IBD 2017 – Therapeutic and Biological Barriers

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Abstracts of Invited Lectures
Poster Abstracts

Symposium 209

IBD 2017 – THERAPEUTIC AND BIOLOGICAL BARRIERS

Berlin, Germany
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Scientific Organization:
B. Siegmund, Berlin (Germany)

Scientific Co-Organization:
M. Allez, Paris (France)
I. Dotan, Petah Tikva (Israel)
H. Herfarth, Chapel Hill (USA)
J. Wehkamp, Tübingen (Germany)
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K. Zheng, H. Shen, J. Jia (Nanjing, CN)

152. Significantly decreased colonic ERβ in immune cells may contribute to the disease progression in a murine colitis model
L. Zhu, D. Guo, L. Cheng (Wuhan, CN)

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L. Zhu, L. Cheng, R. Zhao, D. Guo, K. Zou (Wuhan, CN)
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Y. Zhu, H. Zhang (Nanjing, CN)

155. Modulation of immune cell composition and epithel barrier function by leptin in a patient with acquired generalized lipodystrophy and combined Crohn’s disease
J.F. Ziegler, C. Böttcher, H. Wu, M. Letizia, I. Anagnostopoulos, B. Siegmund, C. Weidinger (Berlin, DE)

156. Usefulness of TNBS colitis in inflammatory bowel diseases
L. Zouiten, M. Naouar, L. Charfi, A. Laabidi, J. Boubaker, A. Filali (Tunis, TN)
Session I

Microbiome/metabolome – Impact on barrier function
The interleukin (IL)-1 family of pro-inflammatory cytokines are the most potent pyrogens in the body, and their excessive production can cause several auto-inflammatory syndromes, or contribute to a range of inflammatory and metabolic disorders. The expression of the key members of the IL-1 family, such as IL-1β and IL-18, is regulated at both the transcriptional and post-transcriptional levels. IL-1β and IL-18 are produced as inactive precursors, which require activation of caspase-1 by the inflammasomes for their maturation and release by immune cells, occasionally at the cost of caspase-1-mediated cell death. We have recently discovered that inflammasomes are released into the extracellular space where they remain active after the demise of activated cells, and that extracellular inflammasomes can amplify inflammation by sustaining extracellular production of IL-1β. However, the sources of extracellular pro-IL-1β are not known. Recent advances in platelet proteomics have revealed that these non-nucleated cells are able to produce their own cytokines, including soluble IL-1β and membrane-bound IL-1α, and are able to significantly magnify IL-1 production by immune cells. As platelets outnumber leukocytes by several folds, they could potentially be the major source of extracellular inflammasomes in the body, or be a major producer of IL-1 precursors that are cleaved by extracellular inflammasomes released from dying immune cells. In this study, we investigated the mechanism(s) by which platelets produce IL-1, and the specific contribution of platelet-derived IL-1 to sterile inflammation, or host resistance to infection. We believe that a deeper understanding of platelet-IL-1 and their interaction with immune cells during sterile inflammation, or infection might help to uncover new targets for immune-therapies.
Colitis: Interplay between microbiome and genome

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Human cohort studies in patients with inflammatory bowel diseases (IBD) demonstrated changes in gut microbiota composition and function often referred to as dysbiosis. Genome-wide association studies (GWAS) substantiated these clinical studies in assigning a mechanistic role of microbe-host interactions for disease etiology. Nevertheless and beyond considerably improved metagenomic resolution and bioinformatic tools, allowing even strain level analysis, the search for microbial risk patterns in these cohorts is often confounded by environmental factors (e.g. medication) and large variations in disease phenotypes, questioning the prognostic and therapeutic value of the currently available information. Thus, a cogent definition of dysbiosis is lacking, as well as an agreement of whether pathobionts or complex shifts in the microbiota trigger inflammation in the host. At the level of mechanistic understanding the molecular integration of pleiotropic signals coming from the complex and dynamically changing microbial ecosystem is one the biggest challenges in this field. In this context, transfer experiments of patient-derived microbiota into germfree mouse models for IBD provide a still underdeveloped tool to substantiate the disease-conditioning nature of dysbiotic microbial ecosystems in the genetically susceptible host.
**Oncobiome: Microbial influences in carcinogenesis**

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Gene-environment interaction plays a key role in disease susceptibility including colorectal cancer. Microbiota, particularly the intestinal biota, plays a central role in host physiology and the composition and activity of this consortium of microorganisms is directly influenced by known cancer risk factors such as lifestyle, diet and inflammation. Accumulating evidences point to a role of microbiota in carcinogenesis. The mechanism by which microbiota impact on cancer development is still unclear but cancer risk factor such as inflammation and diet are known environmental components modulating microbiota. Specifically, inflammation represents a powerful condition by which microbial composition and biological activities is altered. Using gnotobiotic technology, microbial genetic manipulation and genetically engineered mice (Apc\(^{min/+}\); IL10\(^{-/-}\)), we investigated the role of specific bacterial or consortium of bacteria in the development of colitis-associated colorectal cancer. In this lecture, I will provide evidence that specific microbial genotoxic activities originating from various strains such as *Escherichia coli*, *Atopobium parvulum* and *Campylobacter jejuni* promote development of CRC. For example, presence of DNA damaging toxins such as colibactin from adherent invasive *Escherichia coli* or cytolethal distending toxins (cdt) from *Campylobacter jejuni* are critical for development of colorectal cancer. In addition, we recently observed a correlation between presence of hydrogen sulfide (H\(_2\)S)-producing bacteria (HSPB) and severity of new onset Crohn’s disease (CD) in a pediatric population, with strain *Atopobium parvulum* able to promote development of colorectal cancer in Apc\(^{min/+}\); IL10\(^{-/-}\) mice. Although single organism promotes development of colitis-associated colorectal cancer (CRC) in preclinical models, an emerging concept is that polymicrobial interaction is implicated in human pathology, including inflammatory bowel disease (IBD). I will present evidence that consortia of bacteria obtained from human CRC tissues promotes colorectal cancer in gnotobiotic Apc\(^{min/+}\); IL10\(^{-/-}\) mice. These studies represent the first step toward understanding mechanisms by which microbiota influence development of colorectal cancer, and identify new potential therapeutic target for prevention/treatment of cancer.
Pouchitis: Insights into mechanisms of IBD

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Proctocolectomy and ileal pouch anal anastomosis (IPAA) is the surgical therapy of choice in patients with intractable ulcerative colitis (UC) or its complications such as perforation, hemorrhage, dysplasia or cancer. Up to 25% of UC patients will undergo proctocolectomy and IPAA. This procedure enables removal of the diseased mucosa, avoidance of permanent ileostomy and preservation of the defecation mechanism, and avoidance of inflammatory bowel disease (IBD) therapies. However, several short and long-term complications are associated with IPAA, the most common being pouchitis. Pouchitis occurs in up to 60% of the patients, depending on definitions and time of follow up and may be acute, recurrent acute or chronic. Its treatment usually includes antibiotics, probiotics, but most known IBD-related treatment was used in patients with pouchitis. Pouchitis has multiple similarities with "traditional" IBD phenotypes, including clinical presentation, endoscopic and histologic findings, laboratory indices, serologic and genetic biomarkers, and dysbiosis. The development of small intestinal inflammation in a previously normal small bowel suggests that pouchitis may reflect processes occurring at the early stages of IBD, specifically Crohn's disease. In the talk we will discuss data obtained in pouchitis-focused research which offer insights on the pathogenesis-and clinical approach to IBD.
Session II

Breaking polarization towards IBD
The immunological point of view

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In most patients, refractory of inflammatory bowel (IBD) disease to conventional therapy is imprinted in the patient’s immune system. When a patient’s immune system is ablated with specific therapeutic antibodies, and regenerated from autologous progenitor cells, more than 60% of refractory patients achieve long-term therapy-free remission. This “immune reset” is eliminating the experienced lymphocytes of the patient, which obviously had driven the inflammation. But why are these “memory” lymphocytes refractory to conventional immunosuppressive therapy? One reason may be that they are adapting to survival in chronic inflammation, making the cells refractory to therapies targeting primarily activated, naïve lymphocytes, as most conventional therapies do. We have shown that in murine IBD, T helper (Th) lymphocytes controlling the inflammation (a) inevitably develop into Th1 lymphocytes expressing the master transcription factor T-bet, and (b) that T-bet and repeated antigenic restimulation induce expression of the transcription factor Twist1. Twist1 controls survival of Th1 cells by inducing microRNA148a, which suppresses the pro-apoptotic protein bim. Twist1 also supports the metabolism of the Th cells in chronic inflammation, by upregulating genes involved in fatty acid oxidation and protecting against reactive oxygen species. This is just one example of the molecular adaption of proinflammatory T lymphocytes to chronic inflammation. The good news is that these adaptations represent novel and selective targets for a causative treatment of chronic inflammation.

A second reason may be that currently we have a limited understanding of the lifestyle of experienced lymphocytes und “Immunological Memory” as such. Most of our understanding is derived from the analysis of blood-borne migratory lymphocytes, populations of unknown significance as drivers of chronic inflammation. The concept of experienced lymphocytes as circulating lymphocytes has been challenged recently by the discovery of tissue-resident memory lymphocytes. We and others have shown that these lymphocytes persist as cells resting in terms of proliferation and migration, in epithelial tissues and in the bone marrow. In particular we could identify a novel population of memory plasma cells maintained in the bone marrow in niches organized by stromal cells. Survival of these memory plasma cells is critically dependent on cell contact to the stromal cells and cytokines addressing the BCMA-receptor of the plasma cells. Memory plasma cells secreting pathogenic autoantibodies are not affected by conventional therapies. They are a novel therapeutic target, aiming at a reset of chronic inflammations caused by (auto)antibodies.
Fecal microbiome transplantation in IBD – Choosing the right donor and recipient

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From the first description of Crohn’s disease, the link with bacteria has been made and the implication of the intestinal microbiota in the pathology of both Crohn’s disease and ulcerative colitis has been well-established during the past decades. The use of microbial transplants to eliminate or at least ameliorate the disease symptoms in IBD is therefore an appealing treatment strategy.

The knowledge on the interaction between the human intestinal microbiota and its human host is however currently expanding rapidly. The full picture seems still far from being in place. This hampers not only the improvement of describing the disease associated microbial signatures of IBD, but also the targeted adaptation of the microbiota in patients to relieve the disease symptoms.

The past years, several studies on fecal microbial transplantation in IBD have been performed and published. Similar to other FMT trials, from the start, donors were mainly selected based on the absence of pathogens in the donor feces and absence of major diseases in the donor. Patients could often even choose their own donor to cater their resistance against receiving ‘allogenic’ feces for treatment. Although the current European recommendations refer to the selection requirements for human tissue transplants, large scale research on the intestinal microbiota of average people revealed that probably many more factors should be taken into account when choosing a donor for FMT to enhance efficacy and long-term safety of this treatment. Likewise, in-depth screening of patients will lead to better outcome. Currently, it is not clear yet which phenotypic subcategories of IBD patients will potentially benefit most from this treatment, although studies in patients with ulcerative colitis were most promising so far.

In conclusion, we are at an interesting stage in medicine were scientific breakthroughs are being rapidly implemented and converted to novel treatment strategies. However, despite the accumulating data, at this moment still more evidence-based arguments are needed to match specific IBD patients with their most promising donor.
Postoperative strategies in Crohn‘s disease

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Despite the advances in medical therapies surgery for Crohn’s disease remains common. Endoscopic and clinical recurrence is common although time to recurrence varies. Recurrent disease will require further medical therapy and less commonly endoscopic treatment or repeated surgical resection.

The role of medical therapies in preventing post operative recurrence has been the subject of debate over recent years although a number of clinical trials have addressed this issue more recently and have given more insight into the most appropriate drugs to use.

The presentation will address who is most likely to suffer recurrent Crohn’s disease, how best to assess the risk of recurrence and what medical therapies may be effective in this situation. It will specifically address the role of antibiotics, thiopurines and anti-TNFα agents in this situation. It will also explore whether there are any evidence for the use of newer drugs.
Session III

Barriers in therapy
Management of IBD in the elderly

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With the aging of the western world population IBD in the elderly will remain a hot topic for the next coming decades in the IBD field. Diagnosis and management of ulcerative colitis and Crohn’s disease in the elderly are challenging. First, the diagnosis of IBD in elderly patients is not as straight-forward as it is in younger patients, partially because IBD can easily be confused with other more common diseases especially in patients with isolated colonic disease. Then, once the diagnosis is established elderly patients with IBD are already a higher-risk group as increased age is associated with various co-morbidities and with an increased risk of serious infections, including \textit{C. difficile} infections, venous thromboembolic events, hospitalizations, postoperative complications and mortality.

Studies looking at prescribing patterns among elderly patients with IBD usually show high rates of aminosalicylates and corticosteroids with lower rates of immunomodulators or biologic use. These trends reflect prescriber’s concern about safety, including drug interactions, and efficacy among the higher risk age group. However, some elderly patients may also required immunomodulators and biologics especially in severe UC flare and complicated perianal Crohn’s disease. Elderly people are usually less able to tolerate the increases disease burden and lack of disease control constitutes a life threatening condition. Although biologics may be associated with increased adverse event rates appropriate prescribing of these steroids sparing agents earlier during the disease course may improve disease related outcomes. Prevention of infectious complications by appropriate prophylaxis and vaccination program are also mandatory. Rapid and early recognition of disease flares, adverse events related to therapy as well drug failure to control disease are of major importance in frail elderly patients. Careful monitoring of patients and quick decisions are the best available options to remain on stable ground in the challenging management of IBD in the elderly.
IBD therapy after cancer

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

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Crohn’s disease (CD) and ulcerative colitis (UC), referred to as inflammatory bowel disease (IBD), are chronic, relapsing conditions. IBD typically arises at a reproductive age and because the age of first pregnancy is increasing, an increasing number of IBD women will become pregnant after diagnosis. Preconceptional counseling is the most important aspect in the management IBD patients with a pregnancy wish. Patients should be counseled on the influence of IBD and IBD drugs on the pregnancy. In general it is advised to strive for disease remission at least 6 months before conception, since disease activity negatively influences fertility and pregnancy outcome. IBD patients have fewer children compared to the general population [1, 2]. Incorrect believes and poor knowledge on IBD and pregnancy probably contribute to the high rate of voluntary childlessness within the IBD population, resulting in a lower average number of offspring [3, 4]. Recent studies show that fertility is not influenced by the presence of UC or inactive CD [5, 6]. However, active disease is related to subfertility in both male and female patients [7]. Possible reasons are inflammation of the colon involving the fallopian tubes and ovaries, poor nutrition, depression, decreased libido and dyspareunia caused by perianal disease [8]. Female UC patients that had a colectomy with an ileal pouch anal anastomosis (IPAA) have a 3-fold increased risk of subfertility than female UC patients that did not [9–11]. The reason for subfertility after IPAA surgery is most likely destruction of fimbria, the higher rate of hydrosalpinx and tubal obstruction following pelvic surgery [12]. Although there are still misbelieves with regard to pregnancy and IBD, it has been generally accepted that IBD or its treatment is no reason to advise against pregnancy. Disease activity at time of conception and during pregnancy is associated with a higher rate of spontaneous abortion, preterm delivery, thromboembolic events, emergency caesarean section and low birth weight, whereas the majority of pregnancies in women with quiescent IBD are uncomplicated. Most drugs used in IBD are of low risk for the child when used during pregnancy and because disease activity poses the unborn child at risk it is advised to maintain drugs during conception and pregnancy [12].

References:


Session IV

Fistulizing disease – Avoiding breaking barriers
The pathophysiology of fistulising disease

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Fistulae represent a critical clinical complication in Crohn's disease (CD) patients. Up to 50% of CD patients are affected during disease course from fistulas and about one third of patients suffer from recurring fistulae formation. Since medical treatment options often fail, surgical approaches are often needed, however frequently also not successful. Current knowledge suggests that CD fistulas develop as a result of a process called epithelial-to-mesenchymal transition (EMT), probably in areas with chronic ongoing inflammation. During EMT, differentiated and resident intestinal epithelial cells become dedifferentiated and acquire a mesenchymal phenotype. In particular, IEC downregulate epithelial markers, such as E-cadherin and upregulate the expression of mesenchymal markers, such as vimentin or alpha-SMA. Furthermore, fistula-associated cells acquire markers associated with cell invasiveness what then contributes to the development of invasive fistula tracts. Emerging evidence suggests that a specific immune cell and cytokine profile can be detected around CD fistulas, in examples high expression levels of TNF, IL-13 and TGF-β what seems to promote onset of EMT and cell invasiveness. Notably, also genetic factors as well as the intestinal microbiota might be involved in fistula development. A major drawback in investigating fistula pathogenesis and in the development of novel fistula therapies is the absence of a suitable animal model. Current knowledge about fistula pathogenesis is still poor. Future research needs to be directed towards the generation of an in vivo model to allow fistula research in real-life circumstances. The aim would be to identify the driving forces for fistula development, fistula progression and, ideally, fistula closure in vivo. This might critically support the development of new and more effective therapeutic strategies for the treatment of patients suffering from CD fistula.
Fistula imaging

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Fistulas, represent important complications in up to one-third of Crohn's disease (CD) patients along the disease course. Many of these episodes are represented by perianal fistulas that frequently impair patients’ quality of life. Therapeutic options for perianal fistula are limited and at times even inappropriate. Many patients undergo repeated surgery to control symptoms, while often complex fistulae are not closed. Randomized controlled trials (RCTs) with fistula healing as the primary endpoint are scarce, and therefore current knowledge is largely based on retrospective series, and expert opinion. Patients management should be individualized, based on fistula anatomy, patient factors, and defined management goals (closure versus sepsis control), a task that requires a multidisciplinary approach.

