IBD with complications in the urinary tract has been reported in many studies with urolithiasis being a common manifestation. The aim of this study was to assess the frequency of urolithiasis and urinary tract infection in IBD patients.

**Methods**: We conducted a descriptive cohort study with prospective data collected from all patients with IBD admitted to our tertiary referral center in North East Romania in a five-year period. Demographic data and clinical characteristics were reviewed.

**Results**: The study population included 329 IBD patients (mean age 44.11 ± 15.51 years), predominantly male patients (58.9%). A total of 228 (69.3%) were diagnosed with ulcerative colitis (UC) and 101 (30.7%) with Crohn’s disease (CD). The study group consisted of predominantly left-sided colitis (51.7%) and colonic CD cases (43.5%). We found a number of 22 (6.7%) patients with IBD and urolithiasis. Amongst them, 15 (49.3%) had UC and 7 (23%) had CD. Moreover, we identified 21 (6.3%) patients diagnosed with urinary tract infection, most of them (66.6%) being with UC.

**Discussion/Conclusion**: Urolithiasis is the most common urinary complication in patients with IBD. While urinary tract manifestations are more common in patients with CD, in our study these manifestations were predominantly diagnosed in UC subgroup.
The role of capsule endoscopy in evaluating small bowel involvement in patients with perianal Crohn’s disease

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Introduction/Aim: To investigate whether concurrent small bowel involvement in patients with colonic Crohn’s disease (CD) increases the likelihood of perianal disease.

Methods: Retrospective analysis of prospectively collected data (March 2003–March 2018) in patients with diagnosed CD that have been subjected to Small Bowel Capsule Endoscopy (SBCE) in our department. Indicative findings of small bowel involvement were the presence of aphthous ulcers or deep ulcers, with or without inflammation of the adjacent mucosa. We assessed the presence or absence of small bowel involvement in CD patients with colonic involvement and perianal disease.

Results: Overall we assessed 712 CD patients (men/women 349/363, mean age 49.8 ± 28.4 years) with either colonic or small bowel involvement, confirmed by ileocolonoscopy and biopsies who had been subjected to SBCE. Among these, 242 patients had only colonic disease, 203 had ileocolonic disease, 76 had only the small bowel disease and the remaining 191 patients had colonic involvement but the ileocecal valve could not be intubated. In the latter 191 patients, small bowel involvement was found by SBCE in 84 (43.9%) increasing the number of patients with small bowel and colonic CD in 363. Active perianal disease was seen in 27/363 (7.4%) compared to 773 patients with perianal CD amongst patients with solely colonic involvement (349, 22.1%). Although the latter group was numerically higher, differences did not achieve statistically significant level [p = n.s.].

Discussion/Conclusion: It appears that concurrent small bowel and colonic involvement in CD does not increase the likelihood of perianal disease.
Cholestatic hepatitis preceding the appearance of colitis in two boys

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Aim: The aim is to present a case of two boys in whom cholestatic hepatitis preceded the diagnosis of AIH/PSC overlap syndrome with concomitant colitis.

Case 1: A 7-year-old boy with unencumbered medical history in the first years of life, remained under gastrological control from the age of 5 due to elevated activity of aminotransferases (AlAT 4xN, AspAT 3xN, GGTP 5xN). The child had no gastrointestinal symptoms. The laboratory tests were performed while diagnosing headache. In 2016 hepatotropic virus infections, parasitic infestations and coeliac disease were ruled out. The boy was left without any causative treatment.

In 2018, due to the unknown cause of hypertransaminasemia and elevated IgG he was admitted for more profound diagnostics. A transcutaneous biopsy of the liver revealed signs of AIH of minor activity with no sighs of PSC in the small bile ducts. The FOBT was positive and fecal calprotectin elevated up to 1480 ng/g. A colonoscopy was performed, revealing continuous changes in the whole large intestine, in the form of loss of vascular pattern and punctuate fibrinous exudates. Histologically, fragments of the mucus membrane of the large intestine had preserved architectonic crypts with increased leukocyte count and follicular lymphocytic infiltrates.

Considering the possibility of overlapping liver disease and IBD, and MRCP was performed, showing discrete narrowing of the common hepatic duct close to its connection with the cystic duct. ASA, UDCA and Prednisone in gradually reduced doses were used in the treatment, resulting in biochemical improvement and gradual reduction of calprotectin.

Case 2: A 15-year-old boy, remaining under gastroenterological care since 3 years because of hypertransaminasemia of an unknown etiology.

In 2014 Wilson’s disease, coeliac disease, EBV, CMV, HBV, and HCV infection as well as autoimmune disease, CF were excluded. A liver biopsy was performed and revealed: hepatitis cryptogenes probabiliter toxica minoris gradus fibrosis septalis. After 2 years, due to sustained elevated AST, ALT, GGTP and ALP activity the boy was readmitted to the hospital. Laboratory tests showed increasing concentrations of IgG and appearance of anti-nuclear antibodies. Because of the whole clinical presentation Prednisone treatment was started – with a good biochemical response.

In 2018 the boy was consulted and the diagnosis of an autoimmune hepatitis and primary sclerotising choanalgitis overlap syndrome was put forward. At that time gastroscopy and chlangio-MR showed no abnormalities. In autumn a 10-day episode of diarrhea, accompanied by a loss of 6 kg weight, occurred. Laboratory tests revealed elevated parameters of cholestasis (GGTP and ALP). Proteinogram and anti-tTG IgA were normal. Fecal calprotectin was elevated (771 µg/g). Cholangio-MR showed irregular contours and discrete narrowing of the intra- and extrahepatic bile ducts as well as an irregular inner contour of the gall bladder. Colonoscopy revealed an abnormal mucus membrane of the cecum, ascending and transverse colon – loss of vascular pattern, flat small ulcerations covered with fibrin and a continuous character.
of these changes. Because of that ASA preparations were added to the former treatment. The whole clinical presentation suggests an AIH/PSC and ulcerative colitis overlap syndrome.
The levels of vitamin D in children with an inflammatory bowel disease during the year

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Introduction: The decrease of vitamin D (VD) is associated with an inborn and acquired response from the immune system in different autoimmune diseases but its significance in children and adolescents with an inflammatory bowel disease (IBD) has not been studied enough. The aim of our study is to investigate the serum levels of 25-hydroxyvitamin D (25[OH]D) in children with IBD according to every month of the year.

Methods: We have performed a retrospective study, during the period of 12 months (January–December 2018). The inclusion criteria were the children under the age of 18 with a firmly established diagnosis Crohn’s disease (CD) or ulcerative colitis (UC). The children with other known causes of VD deficit were excluded. The determination of the hydroxyvitamin D was carried out microparticle electrochemoluminescence assay (Cobas, Hitachi-Roche). Our interpretation of the VD serum levels was to conclude the following: between 21–29 ng/ml 25-(OH)-D levels mean insufficiency, deficit as a 25-(OH)-D is below 20 ng/ml, severe deficit from 10 ng/ml and less, and VD values levels 30 ng/ml and more considered as normal.

Results: We have included 112 children with IBD (152 blood samples) and found that an adequate concentration of vitamin D has been observed only in 26 (17.1%) of cases. The others have had VD deficiency: 71 (46.7%) samples have had moderate lack of vitamin D and in 17 (11.2%) of cases we have enrolled a severe deficiency of vitamin D (less than 10 ng/ml). The Insufficiency of vitamin D has been noted in 38 cases (25.0%). The most remarkable decrease level of VD has been observed from January till April with a further increase in summer months.

Conclusion: Our results suggest that there is a high prevalence (82.9%) of reduced levels of VD in children with IBD deficiency (57.9%, including severe – 11.2%). The most remarkable insufficiencies have been observed from January till April. In this period patients may need VD supplementation but a further research is needed to clarify these results.