In order to make optimal decisions high quality fistula imaging is imperative, it provides information on the anatomy, as well as the complexity of the fistula, and its potential impact on sphincter function and the adjacent structures. The pelvic magnetic resonance imaging (MRI) is considered the gold-standard imaging modality for perianal CD, when performed with different techniques it has an accuracy rate of 76–100% for characterizing fistula tracts and abscesses. Notably, trans-anal endoscopic ultrasound (TRUS) alone, or combined with transcutaneous perineal ultrasound (PUS) in skilled hands, maybe a useful alternative to MRI. Examination under anesthesia (EUA), aside for being a therapeutic tool, may add an additional perspective of the complexity of the disease, and often completes the assessment and accurately classify the fistula and its functional impact. Finally, all these tools may also be used to evaluate outcome measures, either perianal fistula activity scores or response to treatment.

To summarize, all three imaging modalities are essential for fistula classification and for patients’ assessment. These modalities are often complimentary, supporting the importance of routine interplay within experts in a well-functioning multidisciplinary team.
Therapy for fistulising disease – Medical therapy

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Fistula cause considerable morbidity and impairment in quality of life with serious clinical and psychological consequences in patients with Crohn’s disease including permanent sphincter and perineal tissue destruction, as well as short bowel syndrome and debilitating external fistula secretion from perianal as well as abdominal fistula. While currently more treatment options become available, the overall progress in this area is still limited and the management of fistula remains a difficult clinical challenge. Relapse rates following medical and surgical treatment are still high and medical treatment is often limited by side effects under long-term medication or loss of response to treatment. 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 Crohn’s disease.

Symptomatic simple perianal fistulas require treatment. Seton placement in combination with antibiotics (metronidazole and/or ciprofloxacin) is the preferred strategy for these patients. In recurrent refractory simple fistulising disease not responding to antibiotics, thiopurines or anti-TNFs can be used as second line therapy. Third line therapeutic options are provided by vedolizumab and ustekinumab. In complex perianal fistulising disease infliximab or adalimumab can be used as first line therapy following adequate surgical drainage if indicated. A combination of ciprofloxacin and anti-TNF improves short term outcomes. To enhance the effect of anti-TNF in complex fistulising disease, combination of anti-TNF treatment with thiopurines should be considered. Second line therapeutic options for patients with complex fistula are provided by vedolizumab and ustekinumab.

Most treatment options have shown initial dramatic beneficial effects in patients with complex refractory fistulising Crohn’s disease, however, the long-term benefit after discontinuation of these drugs has been disappointing and long-term treatment is generally needed.
Every third patient with Crohn’s disease develops at least one fistulising episode and the greatest proportion is represented by perianal fistulas. Treatment of Crohn’s perianal fistulas remains challenging. The approach is depending on location and extent of disease. The most commonly used classification is the AGA classification with an empiric approach defining a fistula as ‘simple’ or ‘complex’. A simple fistula is low (less than one third through external sphincter complex), has one single external opening, no abscess, no rectovaginal fistula or anorectal stricture and no proctitis. Simple fistulas are relatively uncommon in Crohn’s disease, but can be easily treated by fistulotomy with healing rates between 80% and 100%.

All other fistulas are classified as ‘complex’. Management of ‘complex’ fistulas requires a multidisciplinary approach for choosing optimal medical and/or surgical treatment. The main pillars that influence management are luminal inflammation, the course of the fistula tracts in relation to the external sphincter, the number and location of external and internal openings, and anal stricture.

After drainage of an accompanying abscess, seton drainage is generally considered to be the first step for any form of treatment of complex fistulas, medically or surgically. A seton is often considered as a step up procedure for further treatment, but can also be used as final treatment (chronic seton). After resolution of inflammation, the seton can be removed with sometimes subsequent spontaneous closure. A systematic review demonstrated complete closure in Crohn’s patients ranging from 13.6% to 100%. Recurrence was seen in 0–83.3%.

More often, the seton is used as a bridge to medical or surgical closure. Surgical closure can be performed by advancement plasty or ligation of the intersphincteric fistula tract (LIFT). In a systematic review, the success rate of advancement plasty for Crohn’s disease was 64%. The procedure can be complicated by faecal incontinence (up to 10%), and there is a substantial risk of fistula recurrence in various studies (up to 50%). A LIFT is a relatively new technique with promising success rates varying from 57% to 94% in literature.

Other therapeutic options consist of fibrin glue and fistula plug. Both techniques were previously considered as less invasive strategies which could be tried harmlessly as there is little morbidity and low risk of incontinence. However, most guidelines nowadays advise against these techniques as recurrence rates are unacceptably high (up to 80%), and two RCT’s comparing glue and plug repair to advancement plasty showed no difference in pre- and postoperative soiling and incontinence scores.

The most promising new development in the treatment of perianal fistulas is stem cell therapy. Although the exact working mechanism has not been unraveled, deposition of pluripotent stem cells with anti-inflammatory and immunomodulatory properties in and around the fistula tract, has been demonstrated to down-regulate the local immune response and induce wound healing. Recently, a large placebo-controlled RCT has been performed in 212 Crohn’s patients which demonstrated a significantly greater proportion of patients in remission after stem cell injection when compared to placebo treatment (50% vs. 34%).
Patients with recurrent and intractable fistulas (frequently combined with severe proctitis), can be counseled for temporary colostomy/ileostomy. Most stomas have a good temporary effect, but disease often recurs and most stomas will never be reversed. A systematic review showed that restoration of bowel continuity was attempted in 35% of patients, but it was successful in only 17%.

In conclusion, Crohn’s perianal fistulas are a challenging multidisciplinary problem and despite the best medical and surgical options available to date, unfortunately a significant proportion of these patients continue to suffer from persistent or recurrent perianal suppuration.
Adipose tissue-derived stem cells and other new therapeutic approaches for fistulizing disease

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Mesenchymal stem cell (MSC) research has developed rapidly during the last decade and the promising results obtained from in vitro and in vivo studies have generated growing optimism. Although bone marrow is the most often used source, MSCs with similar biological properties have also been isolated from other tissues including adipose tissue, skeletal muscle and cord blood. Of special interest is adipose tissue since it represents an abundant and accessible source of MSCs. These cells are denominated adipose-derived stem cells (ASCs) and have been widely studied since they were first described in 2001. In recent years, substantial knowledge of ASCs interaction with the immune system and the inflammatory process have been acquired. The mechanisms underlying these effects have not been clearly defined, but it seems that ASC modulate the function of different cells involved in the immune response.

Healing is the basis of surgery and then, we hypothesized that some of the above mentioned properties of ASCs could be involved in the earlier stages of the immune response and modulate the local acute inflammation and hence could improve healing.

Available data indicate that Crohn’s disease-associated fistula originate from an epithelial defect that may be caused by ongoing inflammation. As ASCs have anti-inflammatory, immunomodulatory and tissue-regenerating potential they appear to be suitable candidates to treat this condition. Initial clinical results since 2002 suggested they may have therapeutic potential in this setting.

The first randomized, placebo-controlled study of adipose-derived mesenchymal stem cells (Cx601) for the treatment of complex therapy-refractory perianal fistulas in patients with Crohn’s disease (CD), indicated that local therapy with Cx601 added on to established therapies for CD may open new therapeutic options for refractory perianal disease. This study evaluated therapeutic effect using an innovative and distinctive endpoint combining both clinical assessment of fistula closure and MRI imaging. Approximately 50% of patients treated with Cx601 achieved combined remission 24 weeks after treatment, and the stem cell treatment was well tolerated in the study population. Our findings suggest that this kind of stem cells may offer CD patients with therapy-refractory complex perianal fistulas a novel and minimally invasive closure alternative to avoid the need for systemic immunosuppression or surgery. Today, cumulative evidence that mesenchymal stem cells promote healing of perianal fistulas of patients with Crohn's disease, show a real "Going From Bench to Bedside".

Other new therapeutic approaches for fistulizing disease in Crohn’s disease need further scientific evidence.
Session V

Luminal versus systemic therapy
Luminal therapy with small molecules

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Small molecule inhibitors represent an upcoming therapeutic substance class in IBD. They offer the advantage of low molecular weight, oral intake, simple manufacturing process, short serum half-life and absence of immunogenicity, which may lead to sustained efficacy over time. The potential downside of this therapeutic approach may be increased toxicity due to “off-target” side effects by unintended binding and inhibition of multiple signaling pathways.

Tofacitinib, which selectively inhibits Janus kinase (JAK)1, JAK3 and to a lesser degree JAK2, is expected to be the first small molecule compound to be approved for treatment in IBD. It modulates signaling for various subsets of pro-inflammatory cytokines. Its efficacy was successfully tested in phase 3 induction and maintenance trials in moderate-to-severe ulcerative colitis patients, but however failed to induce marked clinical benefit in Crohn’s disease patients. Possible occurrence of infections might have to be observed in clinical use.

Other JAK inhibitors currently under development are the selective JAK1 inhibitors filgotinib and upadacitinib, which might be associated with an improved safety profile. Another approach by small-molecule drugs is the selective modulation of sphingosine-1-phosphate receptors (S1PRs), which leads to their internalization and degradation, thus preventing lymphocytes from leaving lymphoid tissues. Representatives of this class are ozanimod (selective modulation of S1P1 and S1P5 receptors) and etrasimod (selective modulation of the S1P1 receptor).

Very promising data have been obtained in clinical trials with mongersen, which contains a synthetic oligonucleotide that hybridizes to SMAD7 mRNA and induces its degradation via an antisense mechanism. This may lead to heightened expression of TGF-β1, which might add to restoration of mucosal homeostasis in IBD. The compound showed remarkable efficacy in a phase II trial in Crohn’s disease patients and recent data indicated endoscopic improvement upon mongersen treatment. Data of a currently running phase III trial are eagerly awaited.

Altogether, small-molecule drugs represent a promising treatment option in IBD and further data will have to indicate when and how we should use these drugs. As with all other available IBD treatments, characterizations of the molecular mechanism of action and biomarkers for predicting therapeutic efficacy are urgently needed to enable rational treatment with this emerging new substance class in clinical practice.
Taking advantages of our own strategies

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The gut represents a unique interface towards our environment. It not only facilitates digestion and resorption, but also battles ingested pathogens, while also controlling an immense community of commensal microorganisms. To aid with the latter, it produces a wide range of innate immune mediators, such as antimicrobial peptides (AMPs), which can combat viruses, bacteria, and fungi. Gut AMPs have differing activity ranges and modes of action, so their expression varies depending on the present conditions and threats. The most famous examples for site specific AMPs are probably the two α-defensins HD5 and HD6. In a homeostatic state, they are exclusive to the Paneth cells of the small intestine. On the other hand, different diseases are genetically linked to beta defensins which can be found at all human epithelial cells including the intestinal tract. Since the importance of gut microbiota has become more and more evident, research on AMPs has also increased and recent developments include preclinical drug studies. This is particularly obvious in the case of inflammatory bowel diseases, but also noticeable in other disorders. Defects in the AMP machinery have been linked to increased susceptibility to infections, chronic inflammation, and disturbances in commensal composition. The gut provides a complex and challenging environment for the study of interactions between AMPs and microbes; and while we are now widely aware of their crucial role in keeping us healthy, more research is needed to fully uncover the involved multi-level crosstalks of their actions. Besides environmental factors, which control epithelial host defense, new data which will be presented here, indicate prominent regulation by bone marrow derived cells which can also impact on the expression of defensins. Understanding these mechanisms will aid in developing new anti-infectious, anti-inflammatory, and maybe even anti-tumorigenic drugs. Some of the latest data which support the rationale for clinical studies of these peptides will be presented during the talk.
New tricks, known drugs

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Many therapeutic choices now exist for inflammatory bowel disease, but it can be difficult to select the right drug for each patient, and to optimize medical therapy. Many of the available therapies are quite expensive, and it is important to use less costly options where possible, and to get the most value out of expensive medications when these are chosen. Several off-label approaches to IBD therapy will be discussed. These will include the use of high dose infliximab in patients who are likely to rapidly clear the drug, often those with high CRP/albumin ratios who are quite ill. The goal CRP in acute severe ulcerative colitis will be discussed. The use of tofacitinib in severe acute ulcerative colitis will be reviewed. The use of algorithms to optimize thiopurine therapy and dosing regimens will be discussed, including the benefits for steroid sparing. The use of methotrexate in patients with penetrating complications, and the interaction with ciprofloxacin will be discussed. The use of tofacitinib, and the modification of its metabolism with fluconazole will be considered. The use of laboratory value-based algorithms in the prediction of outcomes with vedolizumab will be presented for both ulcerative colitis and Crohn’s disease. Several bleeding edge and off-label options are being used to maximize the therapeutic value of therapies in IBD.
Pre-, pro- and synbiotics: Update and future directions

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The microbiome is a key player in the pathophysiology of inflammatory bowel disease (IBD). Manipulating the microbiota for either treatment or prevention of intestinal inflammation via reestablishment a balanced gut microbiota appears attractive. Probiotics, prebiotics and synbiotics, refers to microbial strains, indigestible carbohydrate mixtures and their combinations, accordingly, are potential modes of such intervention. Several mechanisms of action have been attributed to these manipulations: immune-modulation, anti-microbial activity and enhancement of the intestinal barrier activity. However, the efficacy of these strategies demonstrated conflicting results. In ulcerative colitis (UC) a recent systemic review and meta-analysis of twenty-two randomized control trials demonstrated no benefit to probiotics over placebo in inducing remission for active UC, on the other hand, probiotics appeared equivalent to 5-aminosalicylic acids (5-ASAs) in preventing UC relapses and some efficacy for treating mildly active disease was demonstrated. In Crohn’s disease, there was no benefit shown for probiotics in inducing remission, preventing relapse for quiescent disease or for surgically induced remission. Nonetheless, probiotics, specifically the probiotic VSL#3 has shown benefit in treatment and prevention of pouchitis and it is an acceptable recommended strategy. Additionally, data also suggests potential efficacy for Escherichia coli Nissle 1917 in the maintenance of UC. While probiotics contain some species of normal residents of the human digestive system that do not display infectivity or toxicity, long-term effects are not known. There is inadequate evidence to support any particular prebiotic or synbiotic in IBD management.

As IBD is a complex heterogenic disorder, optimal patients’ stratification that will also consider the microbial profile, may assist in understanding the pathogenesis of this condition and in personalizing treatments and strategies including microbial manipulations. Well-designed randomized control trials are required to formulate adequate directions for prevention and therapy.
Session VI

The patient in the center of our therapeutic aims
Real impact of an education program on IBD patient’s skills

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IBD patients represents an ideal ground for a program of therapeutic education aimed to a better quality of life. Thanks to a narrow support, they can improve the efficiency and the tolerance of their treatment and potentially better control the evolution of their disease. Some centers from the GETAID group developed an educational program (EP) specifically dedicated to the coverage of IBD. Scientific demonstration of its efficiency has been recently achieved with the ECIPE study. The main aim of the study was to demonstrate that an educational program could have a significant impact on IBD patient’s skills with regards to their disease. 263 patients were included. Patients were randomized into “educated” or “non-educated” groups for 6 months. Uneducated patients where then allowed to benefit from the educational program the next 6 months. The primary endpoint based on a specific psycho-pedagogic score measured at M0; M6; M12 was reached with a 27.8% variation of the ECIPE score at M6 in the educated group vs. 9% in the non-educated group (p = 0.0007). Within ECIPE score, variations were significant for items regarding competences and behavior. These patients also significantly improved quality of life (SIBDQ) and work productivity scores (WPAI). At M12 both groups early (M0–M6) and late educated (M6–M12) have reached the same level of the ECIPE score. At M12, the ECIPE score remained stable in the early educated group six months after discontinuation of the education. This large prospective controlled multicenter study shows for the first time, that an educational program improves the skills of IBD patients, as demonstrated by a significant and stable increase of a psycho-pedagogic score. Prospective data accumulate to demonstrate the interest of numerous resources of support on IBD patients by using various educational tools and live coaching or by internet platforms.
Patients’ perceptions of treatment for inflammatory bowel disease

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There are currently multiple classes of drugs available for the treatment of both Crohn’s disease and ulcerative colitis, with further novel classes on the horizon. Each therapy has its own specific data on efficacy and safety. Importantly, there are differences in patient and provider perceptions of the outcomes and risks that matter most in the treatment of inflammatory bowel disease (IBD). For patients, factors such as quality of life and social outcomes are generally most important when deciding whether to start a therapy. For providers, objective outcomes such as mucosal healing or scientific measures of remission are often of utmost importance. Additionally, patients’ concerns surrounding safety and side effects weigh heavily in decisions surrounding therapy initiation and continued adherence. Effectiveness, long lasting action, rapid start of action, and fewer side effects have been attributes considered important or very important by IBD patients. We contrast patient and provider perceptions of IBD therapy safety. We then describe optimal communication techniques to discuss the risks and benefits of IBD therapy with patients. Finally, we review research questions patients have prioritized in IBD Partners, a large, prospective US-based cohort of over 15,000 patients with IBD and compare this agenda to a physician-prioritized IBD research agenda. Incorporating patients’ perceptions into clinical interactions and therapeutic study design may ultimately improve IBD outcomes.
Session VII

Novel concepts for therapy – Monitoring, conflicts, gadgets
Very early onset IBD – Can we translate diagnostic and therapeutic concepts?

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A subgroup of patients with very early onset IBD under the age of 6 years suffer from severe and therapy resistant intestinal inflammation. Compared to the classical polygenic IBD, this group is enriched in Mendelian disorders that can present with intestinal inflammation. Understanding the molecular mechanisms of Mendelian disorder associated IBD helps to identify key checkpoints that control intestinal inflammation in humans. This includes epithelial barrier defects, disorders of the innate handling of bacteria causing primary or secondary inflammasome activation, defects in T cell activation and defects in the immune regulation. Genetic screening for multiple gene defects has developed from a research tool towards standard of care. Depending on the gene defect, treatment options for those patients include stem cell transplantation, IL1 targeting therapies and restoring the immune tolerance by CTLA4 fusion proteins. We discuss how some of the diagnostic and therapeutic concepts developed for patients with very early onset IBD may be translated more broadly as part of individualised care in IBD.
Treatment to target: Is this a meaningful paradigm – PRO

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Modern IBD management includes a patient centered approach with a thorough discussion between all care takers the patient and his relatives. Primary target should be relief of symptoms including all the broader symptoms like fatigue, anxiety, depression etc. and addressing any other concern your patient might have. Ideally this will usually involve a multi-disciplinary team with an IBD Nurse coordinating the care.