![Vitamin D level in children with IBD according month of year](image)
Correlation between endoscopic index of disease activity and values of CRP in IBD patients

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Introduction: Laboratory markers have been investigated in inflammatory bowel disease (IBD) for assessment of disease activity. Of all the laboratory markers, (C reactive protein) CRP is the most studied and has been shown to have the best overall performance. CRP is an objective marker of inflammation and correlates well with disease activity in Crohn’s disease (CD) and less well with ulcerative colitis (UC). Colonoscopy is a standard procedure in assessment of IBD activity disease. The aim of this study is to explore the correlation of endoscopic index of disease activity and values of CRP.

Methods: We have conducted a retrospective study at the Department of Gastroenterology with Endoscopy of Prijedor Hospital. The study included 40 patients, 16 of whom were females and 24 were males, the average age was 51.8 and the patients were on endoscopic examination in the period from January to December 2018. For endoscopic activity index in UC patients, Mayo endoscopic subscore was used, and in patients with CD simple endoscopic score for Crohn’s disease (SES-CD).

Results: 30 (75%) patients were with diagnosis UC and 10 (25%) patients with diagnosis CD. The average age of patients with UC was 55.1 and 35.9 of patients with CD. 16 patients (40%) had endoscopic index of disease activity score 2, while 14 patients (35%) had endoscopic index of disease activity score 1. The highest value of CRP was 176, while the average value was 22.8. The results of Spearman’s correlation ($r = 0.763; p = 0.000$) showed that there was statistically significant, positive and strong correlation between values of CRP and endoscopic activity.

Discussion/Conclusion: Patients were most often diagnosed with score 2 of endoscopic index of disease activity, with significantly lower average age in patients with CD. Our research has established a good correlation between endoscopic index of disease activity and values of CRP in IBD patients.
Expression of survivin and PCNA proteins in inflammatory bowel diseases

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Introduction: Survivin is one of the apoptosis related inhibitors and participates in the regulation of the cell cycle. Physiologically, survivin is present in a diverse population of normal cells: endothelial cells, multinuclear cells, T lymphocytes and precursor forms of erythrocytes. Survivin blocks the effects of various vascular factors and maintains the integrity of endothelial cells. The proliferating cell nuclear antigen (PCNA) is a polymerase-associated protein and is synthesized in early G1 and S phases of the cell cycle. But PCNA protein has a lower specificity in determining cell proliferation because it also participates in the repair of DNA. Due to their role in cell cycle, the purpose of the research was to evaluate and compare the expressions of survivin and PCNA proteins in inflammatory bowel diseases (ulcerative colitis and Crohn’s disease).

Methods: The study included a group of 38 patients with ulcerative colitis and 11 patients with Crohn’s disease. The expressions of survivin and PCNA in tissue material was evaluated and determined by the immunohistochemical technique. The staining reaction was observed in details in the glandular epithelium and in inflammatory cells and was assessed as % of positive cells with nuclear reaction.

Results: In glandular epithelium expression of survivin was present in 84.2% cases of ulcerative colitis. In inflammatory cells, the expression of survivin was similar. In contrast, in Crohn’s disease it was positive in 63.6% of patients in glandular epithelium, whereas in inflammatory cells in 81.8% of patients. Positive, glandular epithelium expression of PCNA protein was present in 100% cases and in 71.4% cases in inflammatory cells of ulcerative colitis. In Crohn’s disease, glandular epithelium PCNA expression was present in 88.9% cases and in 100% cases in inflammatory cells. Statistical analysis showed a positive correlation between survivin and PCNA expression in inflammatory cells of ulcerative colitis (p = 0.028). In Crohn’s disease, the expression of survivin in inflammatory cells correlated inversely with the expression of PCNA in glandular epithelium (p = 0.044).

Conclusion: In Crohn’s disease, survivin and PCNA proteins expressions are higher in inflammatory cells than in glandular epithelial cells. In contrast, in ulcerative colitis, the expression of both proliferative proteins appears to be higher in glandular epithelium than in inflammatory cells. Perhaps this is due to more advanced damage of the mucosa or more frequent dysplasia in ulcerative colitis.
Treatment of induced colitis in mice by the Ras antagonist farnesylthiosalicylic acid (FTS)

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Background and aims: Ras proteins have been shown to regulate cell growth, proliferation, differentiation. Targeting the Ras family has been suggested as a therapeutic strategy in proliferative and inflammatory diseases. 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. After 7 days the mice were sacrificed and the colon was isolated for further evaluation. 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 immunoblotting 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 IL-1β ($p = 0.01$).The expression of 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 ($p = 0.003$).

Conclusions: Ras inhibition significantly ameliorates the severity of experimental colitis, and may offer a new therapeutic approach.
Case report: Telogen effluvium as the first symptom of Crohn’s disease in a child

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Introduction: Crohn’s disease usually manifests itself with gastrointestinal symptoms however in some cases the patients presents with prominent or even exclusive extraintestinal involvement. Alopecia has been reported as a complication of therapeutic agents and in a few cases of adult patients prior of the appearance of gastrointestinal symptoms.

Methods: We present a 10-year-old child with telogen effluvium that appeared one year before the diagnosis of Crohn’s disease, as the first and single symptom at that time.

Results: Patient was admitted because of weight loss of 5 kg, mild fever (37.6–38 °C) 2–3 times/week and 1–2 episodes of vomiting /week the last two months. Her medical history was unremarkable till she developed diffuse alopecia last year refractory to treatment with topical steroids. Two months before admission recurrent oral aphthous ulcers appeared and softening of her stools without episodes of diarrhea was noticed. Her growth was normal. Physical examination revealed scalp alopecia with a friable hair and positive hair pull test.

Laboratory investigations revealed white blood count within normal limits, erythrocyte sedimentation rate at 51 mm/h; CRP 21 mg/l, hemoglobin 12.9 g/dl and platelet count 508,000 k/μl. Total proteins were 7.7 g/dl, serum albumin was 3.8 g/dl. Serum electrolytes, iron, TIBC, ferritin, cooper and zinc liver function tests, vitamins, endocrinological workup, serum immunoglobulins were within normal limits. Celiac abs were negative. MRI enteroclysis showed thickening of terminal ileum wall. Endoscopy showed aphthous ulcers in duodenum and ulcers with mucopurulent exudate in terminal ileum. Mucosal biopsies confirmed the diagnosis Crohn’s colitis with presence of granulomas in terminal ileum and chronic inflammation in colon. After one year in sustained remission under infliximab hair has gradually regrown by negative hair pull test.

Discussion/Conclusion: The association of Crohn’s disease and diffuse effluvium should be considered as an extraintestinal manifestation of Crohn’s disease especially when other alarming symptoms are present.
CD83+ dendritic cells (DC) in Crohn’s disease (CD) and ulcerative colitis (UC)

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Introduction: CD and UC are chronic inflammatory bowel diseases (IBD), with unsatisfactorily understood pathogenesis. Different pathophysiological models give us an insight in an important role of DC in pathogenesis.

Methods: There were 162 subjects were included in study: 68 with UC and 19 with CD (all without treatment), and 75 subjects in control group. Colonic biopsy specimens had been obtained from all study subjects. Specimens were incubated with primary antibody anti-CD83. Intraepithelic DC were then counted per each 100 enterocytes and results expressed as DC present (DC ≥ 1) or not present (DC = 0). Presence of DC was statistically analyzed according to demographic data, type of IBD and histopathologic activity of the disease.