However relief of symptoms off steroids no longer suffices. Recently different classes of new biologics and small molecules have become available all with the potential for mucosal healing. This should guide our therapy and hence avoid the classic complications: bowel damage (such as stenosis, fistula formation, surgery), hospitalization, dysplasia/cancer formation etc.

New evidence from the CALM study suggests that, at least in early Crohn’s disease, a more patient friendly approach with a quick step treatment with adalimumab first line after a single course of steroids guided not only by symptoms, but also normalization or not of CRP and calprotectin leads to higher rates of mucosal healing and better clinical outcomes compared to conventional management based on symptoms alone. This adds to other series including population based studies like IBSEN and the long term follow-up of the Step Up Top Down study underscores the clinical relevance of achieving mucosal for the longer term follow-up.

More pragmatic trials are needed with longer term follow-up to validate this concept for other populations and other agents.

Pro’s and con’s of treat to target approach will be discussed in ulcerative colitis and Crohn’s disease including an interactive discussion with the participants.
Treatment to target: Is this a meaningful paradigm – CONTRA

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Treatment to target or “T2T” has been discussed in recent years as an advance in IBD therapy. The role model for a “treat to target strategy” in medicine has been diabetes treatment. Here, certain levels of glycated hemoglobin (hemoglobin A1c, HbA1c) were defined as a treatment target. HbA1c is measured as an indicator of the three-month average plasma glucose concentration. HbA1c is formed in a non-enzymatic glycation pathway by hemoglobin's exposure to plasma glucose. In diabetes patients higher amounts of HbA1c indicate poorer control of blood glucose levels. In patients with type 1 diabetes a treat to target monitoring of HbA1c led to improvement of metabolic control. However, this example exactly shows how dangerous it is in medicine and science to extrapolate from one disease to another or how misleading it can be to adopt “self-evident” conclusions without support of clinical data from respective trials: A large clinical trial designed to determine whether reducing HbA1c below the normal 6% would reduce the rate of cardiovascular events in type 2 diabetes found higher mortality in this “treat to target” population (Gerstein HC, Miller ME, Byington RP et al. Effects of Intensive Glucose Lowering in Type 2 Diabetes. N Engl J Med. 2008;358[24]:2545–59). Risk and benefits of therapy therefore need to outweigh another. Treatment risks are age dependent. In diabetes recent reviews for example suggest that a less aggressive treatment target is more beneficial (“For the majority of older adults, an HbA1c target between 7.5% and 9% will maximize benefits and minimize harms.”; Lipska KJ, Krumholz H, Soones T, Lee SJ. Polypharmacy in the aging patient: a review of glycemic control in older adults with type 2 diabetes. JAMA. 2016;315[10]:1034–45.)

What do we learn for IBD therapy from this striking example? First, we should be very careful when we adopt certain treatment strategies or concepts form other diseases. IBD is a group of specific diseases and our patients have specific needs. Second, there is no treatment target for IBD patients that will fit for all forms of IBD, each severity of disease and all patients. Therapy has to be individualized. In the age of personalized medicine, only one treatment target for all IBD patients is insufficient. Third, the risk/benefit evaluation for all therapeutic interventions is important. For treatment decisions, we need to take into account specific risk factors such as patient age, concomitant diseases or specific environmental risks.

Treatment of IBD patients should not only focus on the avoidance of structural damage to the gut wall as it was postulated in recent years. It may be an important goal (but surgery in most cases is not as damaging as it was delineated). However, the avoidance of structural damage to the gut on the costs of damage to other organs or severe infections does not reflect a reasonable risk/benefit consideration. Therefore, treatment to target becomes only meaningful when the treatment targets are defined on an individual and patient specific basis. – And then the question arises, whether we really need this slogan to improve patient care.
Drug monitoring of biologicals: When it makes sense and when it is nonsense

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Monoclonal antibodies are widely used in the clinical management of inflammatory bowel disease. Unfortunately, up to 40% of patients fail to respond to biologics, and a significant proportion of patients loses response to these agents or develops adverse effects during the course of the treatment. Recently, several studies have demonstrated the value of therapeutic drug monitoring of drug levels and anti-drug antibodies (at least for TNF-α inhibitors) in managing these situations, and their proactive role in guiding further medical decisions.

However, the cost-effectiveness of strict therapeutic drug monitoring is yet to be clarified. The TAXIT trial showed that targeting the serum concentration of infliximab to 3–7 μg/ml results in a more efficient use of the drug, but continued concentration-based dosing was not superior to clinically based dosing for achieving remission after 1 year. Other studies show that dosing drug levels and anti-drug antibodies in case of primary failure, loss of response, or adverse events can drive efficiently the right therapeutic strategy (dose optimization, switch in the same class, or to another agent with different mechanism of action) with significant reduction of cost and higher benefits for the patients compared to the clinically based approach alone.

More data are needed to confirm the clinical utility of therapeutic drug monitoring in course of anti-TNF in different settings of patients, and to standardize this approach for new biological agents appearing in the market.
Costs and problems of biological therapy – Do biosimilars change our treatment?

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In the last two decades, the treatment of inflammatory bowel disease (IBD) has been revolutionized with the introduction of biological therapy.

However, biological drugs are very effective in treating IBD patients with active disease not responding to conventional therapy, their use is associated with high costs and the access to biological agents varies among countries. Recently, as the patent for the reference products are about to expire, advent of biosimilar monoclonal antibodies in the treatment of IBD is expected.

CT-P13 was the first biosimilar infliximab approved for use in all indications of the reference product and received marketing authorization from the European Medicines Agency (EMA) in 2013 and from the U.S. Food and Drug Administration (FDA) in 2016. Phase I and III studies were conducted in rheumatoid arthritis and ankylosing spondylitis and the use of CT-P13 in IBD was extrapolated based on the results of these trials. The short-term and the first long-term data from real-life cohorts in IBD demonstrated comparable outcomes in terms of efficacy, safety and immunogenicity compared to the reference product. Furthermore, according to the results of the “switch” studies available so far, switching from the reference product seems to be safe and the efficacy seems to be maintained after switching from the reference product to biosimilar infliximab.

Biosimilars represent less costly alternatives compared to the reference product; the price of biosimilar infliximab is assumed to be 40 to 60% lower compared to the list price of the reference product in most of the European countries. According to the results of the currently available budget impact analyses, the introduction of biosimilar infliximab in the treatment of IBD could lead to substantial cost savings, which may cover the biological therapy for additional patients.

The use of biosimilar infliximab in IBD is increasing worldwide. Due to budget savings, the access to biological therapies may improve leading to significant health gain of these patients.
State-of-the-Art: Therapy of IBD in 2017

One size – Does not fit all?!

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Patients with Crohn’s disease and ulcerative colitis share the problem of chronic progression without therapies that could stop the disease process or induce healing. While we want interventions to halt progression we are confronted with a reality in which the best therapies may truly control disease in less of 20% of patients.

Genetic analyses of disease etiology demonstrate a significant heterogeneity between individual patients. A host of disease associated variants identifies susceptibility factors that are present in wide parts of the “normal” population, too, and hence have a small impact on the likelihood of single individuals to develop disease. Moreover, it appears that genetic architectures of Crohn’s disease and ulcerative colitis are not discrete but rather show a continuum of association with the phenotype from left sided colitis to ulcerative pancolitis, Crohn’s colitis and to isolated ileal Crohn’s disease. In this situation it appears unlikely that a master switch can be identified to be addressed by the one targeted therapy that would control disease in the majority of patients.

The use of biologics as one of the most powerful interventions leads to success rates for disease control in only a fraction of patients. Most effective are drugs inhibiting cytokines or anti-integrins. It has become apparent that non-response to therapy may be linked to a wide variation in drug exposure. Explanations for the variance in blood levels between patients include the loss of proteins through leakage across the inflamed mucosa, immunization and individual differences in compartment effects (i.e. FcRn binding). However, it appears that even doses used in the development of new oral drugs like the JAK inhibitor tofacitinib are representing only the low sides of the dose-response-curve.

The future of IBD therapy calls for drugs that are capable to move the majority of patients into disease control. This may be achieved by new super-targets that allow high dosing not limited by side effects like the blockade of IL-23 in psoriasis which can exert disease control in as many as 90% of patients. Another avenue would be the development of dose optimization strategies allowing to dose drugs according to individual clinical and/or immunological needs. Finally, sequence therapies, that have reshaped the outcome in some malignant entities, may provide a solution to IBD by which programmed cycling through different MOA’s does not allow escape mechanisms in disease pathophysiology. For this however, we would need to know how therapies interact through comparative and cross-over trials, which are not conducted in a sufficient number.
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POSTER ABSTRACTS

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Anti-TNF agents in IBD: Efficiency and predictors of loss of response – A single center experience

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Introduction: The advent of TNF (tumor necrosis factor) inhibitors in the therapeutic arsenal of inflammatory bowel disease (IBD) has immensely changed their prognosis, and made mucosal healing the main target in treatment strategy. The aim of our study is to evaluate the efficiency of TNF inhibitors in IBD patients and the incidence of side effects of treatment. We also assessed the predictive factors of loss of response to biotherapies.

Methods: Retrospective descriptive study, collecting all IBD patients treated by infliximab or adalimumab in our Gastroenterology Division between January 2007 and December 2016.

Results: Sixty Patients (32 men and 28 women) followed for IBD treated with TNF inhibitors, with a mean age of 32 years old were included. 53 (89%) had Crohn’s disease (CD) and 7 (11%) had ulcerative colitis (UC). 20% of CD patients had a stricturing phenotype, penetrating disease in 5% of cases, both stricturing and penetrating behavior in 20% of patients and it was non-stricturing non-penetrating in 55% of cases. 50% of CD patients had perianal signs. 50 patients (83%) were treated by Infliximab and 10 patients received adalimumab. Primary non-response was observed in 2 patients with Humira. Secondary loss of response was observed in 11 cases (18%), 10 with Infliximab and 1 with adalimumab, after a mean follow up of 6 months. Significantly, less patients achieved remission after induction in the group loss of response (p: 0.01), and the mean level of CRP during follow up was significantly higher in loss of response group (p: 0.02). 10 patients (16%) had side effects: 6 with allergic reactions (erythema, edema with dyspnea), one patient presented cerebral demyelinating disease and three had tuberculosis. Mucosal healing was obtained in 4 patients.

Discussion/Conclusion: The predictive factors of loss of response with TNF inhibitors in our study were failure to obtain remission after induction therapy and high CRP levels.
Effects of *Lavandula dentata* and *Lavandula stoechas* on lamina propria cells in DSS-induced mouse colitis

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**Introduction:** The Mediterranean region is an important source of medicinal plants with anti-inflammatory properties that could be used for the treatment of gut complaints. Previous studies have reported the intestinal antiinflammatory effects of polyphenol extracts from *Lavandula dentata* and *L. stoechas*. In the present study we have been evaluated the effects of these extracts on immune cells from the lamina propria in DSS experimental colitis in mice.

**Methods:** Female C57BL/6J mice were assigned into four groups (n = 8): non-colitic, colitic control and two colitic groups treated with each *Lavandula* extract (10 mg/kg). Colitis was induced by incorporating dextran sodium sulfate (DSS) (3%) in the drinking water for 5 days, and the treatment started just after DSS removal and continued for 7 days. Once the mice were sacrificed, the colon was removed and the immune cells from the lamina propria were isolated and analyzed by flow cytometry.

**Results:** Both *L. dentata* and *L. stoechas* extracts exerted intestinal antiinflammatory effects since they reduced the colonic weight/length ratio, which is correlated to the severity of the colonic damage. When lamina propria immune cells were analyzed, mice from the control colitic group showed an intense infiltration of leukocytes (CD45+), which was reduced by the treatments, in particular the CD11b+ F4/80+ cells. In the cell population CD45+CX3CR1+, which comprises monocytes and macrophages, there was an accumulation of cells expressing Ly6C in different phases of differentiation; however, the extracts increased the proportion of Ly6C-, which are mature macrophages displaying an antiinflammatory profile.

**Discussion/Conclusion:** *L. dentata* or *L. stoechas* extracts improved the differentiation of the intestinal lamina propria monocytes, thus reducing the proportion of monocytes with pro-inflammatory properties while increasing the intestinal resident macrophages, which play a key role in maintaining gut homeostasis. This could contribute to the improvement of the intestinal inflammatory status exerted by the extracts.
Crohn’s and ulcerative colitis questionnaire-8 (CUCQ-8), a valid and quick quality of life measure in IBD

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

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

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

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

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

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

Results: There was no significant difference in: quality-adjusted survival [analysable data from 121 participants (90%) in each group; mean difference in AUC/day 0.0297 favouring ciclosporin; 95% confidence interval (CI) from -0.0088 to +0.0682; p = 0.129]; EQ-5D scores; SF-6D scores; colectomy rates (55/135 infliximab vs. 65/135 ciclosporin, OR = 0.741, 95% CI: 0.457 to 1.202, p = 0.223); time to colectomy; patients experiencing serious adverse reactions (11.9% vs. 7.4%); serious adverse events; or deaths (infliximab 3 vs. ciclosporin 0, p = 0.247). Total NHS costs were lower for ciclosporin (mean adjusted difference -£5632, 95% CI: -£8305 to -£2773, p < 0.001). Interviewed participants spoke more positively about infliximab than ciclosporin. Professionals reported advantages and disadvantages with both drugs, but nurses disliked giving intravenous ciclosporin.

Discussion/Conclusion: There was no significant difference between ciclosporin and infliximab in clinical effectiveness, but total cost to the NHS was higher for infliximab.
Recombinant oral human beta-defensin 2 (hBD2) ameliorates experimental induced colitis in vivo

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Introduction: Patients with chronic inflammatory diseases (CED) have a compromised intestinal barrier. This is associated with a reduced expression of antimicrobial peptides (AMPs). The impaired antimicrobial barrier allows the translocation of commensal bacteria into the intestinal mucosa, which in turn causes inflammation. Besides a compromised local defense, a so-called dysbiosis is discussed as an additional trigger for the chronicity of the inflammation, which is influenced by the altered bacterial composition. Here we screened hBD2 for toxicity and investigated the pre-clinical efficacy of hBD2 in different in vivo models of DSS colitis. Furthermore, the efficacy of hBD2 was examined as a possible microbiom modulator.

Methods: First we tested hBD2 for cytotoxicity in different human cell lines and also murine fibroblasts. Next oral administration of hBD2 was tested in a DSS colitis mouse model, compared to prednisolone and cyclosporin A. In addition, changes in the microbiome were analyzed by 16S sequencing after oral hBD2 administration. To investigate the effect of hBD2, the mice were orally gavaged two to three times daily with a dose between 0.1–10 mg/kg per day.

Results: HBD2 showed antimicrobial activity in radial diffusion assays while we did not find any cytotoxic effect. In the DSS colitis model, oral administration of hBD2 resulted in a significant improvement of the colitis. The oral administration of hBD2 resulted in a significantly lower weight loss and an improved disease activity index in the DSS colitis model. Furthermore, significant changes were observed in the microbiome by hBD2 application.

Discussion/Conclusion: HBD2 is a microbiome modulator and shows a promising effect in experimental colitis. The results support the therapeutic application of hBD2 as a future drug for CED. It is a modulator of the microbiome and a barrier-strengthening therapy principle, which may possibly be used alone or in combination with anti-inflammatory active substances.
Patient preferences on the mode of delivery of biologic therapy in inflammatory bowel disease (IBD). A patient questionnaire in a District General Hospital

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Introduction: IBD treatment has changed markedly since the initiation of biologic therapies. The use of adalimumab, infliximab, golimumab and vedolizumab have changed the lives of many patients, who previously would have eventually needed surgical intervention. Patients’ are often given a choice regarding the mode of drug administration.

Method: Patients from the Epsom & St Helier IBD Biologics database received a telephone questionnaire and were asked whether they prefer subcutaneous therapy or intravenous delivery of their biologics with reasoning.

Results: 140 IBD patients received a telephone questionnaire. 50 responded (37 with Crohn’s disease, 13 with ulcerative colitis, average age 45, 27 male and 23 female). 21 patients were receiving adalimumab, 23 receiving infliximab, none of the responders received golimumab and 6 had started vedolizumab therapy. 76% of patients preferred subcutaneous therapy (38% of these were male). Reasons for preferring subcutaneous therapy were unanimously due to feeling that subcutaneous therapy was more compatible with their lifestyle. Of those who preferred intravenous therapy, 6 patients reported they felt more comfortable in the hospital environment and 3 patients had negative prior experience with delivery of their subcutaneous therapy.

Conclusion: These results suggest that in this cohort, patients overwhelmingly prefer subcutaneous biologic therapy. This is contrary to a previous UK study¹ but shows similar results to a Korean study², suggesting preferences differ depending upon the population studied. Thus it represents good practice to give patients a choice, which may improve adherence to treatment and thus potentially rates of IBD flares.

References:


A survey of internet usage amongst inflammatory bowel disease patients. What are patients using and why? Results from a District General Hospital

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Introduction: Inflammatory bowel disease (IBD) is a chronic condition, which often affects young adults. As social media use has increased in the last decade, it is important to monitor how these trends affect our patient’s interactions with the internet. It offers potential opportunities to help our patients engage with their disease.

Methods: 140 patients on the IBD biologic database of Epsom & St Helier NHS Trust were given a telephone questionnaire asking whether they use Facebook, Twitter, Instagram or other internet resources. They were also asked why they do or do not use these resources. 50 patients responded.

Results: Out of the 50 patients (37 with Crohn’s disease, 13 with ulcerative colitis, average age 45), 16 patients use Facebook as a resource for their disease (32%, average age 38.4), 3 patients use Twitter (6%, average age 39.6), 14 patients use the Crohn’s & Colitis forum (28%, average age 41.8), 4 patients use Google (13%, average age 52.8), 3 patients use NHS websites (6%, average age 41.6) and 1 patient each use Instagram (age 21), the IBD passport (age 34), the British Medical Journal (age 57) and a private online forum (age 57).

36% of patients use social media to share experiences, 26% had no interest in using the internet to research their disease, 12% do not use it anymore due to observed negativity about IBD online and 6% have no time. Other reasons for not using the internet included not trusting online information, lacking knowledge of how to use the internet, being morally against social media, they were physically well, or because they were visually impaired.

Conclusion: The results show that patients use a variety of online resources, but Facebook and the Crohn’s & Colitis forum are the most frequented. Many have no interest in using the internet, which perhaps is due to a lack of positive stories and engagement with patients by social media. The internet provides a powerful avenue to help communicate and educate our patients and this is something that should be developed for the future of IBD treatment especially with the advent of mobile health applications.
Rate and predictors of endoscopic mucosal healing in patients with inflammatory bowel disease by azathioprine treatment: A real world experience from a single center in Turkey

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**Background:** There is increasing evidence that endoscopic mucosal healing (EMH) is a key target in inflammatory bowel disease (IBD) therapy. However, there is limited evidence of EMH rates with conventional IBD therapy outside of Western population groups.

**Aim:** To evaluate the role of azathioprine (AZA) in inducing EMH in IBD patients.

**METHODS:** Patients with inflammatory bowel disease were evaluated in terms of endoscopic mucosal healing and the incidence of surgical interventions during the azathioprine treatment between 1995 to 2014.

**RESULTS:** A total of 120 inflammatory bowel disease patients were enrolled. Endoscopic mucosal healing was found in 37% patients with inflammatory bowel disease (42% in chronic ulcerative colitis and 33% in Crohn’s disease). Male gender had a negative impact on the efficacy of azathioprine (p < 0.05). Responder inflammatory bowel disease patients were older (age at the IBD diagnose) than the non-responder (p < 0.05). Azathioprine therapy reduced the number of the surgical interventions (p < 0.05).

**CONCLUSION:** We showed that azathioprine therapy significantly induced endoscopic mucosal healing in biologic naïve patients with active inflammatory bowel disease as well as decreasing the surgical interventions, with negative predictive factors identified by a younger age at IBD presentation and male gender.
Intestinal microbiota and proteins proteomic profile in patients with common variable immunodeficiency

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Introduction: Intestinal microbiota condition in patients with primary immunodeficiency (PID) is still under investigation. The purpose of our research is to study the composition of the microbiota and mucous membrane proteins proteomic profile (PPP) in patients with common variable immunodeficiency (CVID).

Methods: 16 patients with CVID without clinical markers of any digestive disease were examined (control group – 20 healthy volunteers). Estimation of microbiota was performed by bacteriological seeding faeces, hydrogen breath test (HBT) with a lactulose. Content of short chain fatty acids (SCFA) in feces and microbial lipid markers in small intestine and colon mucosa (MLMM) was determined by using gas-liquid chromatographic and gas chromatography-mass spectrometry (GC-MS). PPP of mucosa’ proteins was based on isoelectric focusing techniques (SDS-PAGE, 2DGE). Mass spectrograms obtained using MALDI-TOF-MS/MS (Bruker, USA). Molecular interaction, functional characteristics of proteins were studied using the STRING 10.0 databases.

Results: Through microbiological studies of feces titer reduction of bifido- and lactobacilli in an average of 4.6 ± 0.7 Lg was registered. Conditionally pathogenic flora (CPF) was presented by E. coli lactose-negative forms, S. aureus, Clostridium spp. in the credits of more than 10^5. Subsequent to the results of GC-MS MLMM was received 8 fold increase in the total bacterial load by resident anaerobic microflora, which was represented by Streptococcus mutants, Bacteroides fragilis, Clostridium difficile, Candida albicans and glabrata. HBT showed 4.5- and 6-fold increase of hydrogen production. The SCFA structure was characterized by 6- and 8-fold decrease in propionic and butyric acids: 0.2 ± 0.1 mg/g and 0.1 ± 0.03 mg/g respectively. In PPP (frequency of detection more than 75%) in small intestine samples: claudin 1, 2, 4; okkludin, kalgranulin, in colon – kinogen 1, interleukin-1B, interleukin 8, B2-glycoprotein, heat shock protein 27 were prevailed. In control group PPP was presented by translational elongation factor, apolipoprotein E-C-III and B2-glycoprotein.

Discussion/Conclusion:
1. In patients with CVID without clinical signs of any digestive system disease microbiota composition disturbances, increased titers of hydrogen-producing CPF, total bacterial number of resident CPF, reduced production of SCFA were registered.
2. PPP in patients with CVID was presented by specific proteins, reflecting inflammation, apoptosis progression and epithelial proliferation’s disturbance.
Ulcerative colitis – A severe case in a 7-year-old girl

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Introduction: Pediatric ulcerative colitis (UC) has gained importance over the past decades due to its increasing incidence rate worldwide, especially in adolescents. Although less prevalent in young children, there are some case reports about disease onset at early ages.

Case presentation: A 7-year-old girl was hospitalized for bloody diarrhea and fever with a 7-day onset. The initial laboratory tests showed high levels of white blood cells, iron deficiency anemia, increased inflammatory markers, hypoproteinemia and negative stool tests. It was performed colonoscopy with biopsy and it revealed inflammatory lesions in various stages (diffuse edema, erythema, erosive areas, capillary fragility and polypoid lesions). The histopathological examination was suggestive for UC. It has been established the diagnosis of UC – E4S1 (Paris Classification). The Pediatric Ulcerative Colitis Activity Index (PUCAI) at the time of diagnosis was 75. The initial treatment included nutritional support, intravenous fluid and electrolyte replacement, blood transfusion, antibiotherapy, oral 5-aminosalicylic acid and high dose of intravenous corticosteroids. After 7 days, because the evolution was unfavorable (with 30 completely unformed stools with large amount of blood/day and weight loss – PUCAI > 60), we decided to move up to the next level of treatment - immunosuppresants (thiopurines) and biological therapy (infliximab). Although, the patient received all therapies according to the protocol, and although the infusion rate of infliximab was decreased at 4 weeks and the doses were increased, we have not been able to induce clinical remission – continuous weight loss and persistent PUCAI over 70. A medical committee decided the opportunity to initiate surgical therapy – laparoscopic restorative proctocolectomy (ileal pouch anastomosis) with diverting ileostomy (macroscopic appearance: short and stiff colon with fibrosis). In 2 months the ileostomy was closed.

Conclusion: This is the most severe case of ulcerative colitis under 10 years reported in our country and the youngest case that received surgical treatment.
Variants of IL23R gene and Crohn’s disease

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Introduction: Numerous studies have associated susceptibility genes to inflammatory bowel diseases (IBD). Among genes that have been recently implicated in IBD susceptibility we note the IL23R. Its role in inflammation and innate and adaptative immunity makes it a strong candidate involved in triggering certain autoimmune and inflammatory diseases. This locus includes many polymorphism including 11209026 SNP and the 7517847 SNP

Our aim is to study the 11209026 SNP and the 7517847 SNP of the IL23R gene in our country’s population in order to assess the involvement of these two variants in the susceptibility to Crohn’s disease (CD).

Methods: We began a preliminary study by seeking the presence of mutations for each SNP of IL23R gene in the Tunisian population while relying on studies that concerned the two polymorphisms 11209026 and 7517847. Molecular analysis of IL23R gene was made on 28 patients with CD and 37 healthy controls. We conducted a verification of the presence of SNPs in the DNA sequences extracted from whole blood of patients and controls. Extraction was made using two techniques: phenol/chloroform for healthy controls and by KIT Quiagen for patients with CD. Then amplification of the 11209026 SNP and 7517847 SNP was carried out using specific primers that amplify the exon 9 of IL23R gene for the first and intron 6 of the gene for the second one. The primers’ design was done using a bioinformatic tool. The next step was to confirm that the amplification products correspond to the amplified regions and if they contain polymorphisms at their sequences.

Results: PCR results confirmed the specificity of the primers since we obtained a 208bp band for CD patients. Similarly for the 2nd SNP, we had the expected band size of 378bp for both patients and controls. Analysis of the results showed for the SNP 11209026 the presence of the rare allelic polymorphism A (frequency of 0.08) in the nucleotide sequences of the DNA of patients with CD. The sequence analysis results for the 7517847 SNP showed that the G allele polymorphism is found in the DNA sequences for both CD patients and controls. The frequency of G allele polymorphism was 0.17 for patients and 0.18 for controls. All the frequencies founded are acceptable because close to those founded in other populations.

Discussion/Conclusion: Our results showed the presence of the rare allele A of the SNP 11209026 (Arg 381 Gln) in patients with CD and the G polymorphism of the 7517847 SNP in our population. Our study is the first studying our population by investigating a susceptibility gene as that of IL23R in CD. Further studies with largest number of patients are necessary to allow conclusions about implications of these polymorphisms in susceptibility for CD and may be its severity.
Postoperative recurrence of Crohn’s disease after ileocecal resection: Prevalence and risk factors

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Introduction: Intestinal resection in Crohn’s disease concerns up to 49% and 64% of patients respectively at 10 and 30 years after diagnosis. Despite preventive therapy, clinical recurrence one year after surgical treatment concerns 20% to 30% of patients. The aim of our work was to evaluate the prevalence of clinical postoperative recurrence in Crohn’s disease after ileocecal resection, and to determine the predictive factors of recurrence.

Materials and methods: This is a retrospective study, conducted over a period of 10 years, including all patients followed for Crohn’s disease who underwent ileocecal resection.

Results: From a total of 240 Crohn’s disease patients, 86 (35.8%) underwent ileocecal resection, with a mean follow up of 5.8 years [2–13 years]. There were 26 women and 60 men with a sex ratio (M/F) of 2.3. The average age of our patients was 32.95 years [16–69] and 46.5% of patients were smokers. According to the classification of Montreal, 55 patients (64%) had ileal localization of their disease and 31 patients (36%) had ileocecal localization. 12 patients had perianal lesions. The indications for surgical treatment were small bowel obstruction in 65 cases (75.6%), abscess in 12 cases (13.9%), ileal perforation in 6 cases (7%), and a fistula in 3 cases (3.5%). The average length of the resected small bowel was 13.2 cm [8–105 cm]. All patients were regularly monitored and 68 patients (79.1%) had postoperative medical treatment, after an average period of 33 days (4–116 days) of the surgery. 19 patients (22.1%) received 5-ASA therapy, azathioprine was prescribed in 47 cases (54.7%), and anti-TNF in 2 patients (2.3%). 18 patients (20.9%) received no treatment, with a favorable outcome. During follow-up, clinical recurrence was observed in 24.4% of our patients (9.3% at 1 year and 20.9% at 5 years) with a mean period of postoperative recurrence of 34.6 months [8–116 months]. In univariate analysis, predictors of postoperative recurrence were: the lack of postoperative smoking cessation, inaugural complications of the disease, a mean period of time between diagnosis and surgery < 9.5 months, and healthy resection margins < 2 cm. The multivariate analysis, has shown that the absence of postoperative smoking cessation, a period of time between diagnostics and surgery < 9.5 months and margins of resection < 2 cm, were independent factor for postoperative recurrence.

Conclusion: The clinical recurrence is common after ileocecal resection in Crohn’s disease. It was observed in one patient in four. Smoking, a period of time between diagnostics and surgery < 9.5 months and margins of resection < 2 cm, were significantly correlated with postoperative recurrence.
Efficacy and safety of azathioprine in Crohn’s disease: About 158 cases

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Introduction: Thiopurines are the mainstay of conventional maintenance therapy in inflammatory bowel disease (IBD). Up to 50% of patients discontinue immunosuppressive therapy within 2 years due to intolerance or lack of efficacy. The aim of this study is to assess the effectiveness and the tolerability of thiopurine therapy in patients with IBD.

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

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

Conclusion: Azathioprine is an effective and steroid-sparing agent for refractory CD. Its side effects are generally mild and tolerable.
Anti-tumor necrosis factor alpha and inflammatory bowel disease: Efficacy and safety

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Introduction: Inflammatory bowel disease (IBD), in particular Crohn’s disease (CD) refractory to conventional therapy, fistulizing CD and chronic active ulcerative colitis (UC), generally respond well to anti-tumor necrosis factor (TNF) therapy. However, serious side effects do occur, necessitating careful monitoring of therapy. The aim of this study is to determine indications, response and adverse effects of treatment.

Methods: Retrospective study including patients with IBD received anti-TNF therapy and followed in our department between 2011 and 2017.

Results: Eighty-nine patients with IBD were included. Fifteen patients received anti-TNF therapy: 7 men and 8 women with mean age of 34.8 years [19–62]. The indication of anti-TNF therapy was for CD in 13 cases (86.8%) and for UC in 2 cases (13.3%). For CD, indication was prevention of postoperative recurrence in 4 cases (30.7%), complex anoperineal fistulas in 5 cases (38.4%), intolerance to purines in 2 cases (15.4%), a luminal corticoidependent form in 1 case (7.7%) and extraluminal manifestation in one case. For UC, indication was severe acute colitis corticoresistant in the cases. Infliximab (IFX) was prescribed in 9 cases (60%). All patients completed induction treatment with response well in 86.6%. Response to maintenance therapy was observed in 61.5% of patients. Adverse effects to IFX were early allergic reaction in 2 patients and tuberculosis reactivation in one patient. Adalimumab (ADA) was prescribed in 6 cases (40%). All patients finalized induction treatment and response was obtained in 50% of patients. Response to sequential treatment was observed in 66.6% of patients. Adverse reactions of ADA were allergic reaction in one case.

Discussion/Conclusion: In our series, results of anti-TNF-alpha therapy for CD were similar to those reported in literature. Main side effects were allergic reactions.
Antibodies and hemoglobin levels in inflammatory bowel disease: Monocentric Tunisian cohort

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Introduction: Anti-tumor necrosis factor (TNF) agents are an important component of inflammatory bowel disease (IBD) treatment. However, data on their effect on anemia, a frequent complication of IBD is limited. The aim of this study was to evaluate the influence of anti-TNF agents on hemoglobin (Hb) levels in a monocentric Tunisian cohort.

Methods: Retrospectively collected demographic, laboratory and treatment data from IBD patients who started anti-TNF therapy during the years 2011–2016 were analyzed. Data from the year of anti-TNF initiation (year 0) and the following year (year 1) were compared.

Results: A total of 89 IBD patients were included. Fifteen patients started anti-TNF treatment with mean age of 33 (19–57). The prevalence of anemia did not change between year 0 and year 1 (66.6% vs. 60%). IBD patients with anemia had significantly higher median Hb levels at year 1 compared to year 0 (p < 0.05). Hematopoietic response (increase of Hb ≥ 2 g/dl) was observed in only 33.3% of the 10 anemic IBD patients, despite iron replacement being administered in 6 anemic patients. Improvement in Hb levels was independently significantly correlated with change of CRP levels (p = 0.05) and immunomodulators use (p = 0.05).

Discussion/Conclusion: Anemia remains a significant manifestation of IBD one year after treatment with anti-TNF agents. CRP level and immunomodulators use correlated with improvement of anemia.
Novel human gut xenograft mouse model for intestinal fistulas


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Introduction: Fistulas represent a frequent complication in Crohn’s disease (CD) and surgical resection is often required. Previously, we demonstrated that epithelial-to-mesenchymal transition (EMT) plays a critical role for fistula development. Preceding upregulation of TGF-beta, IL-13, TNF and their receptors along fistula tracts in CD-patients seems to orchestrate a number of events contributing to the onset of fistulas, by inducing EMT. Since in vivo models are missing, new drug developments are complicated. Here, we describe a new xenograft (XGR) mouse model of intestinal fistula, resembling the human condition.

Methods: Human fetal small intestine (12–18 weeks) was transplanted subcutaneously onto SCID mice backs. After 12–16 weeks, ~15% of the mature xenografts spontaneously developed enterocutaneous fistulas. Using systemic LPS-treatment followed by mild skin irritation adjacent to the transplant, we established a reproducible model system, resulting in enterocutaneous fistulas 2–4 weeks later. Tissue specimens were immunohistochemically stained (IHC) for EMT and immune cell markers.

Results: Morphological analysis of the fistulating XGR samples revealed flattening of the intestinal epithelial cells lining the fistula tract, resembling transitional cells described in human patients. IHC-stainings for various EMT markers detected similar expression patterns like for human fistulating CD-patient samples, confirming the hypothesis that EMT plays a critical role for fistula development in the XGR samples, as well.

H&E-staining showed inflammation in the gut XGR up- & downstream to the fistulous tracts, which mainly consisted of human CD45+ cells and very few murine CD45+ cells. Further characterization revealed large numbers of human CD3+ cells and high expression of TNF-alpha and other T cell-derived cytokines.
Moreover, we could confirm massive fibrosis in these inflammatory regions by collagen-staining.

Discussion/Conclusion: Our data demonstrate that the in vivo model recapitulates morphologically and mechanistically the human disease. A strong inflammatory response, predominantly driven by immune cells of human origin, triggers EMT and finally results in fistula formation.
Local application of hydrogel-encapsulated human placenta mesenchymal stem cells ameliorate trinitrobenzene sulfonic acid (TNBS)-induced colitis of rat

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Introduction: Recently topical application of mesenchymal stem cells represents a novel approach for the management of inflammatory bowel diseases patients. A study on TNBS-induced experimental colitis in rats was performed to investigate the therapeutic effects and the possible mechanisms of implanted of hydrogel-encapsulated human placental-derived mesenchymal stem cells (hPSCs).