Results: Presence of DC differed significantly among the three study groups ($\chi^2 = 11.14; p = 0.004$). Odds for presence of DC in patients with CD was 4.5 times higher than in patients with UC (OR = 4.5; 95% CI: 1.2–16.8). Odds for presence of DC in control group was 2.8 times higher than in patients with UC (OR = 2.8; 95% CI: 1.4–5.9). There was no significant difference among three groups according to gender ($\chi^2 = 0.003; p = 0.955$) or age ($z = 0.727; p = 0.67$), regarding presence of DC. Presence of DC was not significantly connected with histopathologic activity of the disease ($\chi^2 = 4.8; p = 0.091$).

Discussion/Conclusion: Study results suggest that the presence and role of these cells depend primarily on type of IBD, and is not connected with gender, age of patient, or histopathological activity of the disease.
Long-term observation of the human gut microbiota diversity changes after the *Helicobacter pylori* eradication therapy

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**Introduction:** Antibacterial therapy can lead to changes in the human gut microbiota. *Helicobacter pylori* eradication therapy can also have a negative impact on gut microbiota composition.

The aim of the study was to access taxonomic (alpha and beta) diversity changes in the human gut microbiota due to *H. pylori* eradication therapy based on Shannon index (SI) and Bray-Curtis distance (BC) metrics.

**Methods:** Stool samples from 233 *H. pylori*-positive patients before and immediately after eradication therapy (proton pump inhibitor, amoxicillin 1000 mg, clarithromycin 500 mg and bismuthate tripotassium dicitrate 240 mg b.i.d. for 14 days) and 29 samples one month after therapy from the same patients were collected. Stool biosamples were analyzed using shotgun metagenomic sequencing (SOLiD 5500 Wildfire platform).

**Results:** Shannon index significantly decreased immediately after the therapy compared to the initial level – (2.45 ± 0.59) vs. (2.69 ± 0.55), p = 0.0082, however, it returned almost completely to baseline one month after eradication therapy – (2.69 ± 0.55) vs. (2.59 ± 0.37), p = 0.1165.

Severe changes of gut microbiota (BC ≥ 0.75) were observed immediately after therapy in case of 34 (33.3%) patients. These changes were associated mainly with increased relative abundance of *Escherichia coli, Bacteroides vulgatus, Enterococcus faecalis* and decreased abundance of *Prevotella copri, Eubacterium rectale, Faecalibacterium prausnitzii*. Moderate changes (BC < 0.75 and > 0.35) were found in 56 (54.91%) patients due to same bacterial species changes which were less pronounced. Mild changes (BC < 0.35) were noted in 12 (11.76%) patients, they were very individual and diverse. Four weeks after the eradication therapy severe changes still persisted in case of 5 (17.24%) patients, moderate changes – in 20 (68.97%) patients and mild changes were detected in 4 (13.79%) patients.

**Discussion/Conclusion:** Thus, eradication therapy leads to gut microbiota taxonomic diversity changes in most of patients, generally due to increased abundance of potentially pathogenic bacteria and decreased abundance of normal gut microbiota.
Acute eosinophilic pneumonia related to a mesalazine usage in pediatric patient – Case report

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Introduction: Mesalazine is a well tolerated medication widely used to treat ulcerative colitis (UC), but very rare (< 0.01%) can cause lung disease including eosinophilic pneumonia.

Methods: Description of the case of 15-year-old male with ulcerative colitis and mesalazine-induced eosinophilic pneumonia.

Results: 15-year-old boy was diagnosed with UC a year ago. He was treated with mesalazine 3 g/day and prednisolone during acute exacerbation 6 month ago. At the time of present admission, the patient presented to the hospital with moderate bloody diarrhea. Treatment with prednisolone was refused from patient, topical and systemic high-dosage mesalazine was started. After 1 week of a chest radiograph was performed because of progressive dyspnoea and fever with suspected bronchopneumonia dextra. 1 week later chest radiograph showed negative dynamic-round, oval subpleural infiltrate in right lung and progressive changes in left with suspicion of eosinophilic infiltrate. Chest CT demonstrated subpleural hyperdense polymorph consolidations. Bronchoalveolar lavage with biopsy was done. Based on the patient’s symptomatic presentation, laboratory findings of leucocytosis with mild eosinophilia, and his radiographic pattern of peripheral parenchymal consolidation, the patient was diagnosed with eosinophilic pneumonia. Because of possibility of mesalazine-induced eosinophilic pneumonia, mesalazine was discontinued, after that patient’s condition improved. Treatment with prednisolone was started, added to ceftriaxone and amikacin for 14 days. Azathioprine 100 mg/day was added 2-weeks later. Control chest CT after treatment course with antibiotics and prednisolone showed positive dynamic.

Discussion/Conclusion: The rapid improvement in clinical and radiographic findings in the above patient after the discontinuation of mesalazine strongly supports the diagnosis of mesalazine-induced eosinophilic pneumonia. Mesalazine was cause of eosinophilic pneumonia in our case although it has been very rarely reported in pediatric patient. It is important to consider mesalazine induce eosinophilic pneumonia if unexplained respiratory symptoms occur while on mesalazine therapy.
30-day mortality following endoscopy in Prince Charles Hospital

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Introduction: The aim of this audit was to review the cases of patients who died within 30 days of undergoing an endoscopic procedure at Prince Charles Hospital in 2015 and to determine the cause of death.

Methods: Patients who died within 30 days of an endoscopic procedure were identified using the hospital coding database system. Patient demographic data and cause of death were determined via a retrospective review of the case notes.

Results: Sixty deaths within 30 days of endoscopy procedures were found, 6 patients (9%) had more than one procedure in the 30 days prior to death (excluding those that had OGD & PEG), they were mostly inpatient procedures. 61% had OGD, 15% PEG, 12% flexible sigmoidoscopy, 8% ERCP, and 4% had colonoscopy. 6 patients had more than one endoscopic procedures, 2 patients had two OGDs, an other 2 had OGD and Flexible Sigmoidoscopy, 1 patient had OGD and Colonoscopy and an other one had Flexible Sigmoidoscopy and colonoscopy. Mortality was higher in older patients, 75% of those who died were older than 70 years old. Death rate was 11% and 8% in age group 61–70 and 51–60 years old respectively. Mortality was about 2% in age group 21–30, 31–40, and 41–50. 26% died during the second week after their procedures, while 25% died between second and seventh days post procedures. 22% and 20% died during the third and fourth week after their procedure respectively. 7% passed away less than 2 days following their endoscopies. One third of patients died from respiratory diseases, 20.5% from cancer, while 11% passed away from cardiac diseases, 11% from sepsis, 9% from cerebral infarcts and 15% from other causes, which includes: GI bleed, decompensated liver disease, bowel perforation and renal failure.

Cancer-related mortality involved different organs like quarter of them died from lung cancer, 19% from oesophageal cancer, 12.5% for each gastric and pancreatic cancer, and 6% for liver, cholangiocarcinoma and cancer of unknown primary separately. 10 patients died following a PEG procedure which was performed for stroke patients. In all cases it was determined that PEG was appropriate.

Discussion/Conclusion: The results of this audit highlighted that endoscopy was deemed appropriate in all patients. There was only one case where it was found to be a contributing factor to patients death, in all other cases frailty and pre-existing disease were noted to be the primary cause of death. It has been recommended to review all deaths in keeping with GRS guidance.
Gut barrier failure biomarkers in IBD: Is there anything new beyond „The Wall”?

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Introduction: Several defects in the components of mucosal barrier have been reported in inflammatory bowel disease (IBD). These alterations may represent a primary dysfunction in Crohn’s disease (CD), but they may also perpetuate chronic mucosal inflammation in ulcerative colitis (UC). Changes in intestinal permeability can predict IBD course.

Methods: We aim to determine the predictive potential of a panel of serological markers that reflect either mechanical or immunological gut barrier dysfunction regarding determination of disease phenotype, therapeutic strategy and long-term disease course in a prospective referral adult IBD patient cohort. Sera of 266 CD and 187 UC patients were assayed for intestinal fatty acid-binding protein (I-FABP) and various immunoglobulin A (IgA) molecules, anti-F-actin [AAA IgA/IgG] and anti-gliadin [AGA IgA/IgG]) by enzyme-linked immunosorbent assay along with 155 healthy controls (HCONT).

Results: In UC, median I-FABP level was significantly lower than in HCONT (p < 0.05). sIgA level was higher in both CD and UC compared to HCONT (p < 0.0001). AAA positivity with IgA type predominance was significantly higher in CD (40.2 vs. UC: 15.7; HCONT: 6.2%). AGA was also more prevalent in CD (16.5 vs. UC: 6.7; HCONT: 7.2%). There was an association between the presence of IgA type AAA or AGA and antimicrobial antibodies. ACA IgA was also more prevalent in case of AAA IgA positivity (p = 0.009). PS/PT IgA positivity was higher in AGA IgA positive patients (p = 0.001). Complicated disease behavior at sample procurement was associated with the presence of AAA and AGA IgA positivity. In Kaplan-Meier analysis concomitant presence of IgA and IgG type AAA was associated with a shorter time to resective surgery along with a higher risk of a second surgery needed. The later remained significant in B1 pts and also remained independent predictor in multivariate Cox-regression analysis comprising relevant clinical factors (HR [95% CI]: 2.88 [1.07–7.78], p = 0.037).

Discussion/Conclusion: The presence of AAA and AGA reflects the ongoing mucosal damage in IBD rather than has a value in predicting the disease course.
The complexity of the differential diagnosis of IBD: Mimicry Entameba histolytica

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Introduction: Entameba histolytica is able to mimic Crohn’s disease. Colitis caused by this infectious agent is difficult to differentiate from true IBD. In such patients, an extremely similar clinical picture with IBD. In addition, with endoscopic examination, it is possible to see signs of segmental inflammation of the intestinal mucosa.

Methods: We present the case of a patient who was initially diagnosed with Crohn’s disease, ileocolitis.

Results: According to endoscopy, we have seen erosion and signs of inflammation of the mucous membrane in the ileocecal zone, the ascending intestine and in the lower third of the sigmoid colon. However, the response to therapy was not received within a few weeks. In connection with refractoriness to therapy, a decision was made on repeated studies. Biopsy materials (initial and postorum) were revised, PAS staining of the samples was performed. Due to this, cystous forms of Entameba histolytica was found in histological materials.

Discussion/Conclusion: Intestinal amebiasis is the most common form of amoebic infection. But this is not the most common cause of diarrhea with blood. However, caution should be exercised in the initial diagnosis of IBD, especially in patients with a positive epidemiological history. In addition, one should think about the need to conduct tests on Entameba histolytica in patients with refractory forms of IBD.
Embedding pharmaceutical care into the IBD multidisciplinary team

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Introduction: Pharmacists traditionally do not get involved in the long-term management of patients with chronic diseases. This service development aimed to integrate a pharmacy led medication optimisation service into the specialist Multi Disciplinary Team (MDT).
We report 4 month experience of extending our specialist pharmacists’ remit.

Methods:
1. Weekly pharmacist outpatient clinics initiate immunomodulating therapies, undertake biochemical monitoring and therapy adjustments due to blood results, adverse drug reactions or concordance.
2. Pharmacists lead biologics infusion clinics strategically and operationally.
3. Pharmacist-led blood monitoring and therapeutic drug monitoring (TDM) service for immunomodulators optimises therapies and guides therapy decisions.
4. Pharmacists support rapid access service.
5. Pharmacists facilitate MDT approved pathways to initiate and review immunomodulators.
6. A workload and prescription audit was conducted, the financial benefit assessed and service anonymously peer reviewed.

Results:
1. 14 pharmacist clinics were analysed: 138 patients managed by pharmacists, 382 patients’ bloods monitored ensuring clinical governance of therapies.
2. The biologics infusion clinic was expanded.
3. 65 patients had their immunosuppressants adjusted due to TDM. Pharmacist prescribers are gatekeepers for testing and responsible of therapy optimisation.
4. The advice required for the rapid access service is primarily nurse orientated with the pharmacist deputising to maximise resources.
5. The MDT reviewed 42 patients according to the developed pathways.
6. The TDM service resulted in a minimum of £60,000 savings. 6 responders returned overwhelmingly positive peer reviews.

Discussion/Conclusion: Involving the pharmacist in the longterm care of IBD patients enhances patient safety, standardises treatments and individualises medical therapies. The focus of the MDT shifted to early medicines optimisation realising considerable cost savings.
Embedding pharmaceutical skills into the multidisciplinary team influences decision making right at the initial stage, ensuring that services incorporate good medicine management and medicine optimisation principles at conception guaranteeing high-quality, compassionate care and strong governance.
Pharmacy technician in the IBD team maintains patient safety whilst freeing up pharmacists and physicians

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Introduction: We previously demonstrated that integrating pharmacy services into the IBD team releases doctors’ time and improves medicines management. A pharmacy technician providing routine drug monitoring and other duties under the supervision of the specialist pharmacist frees up clinicians’ time. We present a 3 months pilot.

Methods:
1. Provide blood monitoring service for immunosuppressant therapies (524 thiopurine patients, 419 biologics patients)
2. Manage infusion medication and infusion preparation in the pharmacy-led infusion clinic
3. Collate up-to-date patient information for the multidisciplinary virtual biologic and immunosuppressant clinic (VBIC) review
4. Manage shared care protocols (SCP)
5. Identify funds released

Results:
1. 260 patients monitored: 63 patients (24%) reminded 48 referrals (18.4%) to the pharmacist:
   – 27 patients (10.3%) had drug levels outside therapeutic ranges or antibodies
   – 9 patients (3.5%) had deranged liver function tests
   – 5 patients (1.9%) had leucopaenia
   – 7 patients (2.6%) had either raised faecal calprotectin (FCLP) levels or anaemia
2. Biologics for 259 patients (average of 20 patients/week) dispensed and prepared, maximising vial-sharing, releasing nurses and pharmacists
3. 42 patients contacted to provide a FCLP, IBD scores and bloods 2 weeks prior to VBIC.
4. 17 SCP were sent to patient GP’s
5. £3212 staffing cost released

Discussion/Conclusion: Pharmacy technicians can safely take over the majority of the drug monitoring and infusion preparation. Released funds of £13K (lower staffing cost) and cost savings £36K (vial sharing) per year are projected. This represents an increased cost saving, freeing up nursing time and releasing clinicians for advanced roles within the team (e.g. outpatient clinics, prescribing, helpline queries, counselling patients, TDM). In addition this audit has identified the ongoing need for active monitoring of the medications as 1/5 of patients had abnormal results and 1/4 had to be chased up to undertake monitoring at the appropriate interval.
Biological therapy reduces the need for intravenous iron supplementation in patients with inflammatory bowel disease

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Introduction: Inflammatory bowel disease (IBD), such as Crohn’s disease (CD) and ulcerative colitis (UC) are chronic, relapsing, inflammatory disorders of gastrointestinal tract with increasing global incidence and prevalence. Among broad spectrum of extra intestinal complications encountered in IBD patients, anemia is the most common. The most prevalent type of anemia in these patients is iron deficiency anemia (IDA), secondary to chronic blood loss and impaired iron absorption due to tissue damage. Several studies have shown that IBD patients receiving intravenous iron incurred lower total health care cost compared to patients receiving oral iron. For several decades, medical treatments for IBD were limited to amino salicylates, thiopurines and steroids, which do not change disease course. With increased understanding of immuno pathology of IBD, novel, targeted therapies have unlocked new era of IBD treatment and allowed us to reach new therapeutic goal such as mucosal healing.