Methods: Isolated hPSCs were labeled with luciferase and green fluorescent protein by lentivirus transfection and then encapsulated in hydrogel which can be injected. Experimental colitis of rat were induced by TNBS. Animals were randomly assigned to groups (n = 6) para-intestinal injection 1 × 10⁶ hydrogel-encapsulated cells or blank hydrogel. Cell in vivo was detected using an IVIS Lumina camera on survival rate and evaluated on sacrificed one by immunofluorescence microscopy. The pro-inflammatory cytokines and anti-inflammatory cytokines in colon tissue and serum, the mRNA levels of transcription factors of Th subsets and polarization marker protein of macrophages (CD68, CD163 and MCP-1) were detected by RT-PCR and ELISA.

Results: Hydrogel-encapsulated hPSCs can significantly improve clinical signs, colon length and histopathological score, and the levels of proinflammatory cytokines in colon and serum were decreased and anti-inflammatory cytokines were increased in hPSCs group. hPSCs also regulate the transcript factor of Th cell subsets and macrophage polarization. The vivo imaging and immunofluorescence results showed that only a small amount of luciferase/GFP positive cells were present in the colon.

Discussion/Conclusion: Hydrogel-encapsulated hPSCs have therapeutic effects on TNBS-induced experimental colitis in rats which could reduce the mRNA level and cytokines level of proinflammatory cytokines and increase the mRNA and protein levels of anti-inflammatory cytokines in the colon and serum. hPSCs can regulate the transcription factor of T cell subsets and macrophage polarization. A few of viable cells were detected at the end of the follow-up.
Topical transplanted human placenta mesenchymal stem cells stimulate fistula healing on rat model

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Introduction: Mesenchymal stem cell therapy is an emerging field of regenerative medicine. Recently local application of MSCs represents a novel approach for the treatment of perianal fistula in patients with Crohn’s disease. Here, we investigated the efficacy of local use of human placenta mesenchymal stem cells (hPSCs) on rat model and detected the distribution of implanted hPSCs by bioluminescence (BLI).

Methods: Isolated hPSCs were labeled with luciferase and green fluorescent protein by lentivirus transfection. A caecostomy was used as a fistula model in Lewis rats. Animals were randomly assigned to groups given injections of 1 × 10⁶ cells (n = 10) or placebo (n = 10) in the perifistular tissue. Fistula drainage assessment was used to evaluate the fistula healing. Cell viability and distribution was detected using an IVIS Lumina camera on days 0, 2, 5, 10 and 14 after application of D-luciferin. Polarization marker protein of macrophages (CD68, CD163 and MCP-1) were detected by RT-PCR.

Results: 50% fistula healing was identified in hPSCs group vs. 1 case in placebo group. hPSCs can regulate macrophage polarization. The BLI was strongest immediately after administration of hPSCs and the values fell by almost 40% within the first 2 days but it was still higher in animals with healed fistulas 10 days after injection.

Discussion/Conclusion: Local application of hPSCs stimulated fistula healing on rat model which may be correlated with macrophage polarization. BLI monitoring showed rapid reduction of the hPSCs mass after application. More viable cells were detected in animals with healed fistula. Topical transplanted hPSCs may play a therapeutic role in fistula healing.
Efficacy and safety of tumor necrosis factor antagonists in Crohn’s disease

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Introduction: Anti-TNF-alpha have proved to be effective in the treatment of Crohn’s disease (CD) particularly in refractory luminal and fistulizing disease. The aim of our study was to evaluate the efficacy and safety of infliximab (IFX) and adalimumab (ADA) in CD.

Methods: Retrospective study including patients with CD receiving anti-TNF therapy and followed in our department between 2011 and 2016. Indication, response to treatment and adverse events were determined.

Results: Eighty patients with CD were included. Thirteen patients received anti-TNF therapy: 6 men and 7 women with a mean age of 35.9 years [19–62]. Localisation was ileocolic, colonic and ileal respectively in 11 (84.6%), one (7.7%) and one case (7.7%). The indication of anti-TNF therapy was prevention of postoperative recurrence in 4 cases (30.7%), complex anoperineal fistulas in 5 cases (38.4%), intolerance to purines in 2 cases (15.4%), a luminal corticodependent form in 1 case (7.7%) and extraintestinal manifestation in one case. IFX was prescribed in 7 cases (53.8%). All patients completed induction treatment with a response in (85.7%). Response to maintenance therapy was observed in 66% of patients. Adverse reaction to IFX were early allergic reaction in 2 patients and tuberculosis reactivation in one patient. ADA was prescribed in 6 cases (46.2%). All patients completed induction treatment and obtained response in 83.3% of patients. Response to maintenance treatment was observed in 80% of patients. Adverse effects of ADA were allergic reaction in one case.

Discussion/Conclusion: In our series, anti-TNF-alpha therapy has high effectiveness in the management of CD. The main side effects were allergic reactions and tuberculosis reactivation.
Altered salivary microbial ecology in active inflammatory bowel diseases

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Introduction: In this study, we focused on characterising the salivary microbial structure and composition in Chinese patients with active IBD, because limited information exists regarding the oral microbiome of IBD patients.

Methods: Unstimulated saliva samples were collected from 11 IBD patients and 11 sex- and age-matched healthy controls from the Gastroenterology Department of Peking University People’s Hospital. 16S rRNA gene V3–V4 amplicons from all samples were sequenced using an Illumina Miseq instrument. The sequencing data were analysed using QIIME, LEfSe and R. Informed consent was obtained from every subject and all procedures in this study were approved by the Ethics Committee of Peking University People’s Hospital.

Results: We found a variation in the phylogenetic structure of the IBD microbial community when compared with healthy controls. Moreover, we found that the relative abundances of the phyla Actinobacteria, TM7 and SR1, and the genera Actinomyces and Bulleidia were significantly increased in the salivary microbiome of IBD patients, while those of the genera Actinobacillus, Abiotrophia and Campylobacter were significantly decreased. Furthermore, we presented a correlation network of differentially abundant operational taxonomic units (OTUs) between the IBD subjects and healthy controls (HC), revealing the interactions of IBD-enriched OTUs and HC-enriched OTUs.

Discussion/Conclusion: Our study provides a blueprint of the salivary microbiome in disease and healthy states, to enhance our understanding of the IBD microbiome.
Malnutrition and associated factors among adult Crohn’s disease patients: A retrospective study from South China

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Introduction: Crohn’s disease (CD) is often associated with malnutrition. Malnutrition may weaken the immune function and influence the effect of treatment. It is of great significance to accurately assess the nutritional status of patients with CD. The aim of our study is to investigate the incidence of malnutrition in adults with CD in South China and analyze the relevant factors.

Methods: Retrospectively analyzed the clinical data of adult CD patients who first diagnosed in our hospital from January 2015 to December 2016. The CDAI (Clinical disease activity index) was used to evaluate CD patient’s disease activity. Nutritional risk screening tool 2002 (NRS2002) was applied to assess the malnutrition risk. According to the diagnostic criteria for malnutrition in the ESPEN guidelines to analyze the incidence of malnutrition. The gender, age, BMI, lesion location and type, ESR, CRP and electrolyte were collected. Relevant factors were analyzed by univariate analysis, correlation analysis and Logistic multiple regression analysis.

Results: 237 patients with CD were included, of which the incidence of malnutrition was 59.9% (142/237). Multivariate analysis showed that the relevant factors for malnutrition were gender, age, disease activity and HCT. The incidence of malnutrition in CD patients was positively correlated with gender (r = 0.159, p = 0.014) and CDAI score (r = 0.320, p < 0.001) and negatively correlated with age (r = -0.250, p < 0.001) and HCT (r = -0.266, p < 0.001). The incidence of malnutrition of female was higher than that of male (71.8% vs. 54.8%, p = 0.014). The incidence of malnutrition of age < 40 was higher than of age ≥ 40 years (68.3% vs. 42.1%, p < 0.001). The incidence of malnutrition of CDAI score ≥ 250 was higher than of CDAI score < 250 (72.4% vs. 40.2%, p < 0.001). The incidence of malnutrition of HCT < 0.350 L/L was higher than of HCT ≥ 0.350 L/L (72.4% vs. 40.2%, p < 0.001).

Conclusion: The incidence of malnutrition in adults with CD is high and it may be associated with gender, age, disease activity and HCT.
Hypergammaglobulinemia as a marker of extraintestinal manifestations in inflammatory bowel disease patients

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Introduction: The search of biochemical markers useful for the management of inflammatory bowel disease (IBD) patients in clinical practice is very important. Hypergammaglobulinemia (HGG) is commonly described in patients with autoimmune, or inflammatory disorders. The prevalence and clinical significance of HGG in IBD patients is poorly known. The aim of the study is to analyze the magnitude and significance of HGG in inflammatory bowel disease patients.

Methods: We included 96 patients with inflammatory bowel disease who were evaluated from 2015 to 2016. These patients had recorded immunoglobulin G (IgG) levels and were categorized as either normal or high IgG levels at diagnosis. Baseline characteristics included age, sex, severity indices, laboratory data, extraintestinal manifestations, endoscopic findings, and anthropometric measurements.

Results: Of 96 subjects, 40 (41.6%) had Crohn’s disease and 54 (56.25%) had ulcerative colitis, and 2 (2.08%) had unclassified inflammatory bowel disease. Overall, 24 patients (25%) had HGG, including 9 (22.5%) with Crohn’s disease and 15 (27.7%) with ulcerative colitis. HGG was associated with the female sex (54% vs. 30%; p = 0.03) and extraintestinal manifestations (65% vs. 12%; p < 0.0001), including arthritis, skin disorders, and primary sclerosing cholangitis. It was also associated with corticosteroid induction (70% vs. 43%; p = 0.02). In ulcerative colitis patients, HGG was associated with a high pancolitis prevalence (p = 0.002).

Discussion/Conclusion: HGG was not uncommon in IBD patients, and it was associated with a higher prevalence of extraintestinal manifestations. Further large prospective studies are required to confirm the presence of HGG in IBD patients with potential clinical relevance. HGG may represent a simple and economic biochemical marker to identify IBD patients with a more complex disease (presence of extraintestinal manifestations) who may need a more intensive management.
Involvement of HLA-G polymorphism in Crohn’s disease

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Introduction: The etiology of Crohn’s disease (CD) remains unclear but environmental factors, e.g the microbial flora, as well as genetic factors play important roles for disease pathogenesis, resulting in dysregulation of the intestinal mucosal immune system. HLA-G, a non-classical major histocompatibility complex class I molecule, is up-regulated under pathological conditions in inflammatory diseases, in viral infection and malignancies. 14-bp polymorphism is involved in the HLA-G protein stability. The present study aimed to investigate whether the 14-bp insertion/deletion polymorphism within the HLA-G gene is associated with CD.

Methods: The study population comprised 38 healthy blood donors serving as controls and 30 patients with CD in whom disease characteristics were defined. We studied then the 14-bp insertion/deletion polymorphism in the two groups and looked for a correlation between the polymorphism and clinical parameters of CD.

Results: The present study involved 30 patients with CD with a sex ratio of 0.8. The control group consisted of 38 individuals with a sex ratio of 1.1. 14-bp + allele has a frequency of 51.7% in patients and 38.2% in healthy control subjects. The genotype 14-bp+/14-bp+ frequency is also higher in patients (26.7%) than in healthy control subjects (13.2%). 14-pb+ allele increases the CD risk in subjects younger than 25 years old (p = 0.014). Similarly, genotype 14-pb +/+ 14-pb when present, is a risk factor for the disease in subjects younger than 25 years old (p = 0.021). We did not find any correlation with either alleles or genotypes in patients who undergone surgery. Our study didn’t reveal any significant difference in the distribution of genotypes and alleles between patients according to the site and phenotype of the disease. However, there was a significant negative correlation between the 14-bp polymorphism and the frequency of uveitis. In addition, there was significant positive correlation between 14-pb polymorphism and extraintestinal complications such as joints inflammation.

Discussion/Conclusion: The comparison of the distribution of alleles and genotypes and the study of different associations showed that the 14-pb + allele and the 14-bp+/14-bp+ genotype were a risk factor for CD in young subjects. Likewise they were a risk factor for extraintestinal complications.
Ileocecal resection for Crohn’s disease: Postoperative recurrence

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Introduction: Despite improved therapeutic strategies, surgery remains common in Crohn’s disease (CD). The aim of this work was to evaluate the results of the ileocecal resection in CD and to determine predictors of postoperative recurrence (POR).

Methods: A retrospective study involved patients with a first curative ileocecal resection for CD. Clinical recurrence was defined as the reappearance of symptoms related to disease activity, as evidenced by laboratory tests, endoscopic and/or radiological.

Results: 71 patients were included. The mean age was 33 years. The sex ratio was 1.73. 51% of patients were smokers. Symptomatic stenosis was the main indication for ileocecal resection (76%). The average length of the ileal resection specimen was 30 cm. The average follow-up was 85 months [6–288 months]. The recurrence rate was 49%. The mean time to diagnosis of recurrence was 54 months [6–264 months]. Clinical recurrence actuarial rates were 10% at one year, 60% at 5 years and 90% at 10 years. Perforating disease (p = 0.04), ileal location (p = 0.02), handsewn anastomosis (p = 0.005), the presence of epithelioid granuloma (p = 0.03), hypoalbuminemia (p = 0.018) and the extended period to prescribe maintenance treatment (p = 0.024) were significantly associated with POR. The prescription of medical treatment before surgery, end-to-end anastomosis type, the presence of sclerolipomatosis and the extended operating time were at the limit of statistical significance in univariate analysis. Neither smoking nor the presence of perianal lesions or the extensive ileal resection were associated with the POR. In multivariate analysis, medical treatment before surgery, sclerolipomatosis, granuloma, hypoalbuminemia and penetrating form were significantly associated with clinical recurrence.

Discussion/Conclusion: Knowledge of risk factors predisposing to postoperative recurrence after ileocecal resection for Crohn’s disease identifies a group at high risk of POR and optimize the therapeutic management.
Escherichia coli as one of the possible causes of ulcerative colitis and Crohn’s disease

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Introduction: Escherichia coli plays an ambiguous role in the human body. It can contribute to increase of intestinal inflammation or its reduction by inhibiting the formation of hydroxyl radicals. The aim of the study was to evaluate the role of Escherichia coli in the pathogenesis of ulcerative colitis (UC) and Crohn’s disease (CD).

Methods: the study included 46 patients with UC and 12 patients with CD. Total DNA was extracted from stool samples followed by whole genome sequencing (SOLiD 5500 W platform). Results of sequencing of 96 stool samples from healthy volunteers were used as control group. To identify the relative representation of genes encoding virulence factors Virulence Factor Database (VFDB) was used.

Results: The number of bacteria of Escherichia genus, particularly Escherichia coli was markedly increased in UC and CD patients compared to control group. Representation of Escherichia coli was (3.72 ± 8.02)% in UC patients, (8.0 ± 11.3)% in CD patients compared to (1.46 ± 5.22)% in the control group (p = 0.02). 544 genes encoding virulence factors similar to genes in VFDB database were found for UC patients and 251 gene – for CD patients. The presence of 107 virulence genes was detected in study samples of UC patients, 74% of which belonged to Escherichia and Shigella; 150 virulence genes were detected in patients with CD, 71.3% of them belonging to Escherichia and Shigella.

Discussion/Conclusion: The representation of Escherichia coli in patients with UC and CD was significantly higher than in control group. In addition, virulence genes were identified in these species. In this regard, it can be assumed that Escherichia coli probably plays an important role in maintaining intestinal inflammation in UC and CD patients.
Adverse effects of anti-TNFα therapy in inflammatory bowel disease

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Anti-tumor necrosis factor drugs have represented a major advance in the treatment of IBD patients in the last few years and also have a good safety profile.

Introduction: In some patients, infliximab infusion causes systemic adverse reactions that often to discontinuation of therapy even in responsive patients.

Methods: The retrospective study including 68 patients with inflammatory bowel disease treated with anti-TNF agent (infliximab). Patient demographic characteristics, data on skin manifestations, concomitant medications, extraintestinal manifestations and inflammatory markers were collected for analysis.

Results: During a median follow-up of 2.3 years, (interquartile range [IQR], 0.9 to 3.9 years), skin lesions associated with the use of anti-TNF therapy developed in 21 of 68 (30.88%) patients (psoriasiform eczema, 30%; eczema, 23.8%; xerosis cutis, 14.28%; palmoplantar pustulosis, 9.52%; psoriasis, 4.76%; other, 17.64%). Lesions typically developed at flexural regions, genitalia and the scalp, especially the psoriasiform lesions. Thirty-one percent of women and 28% of men developed lesions. The symptoms such as abdominal pain, diarrhea and bloody stool were relieved soon after infliximab treatment, with no recurrence observed. After the 24-week treatment, the white blood cell count, erythrocyte sedimentation rate and C-reactive protein decreased, while the hemoglobin increased significantly compared with those before treatment (p < 0.05).

Discussion/Conclusion: Skin lesions occur frequently in association with anti-TNF therapy at the patients with inflammatory bowel disease, but rarely require discontinuation of therapy.
The prevalence of extraintestinal manifestation in patients with inflammatory bowel disease

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The most common extraintestinal manifestation in patients with inflammatory bowel disease is articular involvement, with a prevalence ranging between 17% and 39%, but also dactylitis and uveitis. Their frequency is similar to that of ulcerative colitis and Crohn’s disease.

**Introduction**: The purpose of this study was to determine the prevalence of uveitis and dactylitis in inflammatory bowel disease patients and to investigate its association with articular and bowel disease activity.

**Methods**: In the study was enrolled 53 patients diagnosed with inflammatory bowel disease and 53 controls. Diagnosis of dactylitis was evaluated using Leeds Dactylitis Instrument (LDI). Demographic and clinical features were recorded. All patients and controls underwent a gastroenterological, ophthalmological and a rheumatological clinical examination.

**Results**: In our study the prevalence of uveitis in inflammatory bowel disease was 13.20%, mainly in patients with Crohn’s disease and peripheral arthritis. The family history of psoriasis represented a predictor of occurrence of uveitis and dactylitis. A significantly higher articular and bowel disease activity was found in patients with uveitis compared to those without it. A significant correlation between disease activity and LDI score was found in patients with inflammatory bowel disease.

**Discussion/Conclusion**: The prevalence of uveitis it was more frequent in patients with Crohn’s disease and peripheral involvement with a higher articular disease activity, confirming that uveitis may be a severity marker and a prognostic factor for inflammatory bowel disease.
Treatment of extradigestive manifestations of intestinal inflammatory diseases

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The extradigestive manifestations of inflammatory bowel diseases most commonly occur in the joints, eyes and skin.

Introduction: The aim of our study was to evaluate the efficacy of immunosuppressive therapy with anti-TNF-alpha agents and corticosteroids in patients with extradigestive manifestations.

Methods: We examined 56 patients diagnosed with inflammatory bowel disease (Crohn's disease and ulcerative colitis) from January 2013 to December 2015. All patients were evaluated by nuclear magnetic resonance of sacroiliac joints, DEXA osteodensitometry, histopathological examination, skin biopsy, ophthalmic examination with lamp with slit.

Results: Fifty-six patients were analyzed, 25 suffered from Crohn’s disease and 31 suffered from ulcerative colitis. 23 suffered from rheumatologic conditions (12 suffered from peripheral arthritis, 3 suffered from sacroileitis and 8 suffered from osteoporosis) and received corticosteroids and anti-TNF-alpha agents. 3 patients suffered from episcleritis and there was also 1 uveitis patient. 4 patients experienced dermatological complications and benefited from corticosteroid therapy, immunosuppressive treatment and anti-TNF-alpha agents.

Discussion/Conclusion: Corticotherapy was used both locally and systemically and improved arthritis and ocular complications. Patients with osteoporosis were treated with calcitonin and bisphosphonates, and Infliximab therapy is a therapeutic option for severe cases of inflammatory bowel diseases.
Choosing effective therapy in intestinal inflammatory diseases

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The choice of treatment is done by the gastroenterologist in certain university centers and according to certain individual factors (patient age, co-morbidities and associated extradigital manifestations, previous treatments).

Introduction: The purpose of our study was to choose effective treatment for Crohn’s disease and ulcerative colitis depending on mild, moderate or severe form.

Methods: We evaluated 52 patients diagnosed with Crohn’s disease and ulcerative colitis between June 2013 and December 2015. The patients were clinically monitored (presence/absence of symptoms), biologically (hemoleucogram, C-reactive protein, VSH, fecal calprotectin), endoscopically and radiologically Magnetic resonance enterocolonography.

Results: Fifty-two patients were examined, 22 with Crohn’s disease and 30 ulcerative colitis. 22 showed mild form and received 5-ASA – 12 treatment with mesalazine 1.5 g/day and 10 with salazopyrin 3 g/day. 28 patients suffered from moderate bowel disease and received corticosteroids (prednisone 40–60 mg/day with progressive dose reduction up to 10 mg/day), immunosuppressive therapy (azathioprine 2.5–3 mg/kg/day) and anti-TNF-alpha agents (infliximab 5 mg/kg in slow infusion and subcutaneous adalimumab). 2 patients suffered from a severe form. In 20 patients with Crohn’s disease or ulcerative colitis moderate form, treatment for induction of remission was initiated. 5 patients experienced adverse reactions to prednisone.

Discussion/Conclusion: The activity of Crohn’s disease and ulcerative colitis was evaluated using the CDAI and Mayo score (Truelove and Witts classification). Anti-TNF-alpha therapy is not indicated in patients with: severe hypersensitivity reactions, infections (tuberculosis, herpes/zoster virus, CMV), malignant lymphoma, tumors, and NYHA class III–IV heart failure.
The immunomodulatory properties of the probiotic *Lactobacillus reuteri* INIA P572 contribute to its intestinal antiinflammatory effects in DSS-colitis in mice

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**Introduction:** Several studies have proposed that probiotics can be considered a safe treatment for IBD. Different mechanisms have been reported to be involved, including their immunomodulatory properties. The aim of the study was to evaluate the effect of *Lactobacillus reuteri* INIA P572 in the DSS model of mice colitis, exploring its ability to modulate the immune response.

**Methods:** Male C57BL/6 were induced colitis by dissolving 3% DSS in the drinking water for 5 days. Treatment with *L. reuteri* INIA P572 (5 x 10⁸ UFC/mice/day) started 14 days before colitis induction and continued until the sacrifice of the mice 24 days later. Non-colitic and non-treated colitic groups were included as reference. Inflammatory status evolution was daily evaluated by a disease activity index (DAI). At the end point of the experiment, the expression of inflammatory markers in the colon was analyzed by qPCR, and the leukocyte populations from colonic lamina propria were studied by multiparametric flow-cytometry.

**Results:** The administration of *L. reuteri* INIA P572 showed an intestinal anti-inflammatory activity as there was a significant reduction in DAI values. Immunomodulatory effects were also evidenced by the ameliorated expression of inflammatory markers, such as IL-6, MCP-1, I-CAM, iNOS and MMP-9. When immune cell infiltration in colonic lamina propria was evaluated, the probiotic-treated group showed decreased leukocyte recruitment, with reduced numbers of neutrophils, macrophages and CD4⁺ T cells.

**Discussion/Conclusion:** *L. reuteri* INIA P572 showed intestinal anti-inflammatory effect in the DSS model of mouse colitis. The immunomodulatory activity exerted by this probiotic encourages performing further studies to evaluate its therapeutic potential for the management of human IBD.
Predictive factors of loss of response to anti-TNF in inflammatory bowel diseases – A single center experience

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Introduction: Monoclonal antibodies against tumor necrosis factor (anti-TNF) are part of the therapeutic armamentarium of inflammatory bowel diseases (IBD). Therapeutic response to these agents is not uniform and a large percentage of patients either fail to improve or lose response after a period of improvement. The aim of our study was to identify predictive factors associated with loss of response to anti-TNF treatment in IBD patients.

Methods: We performed a retrospective study of adult patients diagnosed with an IBD in our department and treated with anti-TNF (infliximab or adalimumab) from 2008 to 2016. The disease activity was assessed by the Mayo score in ulcerative colitis (UC) and Crohn’s disease activity index (CDAI) in Crohn’s disease (CD). Cox-regression analysis was performed to identify potential predictive factors for loss of response.

Results: Forty-three patients were included with a median age of 37 years, 22 (48.8%) of them were male. Thirty-eight patients had CD and 5 had UC with a median follow-up period of 96 months. Thirty-two patients were treated with infliximab (74.4%) while 11 received adalimumab (25.5%). Combotherapy with azathioprine was prescribed in 41 (95.3%) cases. The commonest indication of anti-TNF treatment were refractory disease under immunosuppressors (42.3%) followed by acute severe colitis (16.2%). All our patients responded to the induction therapy. The incidence rate of loss of response was 34.8% per patient-year of follow-up. In univariate analysis, there was no association between failure of anti-TNF and gender, smoking, disease extent, or extraintestinal manifestations. Age < 40 years at diagnosis was the only independent predictor of loss of response to anti-TNF therapy.

Conclusion: In our cohort, approximately 1/3 of patients have lost response to anti-TNF therapy. Younger age at diagnosis seems to have an influence on treatment efficacy.
Thiopurine-induced pancreatitis in inflammatory bowel diseases

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Introduction: Thiopurine drugs, azathioprine (AZA) and 6-mercaptopurine (6-MP), are commonly used to maintain remission in inflammatory bowel diseases (IBD); however, the use of these drugs may be limited by the development of acute pancreatitis (AP) in some individuals. The aim of this study was to determine the incidence and severity of thiopurine-induced pancreatitis in IBD patients.

Methods: We identified retrospectively all cases of AP observed in a monocentric cohort of patients diagnosed with IBD during a 10 year period from 2007 to 2016. AP was diagnosed in accordance with international guidelines. Other aetiologies of AP had to be excluded. Information extracted from the clinical records included demographic data, type of IBD, years from diagnosis, extension according to Montreal classification and characteristics of the AP episode.

Results: Among 292 patients with newly diagnosed or already established IBD, 8 cases of AZA-mediated AP were identified. They were 4 men and 4 women with a mean age of 26 years, all of which had Crohn’s disease (CD). Disease localization was ileocolonic, ileal and ano-perianal in 5, 2 and 1 patients respectively. The mean delay from the onset of treatment to the appearance of AP symptoms was 32 days (range: 11–90 days). Clinical presentation was made of transfixiant epigastric pain and vomiting in all cases. Mean lipase level was 8.2 times above the upper limit of normal. None of the patients showed signs of systemic inflammatory response syndrome (SIRS) at admission. Abdominal CT examination was performed in all cases: 1 case corresponded to Balthazar grade A, 4 to Balthazar grade B and 3 to Balthazar grade C. After withdrawal of AZA, all patients recovered without residual effects.

Discussion/Conclusion: The prevalence of thiopurine-associated AP in our IBD patients (2.7%) is similar to that previously described. Young patients with CD seem to be at higher risk for this particular side effect.
Adverse reactions of anti-TNF therapy in inflammatory bowel disease patients: Frequency and management in a Tunisian population

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**Introduction:** In the last decade, anti-TNF agents have substantially revolutionized the therapeutic management of inflammatory bowel diseases (IBD). Unfortunately, these agents are associated with adverse events ranging from mild symptoms to potentially life-threatening complications. The aim of our study was to determine the frequency and characteristics of adverse reactions to anti-TNF therapy in patients with IBD.

**Methods:** The records of 43 patients diagnosed with IBD and treated with anti-TNF (infliximab or adalimumab) between 2007 and 2016 were analysed.

**Results:** During the study period, 38 patients with Crohn’s disease and 5 with ulcerative colitis were treated with anti-TNF: 32 received infliximab (74.4%) and 11 received adalimumab (25.5%). Median age at induction of treatment was 37 (range: 19–66) years. Mean duration of disease prior to anti-TNF treatment was 96 months. Overall, adverse events were noted in 9 patients (20.9%). Immediate hypersensitivity reaction occurred in 5 patients treated with infliximab, which lead to a switch with adalimumab. Non-severe infectious pneumopathy was observed in 2 patients, managed with antibiotics. One case of hepatitis B reactivation was reported, treated with entecavir and transient anti-TNF cessation. One patient treated with adalimumab developed intestinal tuberculosis and needed ileocaecal resection because of obstructive symptoms.

**Conclusion:** In our series, nearly one fifth of patients developed side effects to anti-TNF therapy. Clinical monitoring during infliximab infusions and pre-treatment evaluation, mainly for infectious disease, are mandatory in the management of IBD patients treated with anti-TNF.
Crohn’s disease or intestinal tuberculosis: The unsolved enigma

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Introduction: Distinguishing Crohn’s disease (CD) from intestinal tuberculosis (ITB) is often challenging as both diseases have similar radiological, endoscopic and histologic features. Since treatment and prognosis of the two conditions are different, it is crucial to diagnose them correctly. We therefore decided to carry out a retrospective cohort study to compare clinical, laboratory, endoscopic and histologic findings of patients with CD and ITB.

Methods: Patients with diagnosis of CD and ITB were retrospectively enrolled in the study from January 2005 to December 2016. The diagnosis of CD was made based on a combination of clinical, radiological, endoscopic and histological features suggested by European evidence based consensus on the diagnosis and management of CD. ITB was diagnosed if any of the following findings were present: a) Caseating granulomas on tissue biopsy; b) AFB positivity on tissue biopsy; c) Positive culture for M tuberculosis; d) Full response to anti-tuberculous therapy. Clinical profile, laboratory tests, endoscopy and histopathology were then compared between the two groups.

Results: A total of 78 patients were included, out of which 56 were diagnosed as CD and 22 as ITB. There was no significant difference in age and gender in patients with CD and ITB. The median duration of symptoms in patients with ITB was 4 months while it was 14 months in patients with CD, the difference being statistically significant (p = 0.015). Abdominal pain was the commonest symptom in patients with CD (89.2%) and ITB (86.3%). Abdominal examination showed right iliac fossa mass in one patient with CD. In patients with ITB right iliac fossa mass was revealed in two patients, hepatosplenomegaly in one, and cervical lymphadenopathy in two patients. Laboratory investigations revealed anemia and high CRP in most patients. Although all ITB patients presented with prominent intestinal symptoms, radiologic examination revealed some findings of pulmonary tuberculosis in 3 patients (13.6%). Quantiferon-TB Gold was positive in 16% of CD and 66.6% of ITB patients with a significant difference (p = 0.023). Colonoscopy showed ulcerated ileocecal valve in 52 (85.7%) patients with CD and 18 patients with ITB (81.8%). Terminal ileum stenosis was revealed in 36 (64.2%) patients with CD and 10 patients with ITB (45.4%). None of these findings were discriminatory in our patients. Granulomas in endoscopic biopsy samples were seen in all patients with ITB and in 11 CD patients (19.6%); the difference was statistically significant (p < 0.001).

Conclusion: Although ITB is often indistinguishable from CD regarding clinical, biological and endoscopic findings, histology and QTF are important tools to help ensure an accurate diagnosis.
Clinical value of fecal calprotectin in predicting mucosal healing in patients with ulcerative colitis

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Aim: To evaluate the clinical significance of fecal calprotectin (FC) in assessment of ulcerative colitis (UC) patient’s disease activity by comparing them with endoscopic disease activity and with clinical disease activity.

Methods: A total of 143 UC patients who received colonoscopy and 108 controls were included. After providing stool samples, patients underwent total colonoscopy. FC was measured by enzyme-linked immunosorbent assay (ELISA). Clinical activity was based on the Mayo score. Endoscopic findings was scored by the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). Receiver-operator characteristic analysis were undertaken to determine the significance levels of measurements.

Results: The median (interquartile range, IQR) of FC levels were 211 (43–990) μg/g in UC and 87.5 (40.50~181) μg/g in the controls. Fecal calprotectin correlated significantly with both Mayo and UCEIS scores (Spearman’s r 0.670 and 0.592, p < 0.01). With a cut-off value of 164 μg/g for a raised fecal calprotectin concentration, the area under the curve (AUC) in receiver operator characteristic analysis was 0.830, sensitivity 85.42%, specificity 73.68%, positive predictive value (PPV) 62.12%, and negative predictive value (NPV) 9.10% in predicting clinical active disease. Similarly, the power of FC to predict MH was modest, the AUC was 0.839 and cut-off value 154.5 μg/g with 72.34% sensitivity and 85.71% specificity.

Conclusion: For evaluation the disease activity of UC, FC is a clinically relevant biomarker of both clinical active disease and MH in patients with UC. But the value of the cut-off still need large and multicenter studies.
**Association between polymorphisms -318 C/T, 49 A/G of CTLA-4 gene and polymorphism IVS 3 +17 T/C of CD28 gene and Crohn’s disease: A controlled study**

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**Background:** Crohn’s disease (CD) is a pathology characterized by a chronic inflammation of the intestinal tract engendered by an excessive activation of lymphocytes T, which would be responsible for a change of the immune answer. The gene CTLA-4 (cytotoxic T-lymphocyte antigen 4) and the gene CD28 (cluster of differentiation), represent two good candidates genes to explain the physiopathology of CD. While the molecule CTLA-4 plays a leading role in the negative control of lymphocytes T activated, the protein CD28 assures an opposing role, by guaranteeing their activation, their survival and their expansion. Besides, several studies analyzed the possible association of these two genes with certain autoimmune diseases as type 1 diabetes, celiac disease and rheumatoid arthritis.

**Objective:** Searching a correlation between polymorphisms of -318 C/T, 49 A/G TL-4 gene and SNP IVS 3 17 T/C CD28 gene studied by PCR-SSP and CD and compare the results to control group.

**Results:** The study concerned 50 CD patients and 108 controls. The frequency of the allele C of the SNP-318 C/T was more important in CD patients (94%) than in controls (91.2%). The frequency of the allele A of the SNP 49 was more frequent in patients (75%) than in controls (70.8%). The frequency of the allele T of the SNP IVS 3 17 T/C was also superior in patients (83%) than in healthy (80.1%) and a frequency of the more considerable haplotype TCA was more frequent in CD patients (61.8%) than in controls (52.3%). However, these differences were not significant (p = 0.3917; p = 0.4422; p = 0.54; p = 0.1133).

**Conclusion:** We concluded to the absence of an association between allelic and haplotypic polymorphisms Crohn’s disease studied population. Our results are in agreement with most of the studies. To our knowledge, for the gene CD28, our study is the first one that searched an association between the disease of Crohn’s disease and the polymorphism. Other studies with more large scales with various ethnic groups and stratification according to the risk factors are necessary to explore the exact role of the polymorphisms of the gene CTLA-4 and CD28 in the physiopathology of Crohn’s disease.
Evaluation of efficacy of anti-TNFα in luminal Crohn’s disease; a single-center study

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Background: Anti-TNFα antibodies are the second-line treatment of moderate to severe Crohn's disease (CD), resistant to conventional treatments. The aim of our study was to evaluate the efficacy of these biotherapies and to identify predictive factors of response under anti-TNFα.

Methods: This was a 15-year retrospective study that included all patients with active luminal CD, anti-TNFα naive, who benefited at least from an induction therapy with anti-TNFα.

Results: Thirty-five patients were included. They were 20 men and 15 women with an average age of 30.5 years. Indication of anti-TNFα agents were, essentially, an immunosuppressive agents (IS) failure in 15 patients (43%) and a severe steroid-resistant CD in 9 patients (26%). After induction therapy, 29 patients (83%) showed a favorable clinical response including 22 (76%) under IS associated with anti-TNFα. Maintenance therapy resulted in a favorable clinical response in 24 (68%), 20 (57%) and 12 (34%) patients, respectively, at 6, 12 and 18 months. Secondary loss of response to anti-TNFα was noted in 7 patients (20%). Five cases of immunogenicity reactions and four cases of severe infections including three cases of tuberculosis have been reported. After induction therapy, a history of ciclosporin use was associated with failure to anti-TNFα antibodies, while hyperleukocytosis at the time of the outbreak was predictive of clinical remission. At 6 months, obtaining a clinical remission after the induction phase was the only independent factor of good response to maintenance therapy with anti-TNFα (p = 0.012) whereas ileal involvement was an independent factor of treatment failure (p = 0.006).