Method: We hypothesized that biological therapy will reduce the need for intravenous iron supplementation in IBD patients with IDA. Study was conducted during in time January 01, to December 31, 2018 in Department of Gastroenterology, University hospital Split, Croatia and included all IBD patients currently treated in our department.

Results: Out of total of 321 IBD patients, 110 (34.3%) were receiving biological therapy. Out of 211 (65.7%) patients who are not receiving biological therapy, 78 (37%) were receiving intravenous iron, while only 10 out of 110 (9.1%) who are receiving biological therapy were receiving intravenous iron.

Conclusion: Biological therapy reduces the need for intravenous iron supplementation in patients with IBD, most likely by achieving significantly higher degree of mucosal healing and subsequent increase in iron absorption.

Key words: IBD, biological therapy, intravenous iron
Laparoscopic ileocolic resection for fibrostenotic and complex Crohn’s disease

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Introduction: Laparoscopic approach has been established as the preferred surgical approach for the management of complicated ileocecal Crohn’s disease. This presentation aims at the analysis of our experience with the laparoscopic ileocolic resection at both simple, drug-resistant and complex cases of Crohn’s disease. Data were prospectively collected on a periodically updated patients’ database.

Methods: Between the years 2012 and 2018 the laparoscopic approach was employed at 27 (16 females) patients with a mean age of mean age: 37 ± 15.5 years. During the same period a total of 42 patients were subjected at ileocecal or ileocolic resections for Crohn’s disease either following the traditional “open” approach or the minimally invasive laparoscopic one. Amongst the patients of the laparoscopic group, 13 had fibrostenotic, 9 inflammatory-penetrating and 6 fistulizing phenotype. Either 3 or 4 trocars, placed supraumbilically or at the left abdominal wall, were used to access the peritoneal cavity. The mobilization of the terminal ileum and the right colon was performed either laterally to medially (10 patients) or medially to laterally (17 patients). The mobilization was carefully completed from the normal-appearing to the affected tissues. The specimen was removed extracorporally via a small peri-umbilical incision and the anastomosis was performed as a wide stapled side-to-side anastomosis at all cases, except for the two patients, where a Kono-S type of anastomosis was applied. The laparoscopic approach was needed to be converted to “open” in two of the fistulizing cases of our series (7.4%).

Results: The time duration of the operation was 170’ ± 50’. Anastomotic leak occurred at 2 patients (7.4%) and both required an open exploration for refashioning of the anastomosis at the one patient and creation of stoma at the other. The length of the hospitalization was 10 ± 5 days. At a follow-up period of 6–70 months, no patients required to be re-operated for either disease recurrence or adhesions-related small bowel obstruction.

Discussion/Conclusion: The laparoscopic approach is technically feasible and safe, leading to acceptable morbidity rates. It may be advantageous over the “open” approach at certain parameters as the reoperation rates and the deleterious post-operative adhesions.
Small bowel capsule endoscopy: A valuable tool for classifying the unclassified

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Introduction: Ulcerative colitis (UC) and Crohn’s disease (CD) are idiopathic inflammatory bowel diseases (IBD) with no unique, gold standard diagnostic test. UC and Crohn’s colitis are in approximately 10\% of cases impossible to be distinguished. The term IBD unclassified is officially proposed for the cases of chronic colitis showing overlapping endoscopic, radiological, and biopsy histological features between UC and CD, while indetermined colitis is reserved for colectomy specimen. Our aim was to evaluate the role of capsule endoscopy in the diagnostic work-up of IBD unclassified.

Methods: We prospectively studied all cases of IBD unclassified explored by capsule endoscopy in our tertiary referral gastroenterology center. Patients were investigated by small bowel CE after contraindications were excluded. Diagnostic criteria for small bowel CD consisted in more than 3 ulcerations, irregular ulcers or stenosis; if fulfilled, Crohn’s colitis was sustained. The absence of CD features in the SB strengthened the assumption of UC. Follow-up data were recorded.

Results: Twelve patients with IBD unclassified were explored by SBCE. Five patients had SB lesions meeting the diagnostic criteria for CD. The remaining seven examinations showed no SB significant findings; therefore, they were classified as UC. No complications occurred. The patients were treated accordingly. Follow-up data recorded a case of colectomy for refractory UC.

Conclusion: SBCE turned out to be a useful safe tool in the management of IBD unclassified. The diagnostic valences of SBCE reinforce the grounds of proper decision making.
Particularities of therapeutic strategies in IBD patients from North-Eastern Romania

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Introduction: Inflammatory bowel disease (IBD) is a chronic and heterogeneous disorder characterized by remitting and relapsing periods of activity. Although there has been much progress in the management of IBD with established and evolving therapies, the choice of an applicable therapy is one of many issues regarding these patients. Therefore, the treatment approach and follow-up of patients have undergone a significant change. The aim of this study was to assess the main treatment approach in patients with IBD in a tertiary referral center.

Methods: All cases of IBD hospitalized in our tertiary referral center from January 2011 to June 2016 were included in the study. Demographic, clinical, laboratory characteristics and disease severity along with type of medication were carefully collected from the patients’ medical charts.

Results: In this study we included 329 IBD patients, most of them males (58.97%), mean age $44.11 \pm 15.51$, predominantly with ulcerative colitis (UC) (69.3%). The majority of IBD patients were treated with 5-aminosalicylates (5-ASA), most of them being with UC (76.17%). Glucocorticoids were recommended in 209 (63.53%) cases, especially in patients with UC compared with those with Crohn’s disease (CD) (61.72% vs. 38.26%). Immunomodulators were used in about 23.71% of all cases predominantly in CD patients (56.4% vs. 43.5%). Out of all 329 patients, 70 (21.28%) received biological therapy, with adalimumab being the most used agent (66.2% vs. 33.8%).

Discussion/Conclusion: The treatment landscape for IBD is rapidly evolving with the recent validation of innovative biologics.
Correlation between Ki67 expression with Fas/FasL expressions in IBD patients

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Introduction: The most popular marker for cell proliferation is Ki67. Ki67 is very useful prognostic factor in many cancers. The expression of Ki67 can be found in immune cells in the lamina propria of colon mucinosum and some epithelial cells. The expression of Ki67 can be correlated with expression of Fas and FasL. Therefore, the objective of the current study was to assess the expression of Fas ligand (FasL) and Fas receptor (FasR) as the proteins of post mitochondrial apoptotic pathway in ulcerative colitis, Crohn’s disease, colorectal cancer.

Materials and methods: Our study was performed on 35 patients with ulcerative colitis, 30 patients with Crohn’s disease. Standard immunohistochemical technique was adopted to detect the expression of Ki67, Fas and FasL. The intensity of Fas/FasL staining reaction was evaluated in 4-point scale was assessed as absynt, weak, medium and strong.

Results: The medium Fas receptor expression was observed in epithelial cells in ulcerative colitis and Crohn’s disease, weak in 75.5% of colorectal cancer patients, as compared to normal glandular epithelium where Fas receptor expression was strong in 100% of cases. Whereas FasL expression was mostly expressed in ulcerative colitis, strong in 70% of colorectal cancers, but absent in Crohn’s disease and normal colorectal epithelium. We found the strong expression of Ki67 80% in the inflammatory infiltration in Crohn’s disease and ulcerative colitis with Fas positive cells. But the expression of Ki67 in FasL positive cells was about 30% in colorectal cancer.

Conclusion: In our study we found correlation between high expression of Ki67 and expression of FasL and correlation between FasL expression and medium expression of Ki67. In our opinion the increasing cell proliferation in Crohn’s disease and colitis ulcerosa can be associated with higher risk of developing colorectal cancer.
Listeria monocytogenes meningitis in a patient with ulcerative colitis using infliximab: A case report

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Introduction: Biological agents such as infliximab are known to increase tendency to infections. A case of Listeria monocytogenes meningitis is presented in a patient with ulcerative colitis using infliximab.