Conclusion: Treatment with anti-TNFα combined with IS resulted in a favorable clinical response at the end of the induction therapy (83%) and at one year of maintenance therapy (57% at 1 year). A severely active CD that required ciclosporin, ileal involvement and stenotic phenotype were predictive factors of poor response to anti-TNFα agents.
Diagnostic and therapeutic management of perianal fistulas during Crohn’s disease

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Background: Anoperineal fistulas (APF) are a frequent localization of Crohn’s disease (CD). A clinical, radiological and endoscopic assessment allows us to classify them into simple and complex fistulas. The still therapeutic management, which is not yet consensual, will depend on this assessment.

Methods: It is a retrospective study over a 14-year period. We included all patients with a definite diagnosis of CD and APF with a minimum follow-up of one year under treatment.

Results: 80 patients were included 34 men and 46 women with an average age of 31.64 years. The frequency of APF in our series was 18.8% of patients with CD. At the end of the initial clinical, radiological and endoscopic assessment, 91% had complex APF and 9% a simple APF. In the case of simple APF, the majority of patients underwent combined treatment with antibiotics (ATB), loose seton drainage and azathioprine (AZA). Clinical remission was obtained in 6 patients. For complex APF, an anti-TNFα treatment was prescribed in 49 patients. Anti-TNF was prescribed in combination with ATB and seton drainage in all cases. AZA was prescribed in 35 patients. After induction therapy, 43 patients showed a favorable clinical response. At 1 year of maintenance therapy, 24 patients were in clinical remission with 20 in both clinical and radiological remission. Secondary loss of response to anti-TNFα was observed in 42% of patients with the achievement of a clinical response in 56% of patients after optimization. The multivariate analysis of the results showed that obtaining a clinical remission after the induction phase was the only independent factor of good response to maintenance therapy with anti-TNFα. Patients with a complex APF who were not treated with anti-TNFα and had ATB, seton drainage and AZA showed a primary failure rate of 33%.

Conclusion: Anti-TNFα is the treatment of choice of complex APF. The association of ATB, drainage and AZA allows to enhance the results. The type of response observed after the induction phase appears to be an early indicator of the type of subsequent response.
HDAC7 as an important mediator of cell motility and tumor growth in intestinal epithelial cells

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Introduction: The intestinal mucosal barrier plays an important role in maintaining gut homeostasis as well as contributing to pathophysiology in inflammatory bowel disease (IBD). In particular, the ability of regeneration in inflamed or damaged epithelial tissue represents a key feature in maintaining the barrier integrity, while excessive proliferation and migration increases the risk of tumorigenesis. Histone deacetylases (HDACs) emerged as promising targets for diagnosis and therapy, since pan-HDAC inhibition could be shown to ameliorate experimental colitis and colitis associated tumorigenesis. However, the function of single HDACs in the intestinal epithelial barrier is still poorly understood. Here, we focus on the implications of HDAC7 in epithelial cell function with special emphasis on IBD and carcinogenesis.

Methods: For functional analysis of HDAC7, knock-out mutants of murine colorectal cancer derived CMT93 cells were generated using the CRISPR/Cas9 technology. Mutants were functionally characterized by migration and proliferation assays. Specific immunostaining revealed spatial expression patterns and cellular localization of the protein. Transcriptome analysis via RNA-Seq was performed to uncover regulated pathways. Furthermore, the impact of HDAC7 on tumor growth was examined in vivo by subcutaneous injection of HDAC7 mutants in mice.

Results: HDAC7 knock-out mutants showed an impaired migratory capacity compared to wild type in wound healing assays. Immunostaining of HDAC7 in a scratched cell monolayer revealed an enrichment of HDAC7 protein in cells located in the migration zone. Additionally, RNA-Seq data revealed a strong implication of HDAC7 in signalling pathways involved in migration and cell adhesion. These findings coincided with a decreased expansion rate observed for cells lacking HDAC7 in first in vivo tumor growth experiments.

Discussion/Conclusion: We could show a novel integrated role of HDAC7 in epithelial cell motility in vitro which also affects tumor growth in vivo. Our findings indicate a crucial role for HDAC7 in intestinal epithelial regeneration, migration and cancer formation.
Fecal BAFF is a sensitive and specific marker in discriminating IBS from IBD

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Introduction: BAFF plays an important role in a variety of autoimmune diseases. Recently, we found fecal BAFF increased in IBD patients. To evaluate the efficacy of BAFF as a biomarker for discriminating IBS from IBD and assessment of intestinal inflammation we conducted a prospective study.

Methods: Patients were recruited prospectively from two medical centers. Stool samples were collected from patients 74 with IBD (36 Crohn’s disease [CD], 28 ulcerative colitis [UC]), 30 with IBS, and 42 healthy controls. Fecal BAFF was measured by ELISA. Clinical disease activity and endoscopic inflammatory score were determined in IBD.

Results: The median (25th-75th percentile) fecal BAFF was 447 (232–728) ng/kg in CD patients, 816 (308–1987) ng/kg in UC patients, 180 (98–191) ng/kg in IBS patients and 158 (85–190) ng/kg in healthy controls. For discriminating IBD from IBS, BAFF ≥ 227 ng/kg gave 82% sensitivity, 96% specificity, 98% positive predictive value, 68% negative predictive value, and an area under the curve (AUC) of 0.924. Fecal BAFF level showed a significant correlation with endoscopic inflammatory score not only in UC (correlation coefficient r = 0.61, p < 0.0001), but also in CD (r = 0.45, p < 0.05).

Discussion/Conclusion: Fecal BAFF is a promising biomarker for discriminating IBD from IBS and evaluation of intestinal inflammation.

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Effects of immunomodulatory tetracyclines in DSS colitis

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Introduction: The immunomodulatory properties of the tetracyclines minocycline and doxycycline have been reported to contribute to their intestinal anti-inflammatory effects, although the mechanisms involved have not been completely elucidated. micro-RNAs could be implicated since they may be modified by the treatments and changes in the microbiota, and play a key role in intestinal homeostasis, which can be influenced by microbiota composition as well as after drug treatment. This study compares the effects of these immunomodulatory tetracyclines with other antibiotics and dexamethasone in the DSS model of mouse colitis, which has been reported to share some features with human ulcerative colitis.

Methods: C57BL6/J mice were distributed into different experimental groups: non-colitic and DSS-colitic groups. Colitis was induced by incorporating DSS in the drinking water (3%) for 5 days. Once the colitis process was established, colitic mice were treated with the different drugs for 4 days: rifaximin (250 mg/kg/day), tetracycline (200 mg/kg/day), doxycycline (25 mg/kg/day), minocycline (50 mg/kg/day), tigecycline (25 mg/kg/day) and dexamethasone (2.4 mg/kg/day). The inflammatory status was evaluated histologically and biochemically. The expression of several inflammatory markers was evaluated by qPCR, including micro-RNAs and TLRs. Finally, the impact on intestinal microbiota composition was also evaluated by pyrosequencing.

Results: Doxycycline, minocycline and tigecycline ameliorated disease evolution and achieved a significant improvement of colonic histological damage, showing restored crypt architecture and the preservation of mucus-filled goblet cells. None of the other drugs exerted a significant beneficial effect. The recovery of the mucosal epithelial barrier integrity obtained by the immunomodulatory tetracyclines was confirmed biochemically when the expression of mucins and tight junction proteins was evaluated. Moreover, the immunomodulatory activity of these compounds was evidenced by reduced expression IL-1β, IL-6, MMP-9 and CXCL2, although CCL2 expression was further up-regulated by tetracycline treatment. A similar effect was observed when miR-142 expression was evaluated, while other inflammation-related miRNAs were reduced (miR-150, miR-155 and miR-233). Additionally, the colonic TLR4 expression, which was reduced in DSS-colitic control, was partially restored in tetracycline treated groups. When the microbial population was evaluated, all antibiotics induced a similar impact on this composition, and restored the abundance of the main higher taxonomic groups, although their effect diverged from the composition of NC mice at lower taxonomic levels.

Discussion/Conclusion: The intestinal anti-inflammatory activities exerted by immunomodulatory tetracyclines encourage considering their application for the treatment of intestinal inflammation. The modulation of some inflammatory pathways suggests that a specific immunomodulatory mechanism may underlay their early effect and the protection of intestinal homeostasis.
**Thiopurines are superior to mesalamine for preventing postoperative recurrence in Crohn’s disease patients with two or more risk factors**

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**Introduction:** This study was designed to confirm the hypothesis that thiopurines (TPs) might be a better choice for patients with 2 or more risk factors to prevent postoperative recurrence of Crohn’s disease (CD).

**Methods:** From November 2007 to August 2015, 87 consecutive CD patients aged 15–60 years old with curative intestinal resection and ileocolic anastomosis were recruited for retrospective analysis: 43 on TPs (azathioprine 2–2.5 mg/kg/day or mercaptopurine 1 mg/kg/day) and 44 on mesalamine (3–4 g/day). Primary endpoints were clinical recurrence (CDAI > 200) and treatment failure (CDAI > 200 or withdrew treatment due to adverse effects) before or at week 52 and secondary endpoint was endoscopic recurrence (≥ i2) at primary endpoint.

**Results:** By week 52, no significant differences of clinical recurrence (37.2%; 16/43 on TPs vs. 54.5%; 24/44 on mesalamine, p = 0.105), treatment failure (44.2%; 19/43 vs. 54.5%; 24/44, p = 0.334) and endoscopic recurrence (55.8%; 24/43 vs. 75.0%; 33/44, p = 0.060) were found between two groups. In subgroup patients with ≥ 2 risk factors, the rate of clinical recurrence/treatment failure (35.7%; 5/14 vs. 81.8%; 9/11, p = 0.042) and endoscopic recurrence (64.3%; 9/14 vs. 100.0%, 11/11, p = 0.046) was significantly lower in TPs group compared with mesalamine group. Patients added one more pre-defined risk factor, the risk of endoscopic recurrence increased 2.201 folds (95% CI: 1.178–4.115) adjusted by treatment group. In mesalamine group, patients add one more pre-defined risk factor, the risk of clinical and endoscopic recurrence increased 3.383 (95% CI: 1.260–9.081) and 5.884 (95% CI: 1.598–21.662) folds, respectively. Three patients withdrew before week 52 due to adverse effects, all in TPs group: 2 due to leukopenia and 1 due to joint pain.

**Discussion/Conclusion:** Thiopurines are superior to mesalamine for preventing postoperative recurrence for CD patients with two or more risk factors.
Immunomodulatory effect of minocycline in intestinal inflammation


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Introduction: Minocycline exerts immunomodulatory effects that could be beneficial in IBD. The mechanisms underlying these effects are not completely understood, and different actions on particular immune cell populations might be implicated. The aim of the study was to evaluate the impact of minocycline on the different immune cell populations involved in the DSS-colitis model in mice.

Methods: Intestinal inflammation was induced in male C57BL/6J mice by administration of dextran sodium sulfate (DSS) in the drinking water (3%) for 5 days. Once the colitis process was established, one group received minocycline (50 mg/kg/day), while colitic control and healthy groups were given water. Mice were sacrificed after 2 and 4 days of treatment. The inflammatory status was evaluated by the disease activity index (DAI), histological evaluation, colonic gene expression and cytokine production, and analysis of the leukocyte populations from colonic lamina propria and blood by multiparametric flow-cytometry.

Results: Minocycline treatment improved the recovery of colitic mice, increasing mucosa barrier protection and ameliorating some of the inflammatory markers. However, some immune pathways were potentiated, especially after 2 days of treatment, which explains the subsequent immunological changes observed at day 4. Thus, type-2 immune responses, with increased eosinophils and Th2 populations, were boosted. Also, it was noted an increment in the dendritic cells and macrophage populations, the latter showing a shift towards resident intestinal macrophages that promote homeostasis. Moreover, numbers of Treg and Th17 cells were higher while neutrophils were lower. Minocycline also increased the production of IL-22 and GM-CSF, especially at day 2, and up-regulated Alox15 expression, which is involved in the synthesis of pro-resolving lipid mediators.

Discussion/Conclusion: Minocycline accelerates the resolution of the acute intestinal inflammation. It induces Th2 and Treg responses, which contribute to control intestinal inflammation. This results in increased mucosal protection, most probably through activating resolution pathways, which prevent tissue damage. These immunomodulatory properties could support its future development in IBD.
Effects of vitamin D supplementation on ulcerative colitis patients

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Introduction: Vitamin D (VD) deficiency is commonly diagnosed among patients with inflammatory bowel disease (IBD). VD normalization is associated with reduced risk of relapse, reduced risk of IBD-related surgeries, and improvement in quality of life. The aim of this study was to evaluate the possible therapeutic role of VD supplementation in mild and moderate ulcerative colitis (UC) patients.

Methods: We performed a double-blind randomised placebo-controlled study, conducted over a period of 6 months (June 2016–November 2016). The study enrolled 52 patients diagnosed with mild and moderate UC with Ulcerative Colitis Disease Activity Index (UCDAI) < 10 and VD deficiency (VD levels < 30 ng/ml). Serum 25(OH)D levels were measured in all patients enrolled in the study. We assigned 52 UC patients with 2400 IU/day VD or placebo for 6 months. We determined UCDAI and serum 25-hydroxyvitamin D (25[OH]D in nmol/l) at 0 and 6 months.

Results: Sixteen (30.7%) patients had VD levels < 10 ng/ml, 27 patients had VD levels between 11–20 ng/ml and 9 patients presented VD levels between 21 and 30 ng/ml. At 6 months, 25(OH)D concentrations were significantly higher in those whom were treated (p < 0.001). In the placebo group, 25(OH)D concentrations stayed approximately the same. At 6 months, patients with 25(OH)D ≥ 30 ng/ml had significantly lower UCDAI scores (p = 0.05).

Discussion/Conclusion: VD supplementation significantly increased 25(OH)D levels in UC patients with mild and moderate disease activity and was associated with lower UCDAI scores. Vitamin D is an inexpensive supplement which has been shown to improve IBD outcomes. However, stronger evidence is needed to support the role of VD in inducing disease response and remission, as well as maintaining this improvement.
Endoscopical method for stopping bleeding in cases with ulcerative colitis and advanced rectal cancers

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Introduction: In last 30 years colorectal cancer frequency was increased from 7% to 33%.
The purpose of our study is to improve the patients with bleeding in ulcerative colitis and advanced rectal cancer.

Methods: For ten years’ periods we have diagnosed 200 colorectal cancers and 220 ulcerative colitis. All patients were endoscopical and histological confirmed. We treated our patients with Tissucol – two-component fibrin sealent. 75% of patients with application of Tissucol-Kit were with ulcerative colitis and 25% with lower inoperative cancer.

Results: In 75% of patients treated with Tissucol-Kit were found clearly Tiseel clot, after first application and stopping the bleeding, but in 20% the same effects were found after the second application-on, 5%-effect after more application. All patients were examined endoscopically and clinically after treatment. In endoscopical examination we found the typical milky white, clearly visible Tisseel clot cover the rectal ulceration and cancers’ surface. Blood in stool was disappeared.

Discussion/Conclusion:
1. Tissucol’s applications is effective in 75% of patients with ulcerative colitis and rectal cancers for stopping bleeding.
2. This method improve anemic cases in patients with bleeding.
3. Tissucol-Kit is suitable in cases with bleeding.
Relationship between bone mineral density and duration of the therapy for induction of remission in inflammatory bowel diseases

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Introduction: Aim of this study was to investigate a possible relationships between bone mineral density (BMD) and the therapy, the treatment duration or the localization and activity of IBD.

Methods: We investigated 32 patients with IBD: the A group consists of 22 patients with moderate ulcerative colitis (UC) and the B group with 10 patients with Crohn’s disease (CD) with mild to moderate activity. In the A group, the therapy for induction of remission was: mesalazine (Salofalk® 2–3 g/day) associated with Budesonide (3 x 3 mg/day) in 16 patients and 6 patients (with contraindicated corticoids therapy) received azathioprine (1–1.5 mg/kg/day). In the B group 7 patients were treated with oral mesalazine and budesonide and 3 patients were treated with azathioprine. All patients follow-up immunosuppressant therapy for maintenance of remission. BMD was measured by dual energy x-ray absorptiometry (DEXA) of the femoral neck and lumbar spines.

Results: The incidence of osteoporosis was significant higher in UC patients (36.36%) comparative with CD patients (20%). Osteopenia were present more frequent in CD (20%). The rheumatic manifestations of UC patients was: pauciarticular peripheral arthropaties (7 cases), polyarticular peripheral arthropaties (3 cases) and only one patient was diagnosed with ankylosing spondylitis. CD patients were present polyarticular peripheral arthropathies in 2 cases (20%) and ankylosing spondylitis in one case. We have not found a correlation between BMD and ages, gender or severity of IBD activity, but T-score was correlated with BMI values, C reactive proteine and hipocalcemia. Also, we identified a moderate correlation between values of T-score and the duration of the combined therapy with mesalazine and budesonide in UC patients, but in CD patients this correlation was insignificant. IBD patients with an abnormal BMD (15 cases) had a significantly higher rate of Vitamin D deficiency. The localization of IBD and values of clinical disease activity index (CDAI in CD and Powell Tuck Index in UC) were not significantly correlated with T-score, but osteoporosis was present more frequent in patients with CDAI > 150 or large extension of disease.