Case: A 19-year-old female patient presented to the gastroenterology outpatient clinic four times a day with bloody stools, severe headache, nausea and vomiting. It was learned that headache started 3 days ago, was on both sides of the head, increased with neck movements, very severe and there was no decrease in pain despite painkillers. She was diagnosed with ulcerative colitis 6 months ago and was hospitalized with methylprednisolone, oral meselazine and mesalazine enema. She was discontinued methylprednisolone after treatment 8 weeks. Than 4 weeks after discontinued methylprednisolone, ulcerative colitis exacerbation was seen and she was reevaluated after infliximab loading therapy. The patient received infliximab maintenance therapy 5 days prior to referring to our clinic. Physical examination revealed poor general consciousness, conscious, cooperative, and minimal sensitivity in the left lower quadrant and suprapubic area. There was normal stool contour in the rectal examination. In the laboratory examination, leukocytes: 12.720, neutrophils: 11.090, hemoglobin: 11.52 g/dl, platelets: 430,000, CRP 20.19 g/dl, ferritin 1438 ng/ml, sedimentation 71 mm/h and feces parasites and no other infection were found. There were 41 leukocytes, 3 (+) proteinuria in urine, and no growth in culture. Electrocardiography and chest radiography were normal.

In abdominal tomography images, no findings of toxic megacolon were found. The patient was started on 4 g of oral meselazine, 2 g mesalazine enema, 2 x 2 g/day ceftriaxone, IV hydration, proton-pump inhibitor, anti-emetic and analgesic treatment. On the physical examination of the patient, general condition deteriorated, and blood cultures were obtained after 3 times fever. Neurological examination revealed nuchal rigidity and brudzinski positivity. Meningitis was considered and neurological and infection departments were consulted. Acute pathology was not found in the brain magnetic resonance imagine. Lumbar puncture was performed in the patient without bleeding diathesis and intracranial mass. Glucose in the cerebrospinal fluid (CSF): 10 mg/dl (CSF/venous blood glucose ratio 10%), total protein 170.3 mg/dl, sodium 144 mEQ/l.t. A total of 150 cells were seen in the CSF direct view and were mostly neutrophil-dominated. Central nervous system multiplex PCR was sent from CSF fluid, and the results were empirically ceftriaxone 2 x 2 g, acyclovir 3 x 750 mg, mannitol 4 x 125 cc (dose reduced with 2 day intervals), nasal oxygen and 30 degrees bed head elevation were applied. Listeria monocytogenes were isolated in the central nervous system multiplex PCR on the third day of the admission. He was transferred to the infectious diseases service for the continuation of his treatment.
**Conclusion:** Listeria monocytogenes is an uncommon infectious disease. However, it may cause life-threatening infections in neonates, pregnant women, elderly, immunosuppressed transplant recipients and special patient groups where cellular immune response is impaired. In our patient, Listeria meningitis occurred in a young patient with ulcerative colitis who received infliximab as a biological agent as immunosuppressive therapy. While taking these medications, attention should be paid to the indications, the possible side effects should be well known and the patients should be followed closely.

**Key words:** ulcerative colitis, Listeria meningitis, infliximab
Is hepatitis B and hepatitis C screening being neglected in patients with inflammatory bowel disease? What is the frequency?

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Objective: The frequency of hepatitis B virus (HBV) surface antigen, (HBsAg) positivity is 4% and antiHcIgG/antiHBs is around 30%. The frequency of hepatitis C virus (HCV) is around 1%. Immunosuppressives, especially corticosteroid, have an important role in the treatment of inflammatory bowel disease (IBD). Hepatitis B exacerbation is a well-defined entity in patients receiving immunosuppressive therapy and all sero-positive patient with hepatitis B are at risk. The aim of this study was to investigate whether the hepatitis B and C screening in IBD patients and whether HBV and HCV seropositivity rates were investigated.

Materials and methods: Patients who were followed-up with the diagnosis of IBD between September 2012 and November 2018 were retrospectively reviewed.

Results: A total of 214 patients, 107 (50%) were female with a mean age of 36.03 ± 13.37 years, (range of 16–75 years). Of the patients, 161 (75%) were ulcerative colitis, 51 (24%), Crohn’s disease, and 2 (1%) indeterminate colitis. Forty percent of the patients had a history of corticosteroid using in the past year. Sixty-five percent of the patients used 5-aminsalicylic acid (ASA) while 35% were on immunosuppressive drugs with or without 5-ASA. Thirty-one patients (60%) were used azathiopurine (AZA), 13 mercaptopurine and others (20%), 11 (20%) were used biological agents such as adalimumab, infliximab, vedeluzimab. Of the patients, 151 (58%) screened for serological HBsAg, antiHBs and antiHCV tests. While HBsAg was positive in 3 patients (1.5%), antiHBs were in 68 patients (45%) and no anti-HCV positivity was detected.

Conclusion: Forty percent of the patients followed up with IBD were used corticosteroid and one third of them were used immunosuppressive drugs, including biological agents. Nearly one third of these patients were not underwent HBV and HCV screening. While HCV was not detected in patients with screened IBD, HBV sero-positivity was detected in approximately half and HBsAg positivity in 1.5%. HBV and HCV should be screened in all IBD patient and HBV prophylaxis should not be neglected in patients who need immunosuppressive therapy.

Key words: inflammatory bowel disease, hepatitis B, hepatitis C, immunosuppression
Efficacy of infliximab after failure of subcutaneous anti-TNF agents in patients with moderate-to-severe ulcerative colitis

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Introduction: To assess the efficacy of intravenously administered infliximab in patients with moderate-to-severe ulcerative colitis (UC) who have failed therapy with subcutaneously administered adalimumab or golimumab.

Methods: Retrospective analysis of prospectively collected data of all anti-TNF naive UC patients who received adalimumab or golimumab for the treatment of moderate-to-severe UC in the participating tertiary referral centers. Patients who showed primary non-response or secondary loss of response to the subcutaneously administered anti-TNF were scheduled to receive intravenously administered anti-TNF (infliximab). Primary non-response was defined as failure to achieve a clear improvement in symptoms and a drop in CRP, if elevated at baseline, at week 6 through week 14. Secondary loss of response was defined as reappearance of symptoms and re-elevation of CRP at any time period after the first 14 weeks of anti-TNF therapy. Clinical response to infliximab was subsequently assessed at week 14 and was defined as a decrease in the total Mayo score of at least 3 points and at least 30% from baseline. Finally, clinical remission, defined as Mayo score of ≤ 2 with no individual sub-score > 1, was assessed at week 54.

Results: From September 2015 till September 2017, 58 anti-TNF naive ulcerative colitis patients (males = 31, females = 27; E1 = 1, E2 = 32, E3 = 25, median age = 40.6 years, median disease duration = 38.6 months) were started on adalimumab (n = 38) or golimumab (n = 20) because of moderate-severe disease. From these patients, 21 (36.2%) were primary non-responders (adalimumab = 13, golimumab = 8), while 8 more (13.7%) showed secondary loss of response (adalimumab = 7, golimumab = 1). Therefore, 29 patients were started on infliximab, because of failure of subcutaneously administered anti-TNF. At week 14, 18 patients showed clinical response (62.1%), while at week 54, 14 patients were on clinical remission (48.3%).

Discussion/Conclusion: UC patients with moderate-to-severe disease that are anti-TNF-naive can be successfully treated with intravenously administered anti-TNF after failure of anti-TNF administered subcutaneously.
Phenotype of inflammatory bowel disease in patients on biological therapy

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Introduction: Inflammatory bowel disease (IBD) is a chronic and disabling condition requiring life-long treatment, presenting a significant burden on patients and the healthcare system alike. The aim of this study was to analyze the phenotype in patients on biological therapy (BT), and the availability of therapy.

Methods: Adult patients (18+) with confirmed IBD receiving BT in the Clinical Hospital Center Rijeka between 2008 and 2018 were included. Patients received anti-tumor necrosis factor (TNF) drugs (infliximab, adalimumab and golimumab), vedolizumab, and ustekinumab. Montreal classification for Crohn’s disease (CD) and ulcerative colitis (UC) was used to determine IBD phenotype.

Results: A retrospective analysis of 152 patients was performed. A total of 103 (67.76%) patients were male. Patients diagnosed with CD totaled 105 (69.08%), and with UC 47 (30.92%). Mean age at diagnosis was 29.88 years. Based on a step-up approach, almost all patients (90.13%) received corticosteroids and immunosuppressants prior to BT. Most patients received one BT (61.84%), 30.26% received two, and only 7.89% three. In 63 (41.40%) patients BT was discontinued. The most common disease phenotypes of CD were A2L3B3 (16.19%) and A2L3B3p (15.24%). A total of 16 (10.52%) patients were diagnosed with CD at a pediatric age (A1). Phenotype E3S3 (38.30%), followed by E2S2 (27.66%), and E3S2 (23.40%) were the most frequent in UC patients. A subanalysis of patients diagnosed with IBD after 2008 showed the mean duration of illness before induction of BT, until 2013, was 3.41 years. In comparison, patients diagnosed between 2014 and 2018 received BT after 1.33 years.

Discussion/Conclusion: In our cohort, patients with the most severe phenotypes of IBD received BT, which has become more available after 2014. This may be due to a greater awareness of the benefits of early induction of BT when indicated, but also due to the advent of biosimilars.
Azathioprine dosing and metabolite measurement in paediatric inflammatory bowel disease – Does one size fit all?

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Introduction: Azathioprine is widely used for maintenance of remission in children with inflammatory bowel disease (IBD). Measuring thiopurine metabolites (6-TGN and 6-MMP) can aid optimising treatment and preventing toxicity. Although weight base dosing regimen is widely accepted, there is evidence reporting clinical remission with less than recommended thiopurine doses. We report a proactive approach combining early metabolite measurements with IBD activity index to achieve optimal azathioprine dosing in children.

Methods: Retrospective review of azathioprine dosing, IBD activity indexes and thiopurine metabolites in 40 children with inflammatory bowel disease. Additional treatments and azathioprine effect on blood counts were also examined.

Results: 40 children (40% females) with IBD (26 Crohn’s disease, 12 ulcerative colitis and 2 inflammatory bowel disease unclassified IBDU), mean age ± SD (12.2 ± 3.4). 5 children were on biologic therapy. Mean azathioprine dose was 1.3 mg/kg ± 0.4, 6-TGN 280 ± 151, 6-MMP 1022 ± 1007. Disease activity index (Crohn’s and UC paediatric specific) at the time of metabolite measurement 6.5 ± 8. 28 children did not require azathioprine dose adjustment, it was increased in 12.

Discussion/Conclusion: In a subset of children with IBD, early monitoring of thiopurine metabolites can help clinical decision making regarding azathioprine dosing regimen. It also supports evidence that therapeutic thiopurine metabolites and subsequent clinical remission can be achieved with lower than the recommended target dose.
Can daily SCCAI measurements over a 6 month period better phenotype the pattern of disease in ulcerative colitis?

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**Background:** Access to daily disease activity measurements may allow more accurate phenotyping of the pattern of disease in UC. Clustering patients by the percentage of time spent in each disease category (remission, mild, moderate, severe) may provide a more objective classification of the pattern of disease.

**Methods:** TrueColours UC, a real-time web-based programme, collected daily SCCAI results from 66 patients for 6 months. Disease pattern was defined as the proportion of time spent in each SCCAI disease activity category: remission (SCCAI 0–2), mild (SCCAI 3–5), moderate (SCCAI 6–11) and severe (SCCAI ≥ 12). Principal component analysis (PCA) and unsupervised clustering was performed. To determine whether clustering provided adequate separation of different disease patterns, each data point was examined with reference to three clinical categories: Remission (> 80% time with SCCAI ≤ 2 and no time with SCCAI ≥ 5), Relapsing (some time spent in remission, but with isolated episodes of SCCAI ≥ 5 requiring escalation in medical therapy), and Persistently Active (> 80% time spent with SCCAI ≥ 3).

**Results:** The unsupervised cluster plot identified 5 clusters (A to E, figure 1), with most clusters matching the pre-determined categories. The Remission category matched Cluster A, with patients in clinical remission for > 80%. Other clusters represented different patterns of active disease. The Relapsing category matched Cluster B, with 11/11 patients having an exacerbation requiring escalation of therapy (prednisolone in 7/11). The Persistently Active category matched with Group D and Group E. In Group D, 3/3 patients spent > 50% in mild disease activity and > 30% in moderate disease activity. In Group E, 6/6 patients spent < 5% in remission and > 80% in mild disease activity. In Cluster C, all patients had some active disease, but had components of both Relapsing and Persistently Active categories.

**Conclusion:** Unsupervised clustering from daily symptom scores of SCCAI accurately classified most patients. Most importantly, it separated those in remission from those with active disease. It also enabled sub-classification of those with active disease.
Analysis of fungal microbiota dysbiosis in IBD

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Introduction: Inflammatory bowel disease (IBD) is chronic relapsing and remitting disease of the gastrointestinal tract. Although the precise etiology and pathogenesis of IBD remains elusive, epidemiological data conclusively point to be attributed to an aberrant immune response against environmental factors such as the gut microbiota in a genetically susceptible host. The bacterial microbiota plays a major role in human physiology and pathogenesis of IBD. The Fungi are often ignored in studies. Although the role of fungi has been suggested in pathogenesis of IBD, the available data are scarce. The aim of our study was to analyze and compare the faecal fungal microbiota in patients with IBD and healthy subjects (HS).

Methods: Our study evaluated fungal composition of the faecal microbiota of 66 patients with CD and 38 patients with UC diagnosed in West China Hospital and 39 HS by ITS2 sequencing. The Qiime pipeline was used to assess composition and diversity. Using LEfSe observed differential fungal composition between subjects.

Results: The faecal fungal microbiota was dominated by two phyla, basidiomycetes and ascomycetes in both IBD and HS. We observed that fungal microbiota was skewed in IBD, with an decreased basidiomycota/ascomycota ratio, a decreased proportion of Aspergillus and Saccharomyces and an increased proportion of Exophiala. Polythrincium, clonostachys, Candida compared with HS. Using LEfSe we observed several differential fungal composition in different subject. Exophiala (p = 0.02), Agaricales (p = 0.02) species were overrepresented in UC, whereas Bulleribasidiaceae (p = 0.01), Ustilaginaceae (p = 0.007), Ustilaginales (p = 0.007), Ustilaginomycetes (p = 0.007) species were overrepresented in HS. We then directly compared the fungal composition between subgroup of CD and UC, we observed Eurotiales (p = 0.007), Aspergillus (p = 0.025), Thermoascus (p = 0.04) species were overrepresented in UC-remission. Ascomycota (p = 0.008) and Didymellaceae (p = 0.02) species were associated with CD-remission, whereas Saccharomyces (p = 0.03) and Xylariaceae (p = 0.006) species were associated with CD-flare. There was no significant difference in fungal Alpha diversity between IBD and HS. Beta diversity analysis showed that one subgroup of IBD samples segregated from HS whereas another subgroup overlapped with HS.

Discussion/Conclusion: There was no significant change in fungal diversity in IBD. However, we observed fungal composition was skewed with decreased basidiomycota/ascomycota ratio on phyla level, particularly in IBD-flare group. The fungal composition was dominated by aspergillus and saccharomyces in HS, while the proportion of exophiala, polythrincium, clonostachys, candida was increased in IBD on genus level.
The impact of surgical resection on bone loss in patients with Crohn’s disease

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Introduction: Bone loss is common in patients with inflammatory bowel disease (IBD). The aim of the study was to evaluate the prevalence and risk factors of bone loss in patients after surgical resection for Crohn's disease (CD).

Methods: Cases of bone mineral density (BMD) and disease characteristics were retrieved from 155 patients with CD who had intestinal resection in a referral IBD center. BMD was measured on dual-energy X-ray absorption (DEXA). Patients were classified into normal BMD and low BMD groups based on the International Society for Clinical Densitometry. Demographic and clinical variables were evaluated with logistic regression analysis to identify potential risk factors.

Results: The DEXA of lumbar spine indicated that 45 (29.0%) CD patients had a low BMD at a median of 2.2 years after bowel resection. Body mass index (20.13 ± 2.56 versus 18.27 ± 2.00, p < 0.001) and history of colectomy (48.2% versus 77.8%, p = 0.001) were independently associated with the BMD of the lumbar spine. The BMD of lumbar spine showed an increase in patients with CD after small bowel resection at a median of 1.4 years and a decrease in patients after colectomy at a median of 1.1 years compared to their LS-BMD before bowel resection.

Discussion/Conclusion: Low BMD was common in CD patients after surgical treatment. A low BMI and history of (hemi)colectomy were significant clinical risk factors for low BMD in CD patients.
Long-term follow-up of a girl with co-occurrence of celiac disease and ulcerative colitis

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Introduction: According to the literature, the co-occurrence of celiac disease (CD) and ulcerative colitis (UC) in children is extremely rare. So far there are only 5 case reports described in which both diseases are present.

Methods: We report about a long-term follow-up of a 18-year-old girl with CD and UC.

Results: Diagnosis of CD and UC was established at the age of 12. Upon admittance the patient presented with chronic diarrhea, nausea and loss of appetite. She was seriously underweight. Laboratory testing revealed anemia, elevated sedimentation rate (ESR), C-reactive protein (CRP) and low albumins. Liver and pancreatic enzymes, fecal elastase and sweat test were normal. Benzidine stool test was positive. Infective etiology was excluded. Considering high values of anti-tissue transglutaminase antibodies (tTG – 163.3 RU/ml; r.v. < 20), and histopathological changes typical for CD (Marsh IIIA), gluten-free diet (GFD) was initiated. In the following period bloody loose stools were noted. Fecal calprotectin was high (FC – 1296 µg/g; r.v. < 50), and colonoscopy revealed left-sided colitis, with ulcers, intraepithelial granulocytes and crypt abscesses. MR-enterography excluded Crohn's disease. After the diagnosis of UC (PUCAI-60), along with CD, the patient was prescribed prednisone and mesalazine, and continued GFD. The stools normalized in a few days, and upon discharge her clinical feature was normal (PUCAI-5). After corticosteroid discontinuation, there were no signs of relapse. The first relapse occurred after 5 years, characterized by bloody chronic diarrhea, weight loss (PUCAI-30), anemia, elevated ESR, CRP, high FC (2328.1 µg/g). Anti-tTG was negative. Ileocolonoscopy confirmed moderate pancolitis (Mayo-2, UCEIS: 2+0+1). CD was in remission. On prednisone regiment, increased mesalazine doses, and slow introduction of azathioprine remission was achieved after 3 weeks and is presently maintained.

Discussion/Conclusion: Due to the high incidence of both diseases, we presume that there should be higher comorbidity prevalence than what is described in the literature. Our patient clinical course was mild, but it remains to be seen whether the shared genetic risk between both diseases predisposes to a more aggressive IBD phenotype.
Correlation between caspase-8 and survivin expression in patients with ulcerative colitis

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Introduction: Apoptosis is a physiological cell death process that contributes to the development and maintenance of healthy cells and tissues. It has been proven that apoptosis plays a significant role in the regulation of homeostasis in intestinal epithelium and controls the cellular immune response to the pathogenic agent. Increased epithelial cell apoptosis induces the loss of epithelial continuity in UC patients. Therefore, the aim of our study was to evaluate the expression of caspase-8 (initiator caspase of apoptosis) and survivin (inhibitor of apoptosis protein) in patients with ulcerative colitis.

Methods: The study included 30 patients diagnosed with ulcerative colitis (UC). The expression of caspase-8 and survivin proteins in tissue sections was assessed by immunohistochemical methods. The color reaction was defined as a negative (lack of expression), weak (< 10% of positive cells), medium (10–50% of positive cells) and strong (> 50% of positive cells).

Results: The color reaction of caspase-8 was observed in cytoplasm whereas survivin in nuclei in dysplastic glandular tubes and inflammatory cells. In patients with UC it was observed the absence and the weak expression in normal glands (41.9% and 32.3%), predominant weak and medium reactions in dysplastic glands and (33.3% and 50.0%) and weak in the inflammatory cells (58.0%). In normal glandular tubes, the expression of survivin was a weak, moderate and strong in 37.5%, 12.5% and 21.8% of cases, respectively. Moreover, it was observed a weak and strong reaction of survivin in the inflammatory cells of 50% cases with UC. Higher expression of caspase-8 in dysplastic glands correlated with higher expression of survivin (p = 0.024).

Discussion/Conclusion: Overexpression of survivin may play a role in the inflammatory reaction in patients with UC. Simultaneously, survivin can inhibits caspase-8 activity and cell death in patients with ulcerative colitis.
Small intestinal bacterial overgrowth in patients with inflammatory bowel disease: Gender and age peculiarities

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Introduction: Inflammatory bowel diseases (IBD) may lead to small intestinal bacterial overgrowth (SIBO), which are may be depended on patients’ age and gender.

The aim of the study is to identify and analyze SIBO in patients with IBD depending their age and gender.

Materials and methods: 80 patients with IBD included in this study: 53 (66.3%) patients with ulcerative colitis (UC) and 27 (33.8%) ones with Crohn’s disease (CD). All patients were undergone colonoscopy. Depending on gender all patients were divided into 2 groups: 40 female patients (50.0%), and 40 (50.0%) male patients. Using Gastrolyzer (Bedfont Scientific Ltd, Great Britain), the hydrogen (H₂) breath test with glucose is done to assess SIBO. Hydrogen breath test was taken 1–3 hours in the morning after a 12 hour fast the night before and a special diet the day before this test. According to age, all observed patients were divided into 3 age groups: young (18–39 years), middle-aged (40–59), or elderly (60+).

Results: The hydrogen breath test with glucose was positive in 50 of 80 (62.5%) patients. 29 among 40 female patients (72.5%) and 17 among 40 male ones (52.5%) had positive SIBO status. Sharp increase of H₂ levels during 60 minutes (47.1 ± 3.3 ppm during 45 minutes and 48.7 ± 3.2 ppm) was revealed in female and male patients with IBD, correspondingly. These data meant disorders of human microbiota in small intestine in these patients. SIBO was diagnosed in 65.5% women with UC and 71.4% male with CD. It was established that SIBO frequency depended on the age observed patients. Positive SIBO status was in 95.0% older patients (60+), 53.3% middle-aged, and 51.1% young patients with IBD.

Conclusion: Disorder of excessive bacterial growth in the small intestine was revealed in most observed patients with IBD, mainly in women with UC and men with CD, and also in older age patients.
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IBD: From Diagnosis to Therapy

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Pribaltiyskaya
St. Petersburg, Russia

Abstracts
Poster Abstracts