Discussion/Conclusion: The low BMD were uncorrelated with the localization and activity of IBD, but high BMI, Vitamin D deficiency and long term treatment with corticosteroids were independents risk factors for osteoporosis.
The beneficial effects of probiotics in association with usual therapy for inducing remission in moderate ulcerative colitis

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Introduction: The aim of this study was to assess the efficacy and safety of mesalazine-budesonide combined therapy in association with probiotics in inducing remission in moderate UC.

Methods: We included in our study 42 patients with mild-moderate forms of UC who was divided in two groups. The A group composed of 24 patients received combined therapy with oral mesalazine (Salofalk® 2–3 g/day) and oral budesonide (3 mg x 3 times/day), for 6–8 weeks in association with probiotics: Lepicol (L. plantarum, L. delbrueckii, L. acidophilus, L. rhamnosus and B. bifidum) or Eubiotic (L. rhamnosus, Bifidobacterium). The B group consist of 18 patients who received oral budesonide monotherapy (3 mg x 3 times/day) or combined therapy with oral mesalazine and oral budesonide. We evaluated the Powell-Tuck index and endoscopic classification at baseline, after 1, 3, 6 and 12 months.

Results: In the A group most of the patients (14 cases) presented left-sided UC, 7 patients had proctitis and 3 patients had extensive colitis. In the B group the localization was: left-sided UC in 11 cases and proctitis in 7 cases. At 3 months, the rate of clinical and colonoscopically confirmed remission was: 62.50% in the A group and 50.00% in B group. Also, a significant decrease of Powell-Tuck index from 1.9 ± 0.5 at baseline to 1.1 ± 0.4 at 2 month was observed in the A group. In the A group rapid response was observed in the young patients. Relapse was reported in 20.84% of patients in the A group compared to 33.34% in B group. There was no significant difference in the incidence of adverse events comparative in the A and B groups. In both groups, the adverse events include: diarrhea, abdominal pain, nausea and vomiting.

Discussion/Conclusion: The modulation of the gut microbiota can assure a significantly improvement of the efficacy of combined therapy with oral mesalazine and oral budesonide in UC patients. The beneficial effect of probiotics in the treatment of UC was associated with decreased rate of recurrences.
Smoking status and effectiveness of thiopurines as maintenance treatment following severe acute colitis in patients with Crohn’s disease

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Introduction: Azathioprine (AZA) has proved its effectiveness as a maintenance treatment of Crohn’s disease. The objective of our study is to evaluate the impact of smoking status on the response to thiopurines in patients with severe Crohn’s disease.

Methods: We conducted a retrospective study including patients with Crohn’s disease who received thiopurines following severe acute colitis from 2000 to 2016. Epidemiologic, clinical and therapeutic characteristics were abstracted from medical records. Results were analysed statistically using SPSS software.

Results: We colligated 70 patients (27 males, 43 females) with a male to female ratio of 0.62. The mean age was 37 years [19.54]. Nine patients had a familial history of inflammatory bowel disease (25%). There were 20 smoking patients (28.5%). The average duration of the disease before Azathioprine was established was 3.7 years [2 months, 6 years]. The localizations of the disease were: ileocolic in 43 cases (61.4%), colic in 17 cases (24.2%) and terminal ileitis in 10 cases (14.2%). A high digestive localization was found in 4 cases (5.71%). AZA was prescribed at an average dose of 2.5 mg/kg/day. Sixty patients (85.7%) were adhered to the treatment. Loss of response was noted in 11 cases (15.7%) and failure of treatment occurred in 6 cases (8.5%). In univariate analysis, loss of response and failure of treatment were significantly more common in smoking patients (p1 = 0.04; p2 = 0.001).

Discussion/Conclusion: In our series, thiopurines was effective in the treatment of severe Crohn’s disease patients. However, smoking status seems to increase the risk of the loss of response and failure of treatment among patients with severe Crohn’s disease.
Clinical features of early onset Crohn’s disease

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Introduction: Children and adolescents with Crohn’s disease (CD) present often with a more complicated disease course compared to adult patients. The aim of this study is to describe the clinical features and outcomes of Crohn’s disease in young population.

Methods: We enrolled a retrospective study from 2000 to 2016 including patients with young onset of CD (age < 20 years) who were hospitalized to treat the first flare of the disease. Epidemiological, clinical and therapeutic characteristics were abstracted from medical records.

Results: We colligated 30 patients 19 males (63.3%) and 11 females (36.6%) with a male to female ratio of 1.72. The mean age was 16.3 years [15–20]. Two patients (6.6%) had a history of inflammatory bowel disease. Three patients had a history of appendectomy. Localization was ileocolic in 8 cases (26.6%). According to the phenotype of Crohn’s disease inflammatory, structuring and penetrating form of the disease were observed respectively in 18 patients (60%), 8 patients (26.6%) and 4 patients (13.3%). Six patients (20%) had anoperineal fistulas. Corticosteroids as an initial treatment was used in 16 patients (53.3%). Immunosupression with azathioprine and Infliximab were required respectively in 14 (46.4%) and 4 patients (13.3%). Surgical treatment was performed in 6 patients (20%) because of CD complications. A statistically significant correlation was observed between severe CD and smoking (p = 0.02) and elevated rate of C-reactive protein (p = 0.037).

Discussion/Conclusion: In our series, young onset Crohn’s disease is associated with a severe course of the disease. Therefore young onset Crohn’s disease require strategic management.
Efficacy of anti-TNF-alpha therapy in luminal Crohn’s disease

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Introduction: Anti-TNF-alpha are nowadays considered as a very important mean of treatment in inflammatory bowel diseases (IBD). The aim of this study was to evaluate the efficacy of anti-TNF-alpha in a population of luminal Crohn’s Disease (CD) patients.

Methods: We investigated all the CD patients admitted in our department in the period between January 2011 and December 2015. Only patients with luminal CD treated with anti-TNF-alpha (infliximab or adalimumab) were enrolled. Patients with anoperineal or extraintestinal CD were excluded. Response was defined as a clinical remission without corticosteroids nor surgery. It was evaluated at induction, 6 months and one year of treatment.

Results: Twenty one patients were included in our study. Their mean age was 44.5 years and the sex ratio was 0.8. The mean duration of evolution of the CD was 9.5 years, longer than 5 years in 73% of cases. The mean age at diagnosis was 34 years.

The localization of CD was ileal (33%), colonic (26%) or ileocolonic (40%). Its behavior was non-stricturing non-penetrating (31%), stricturing (33%) or penetrating (36%). Two thirds of patients had a severe course of the disease before initiating anti-TNF-alpha therapy and 60% had underwent surgery.

All patients were treated by corticosteroids, twice in 53% of cases. 13% of patients became steroid resistant and 33% steroid dependent. Azathioprine was prescribed for 93% of patients, 20% of them developed a bone marrow toxicity, which motivated a switch to anti-TNF-alpha. The other indications of anti-TNF-alpha were a non-response to azathioprine (40%), a postoperative recurrence (20%), a resistance to steroids (13%) and an extensive small bowel disease (6%). Anti-TNF-alpha therapy was started within an average of 6 years after the onset of the disease.

In our study, 66% of patients received an association of azathioprine and anti-TNF-alpha. The rates of clinical remission were estimated to 86% at induction, 86% at 6 months and 53% at one year. The rates of relapse were 13% at induction, 13% at 6 months and 56% at one year. During follow-up, an optimisation of treatment was necessary in 40% of cases and a switch to another anti-TNF molecule was performed in 7% of patients.

Conclusion: In our study, clinical remission at one year of anti-TNF-alpha therapy was observed in 53% of cases. However, more studies with a larger number of patients are necessary to confirm our results.
Predictive factors of surgery in Crohn’s disease

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Introduction: Surgery is an important therapeutic alternative in Crohn’s Disease (CD). The assessment of factors that may predict surgery in CD is therefore crucial in order to improve the management of IBD and have a better prognostic evaluation. The aim of this study was to search for factors predictive of surgery in CD.

Methods: We investigated all the CD patients admitted in our department in the period between January 2011 and December 2016. We analyzed their epidemiological, clinical and therapeutic features in order to identify the factors that could predict surgery.

Results: A total of 80 patients with CD were studied. Their mean age was 37 years and the sex ratio was 1.2. Smoking was noticed in 36% of cases. The CD was ileal in 35% of patients, colonic in 22% and ileocolonic in 39% of cases. Its behavior was non-stricturing non-penetrating, stricturing or penetrating in 33% of patients each. The maintenance treatment was mesalazine (36%), azathioprine (75%) and/or anti-TNF (42%).

In our study, surgery was performed in 45% of patients: 10% had an intra-abdominal abscess, 38% had a symptomatic stenosis, 3.5% were operated on because of failure of medical treatment, 1.7% had an acute severe colitis, and one patient had a colonic adenocarcinoma.

Surgery was significantly associated with ileocolonic localization (p = 0.029), non-stricturing non-penetrating behavior (p = 0.001) and penetrating behavior (p = 0.013). Anti-TNF-alpha therapy was marginally associated with surgery (p = 0.08). Furthermore, cumulative need for surgery significantly increased with the evolution of the disease, with a cut-off limit estimated at 10 years.

Conclusion: In our study, predictive factors of surgery in CD were ileocolonic localization, non-stricturing non-penetrating behavior and penetrating behavior. In addition, surgery was correlated with the long evolution of the disease.
Enteric release butyric acid: Innovation in oral formulation

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Introduction: The availability of oral nutritional supplements that allow the enteric release of butyric acid is currently scarce. Formulate and develop a nutritional supplement that ensures the enteric release of butyric acid and that presents organoleptic characteristics that do not hinder the therapeutic adherence.

Methods: Electro-hydrodynamic technology of monodisperse microcapsules, using tributyrin as butyric acid “pro-drug” (triglyceride containing three butyric acid molecules).
As the excipient, solid fats at room temperature were used to form the microspheres which characterize a granular shape.
Selection of fat-miscible aromas to counteract the immoderate organoleptic characteristics of butyric acid.

Results: Granulate containing 30% tributyrin, (787 mg of butyric acid per 3 g of final product). Excipients: Fully hydrogenated sunflower oil and mono and diglycerides of fatty acids (E-471). They allow solid microspheres to be obtained at room temperature by incorporating monodisperse tributyrin. Total hydrogenation allows the physico-chemical objectives pursued while containing a practically insignificant amount of trans fat, less than 0.1% (0.08% exactly). The final product is organoleptically characterized by its banana aroma and the absence of flavor.

Discussion/Conclusion: This new galenic form is a tool for the treatment of digestive pathologies that deal with dysbiosis of the microbiota, damage of the epithelium and degradation of the intestinal mucosa. The granulated format and the organoleptic characteristics obtained allow to bet for a positive therapeutic adherence.
**Metastatic Crohn’s disease: A rare cutaneous disorder**

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**Introduction**: Metastatic Crohn’s disease is a rare cutaneous manifestation defined as a granulomatous inflammation of the skin at sites anatomically separate from the gastrointestinal tract. It can precede or occur along with gastrointestinal disease. Treatment is mainly based on anecdotal reports. The aim of this study id to describe the clinical features of patients presenting with cutaneous Crohn’s disease.

**Materials and methods**: We conducted a retrospective study including patients presenting to our institution with cutaneous Crohn’s disease over a 5 year period (January 2011–January 2016).

**Results**: A total of 4 female patients were included. The average age at presentation was 48.2 years. The cardinal presenting features included pain and perianal discharge. Anorectal lesions (anal fistulas, fissures, ulcers) were noted in all cases. Three patients presented with edema of the vulva with plaques, nodules and vegetating lesions in the labia majora and minora, and fissures of inguinal skin folds. Skin biopsies in all cases revealed findings consistent with Crohn’s (non-caseating granulomas with multinucleated giant cells in the dermis surrounded by lymphocytes, plasma cells, and eosinophils). None of our patients had gastrointestinal involvement of their disease or were receiving systemic immunosuppression at the time of presentation. All cases required local treatment to the skin lesions including intralesional steroid and topical superpotent steroids. Systemic therapies with antibiotherapy in one case and anti-TNF therapy in 3 cases helped to control the cutaneous disease.

**Conclusions**: Metastatic Crohn’s disease is infrequently documented entity. The involvement of the external genitalia is exceedingly rare, with few documented cases in the literature. There are no definite guidelines for treatment of cutaneous Crohn’s disease. However, we highlight the use of anti-TNF agents as a promising treatment.
A comparison of clinical, endoscopic and pathologic characteristics between Crohn’s disease and intestinal tuberculosis

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Introduction: Differentiating intestinal tuberculosis (ITB) from Crohn’s disease (CD) is of vital importance and has become a clinical challenge because treatment based on misdiagnosis may lead to fatal outcomes. In this study, we reviewed the similarities and differences in clinical, endoscopic, radiological and histological features of these two diseases.

Materials and methods: A retrospective study enrolled 56 Crohn’s disease and 22 intestinal tuberculosis inpatients from January 2006 to December 2016. The characteristics and key points of differential diagnosis between the two groups were comparatively analyzed.

Results: The average age was 33.4 years [19–51 years]. Male predominance was noted (sex-ratio M/F = 1.8) in CD. Comparing with patients with ITB, patients with CD have more cases of chronic diarrhea (17.8% vs. 9%) and perianal lesions (5.3% vs. 0%). The salient features of ITB included fever (68.18% vs. 46.4%) and abdominal mass (4.5% vs. 3.5). Anemia and high C-reactive protein were more frequent in CD patients. TB bacilli were constantly negative in ITB cases. Tuberculin skin test was positive only in one case of ITB. Quantiferon-TB Gold test was significantly positive in ITB cases (66.6% vs. 16%). Based on the imaging, mesenteric lymphadenopathy was more common in CD than ITB (82% vs. 72.7%). The endoscopic examination showed that ileocecal valve stenosis (64.2% vs. 45.4%) and ileocecal valve ulceration (85.7% vs. 81.8%) were more frequent in CD. In terms of pathological findings, non-caseous granulomas were constantly found in ITB, while it was observed in 19.6% of CD cases. On univariate analysis, only positive Quantiferon-TB Gold test and presence of granulomas were significantly associated with ITB diagnosis.

Conclusion: There are many similarities and overlaps in clinical manifestations, endoscopic and pathological features between Crohn’s disease and intestinal tuberculosis. Quantiferon-TB Gold test is very useful in the differential diagnosis between ITB and CD. The presence of granulomas is very important to differentiate tuberculosis and Crohn’s disease.
Therapeutic complications in inflammatory bowel disease

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Introduction: Progress in the treatment of inflammatory bowel disease (IBD) was reached. Medical treatment showed efficiency in controlling disease activity but caused side effects that can be sometimes severe.

Methods: We evaluated in a retrospective study, including 112 patients (period of 5 years), the prevalence and risk factors of side effects of aminosalicylates, immunosuppressants and immunomodulators in IBD. A descriptive study was first realized for the 22 patients who showed side effects. Then analytic study compared these patients to the 90 others without side effects.

Results: Side effects occurred in 22 patients: 10 men and 12 women (sex-ratio 1.2). The median age was 47.7 years (21–75 years). Ulcerative colitis (UC) was predominant: 13 cases (63.3%). Patients had a median disease duration of 30 months (6–56 months). Thirteen patients (40%) from 32 treated by aminosalicylates developed side effects in a median period of 22 days (7–40 days): cutaneous eruption (7 cases), stomach pain (3 cases), cytolysis (2 cases) and dry cough (1 case). One patient showed cross-reactivity to sulfasalazine and mesalamine and required immunosuppressive therapy. Side effects of azathioprine occurred in 27% of cases (8 patients): hematologic toxicity (4 cases), liver toxicity (2 cases), a severe cytomegalovirus infection (1 case) and immunoallergic acute pancreatitis (1 case). No side effects were noted into methotrexate treatment. Six patients were treated by anti-TNF-alpha; one of them who was into azathioprine too, developed iatrogenic Kaposi sarcoma which was diagnosed after surgical treatment for a severe refractory UC. In comparison to the group of patients without side effects, no significant difference was reported concerning age, sex, family history of IBD, body mass index. Side effects were more frequent in patients with UC (p = 0.01). Multivariate analysis showed that independent risk factors for side effects were: UC, extraintesntal manifestations, anoperineal lesions and previous hematologic perturbations.

Discussion/Conclusion: Advances were realized in the treatment of IBD with different drugs which must be carefully selected and used because of their side effects which can be sometimes very severe.
Epidemiologic, clinical, therapeutic and evolutive profile of digestive strictures in Crohn’s disease

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Introduction: The constitution of a stenosis is the most common complication of Crohn's disease (CD). It may result from purely inflammatory or fibrotic lesions, an indication of a medical, endoscopic or surgical treatment. Medical treatment is often proposed, but the results are controversial in literature. The aim of our study was to describe the epidemiological, clinical, therapeutic and evolutive characteristics of patients with symptomatic stenotic Crohn's disease and to determine predictor factors of good response to medical treatment.

Methods: This is a retrospective study of 48 patients with stenotic Crohn’s disease (CD). The diagnosis of digestive stenosis was based on the imaging and/or endoscopy data. We collected the epidemiological, clinical, endoscopic and radiological data. Then we were interested in assessing the clinical response to treatment, the rate of occurrence of complications during treatment and the rate of need of surgery.

Results: They were 32 men and 16 women (sex-ratio = 2). The mean age was 39.27 years (18–83 years). Fifty-four percent of patients were smokers, 52% of patients were aged less than 40 years at the time of the diagnosis, 12.5% of patients had a family history of chronic inflammatory bowel disease. The stenosis site was ileal in 40 patients (83%) and colic in 8 patients (17%). The median BEST index was 234. Corticosteroid therapy was prescribed in 42 patients (87%) and anti-TNF α in 9 patients (19%). Thiopurines were indicated in the attack treatment in 28 patients (58%). The mean follow-up was 18 months. A clinical response to medical therapy was achieved in 22 patients (46%). Endoscopic dilatation was performed in 8 patients (16.6%). The surgery was noted in 18 patients (38%). CRP > 35 mg/l, the presence of a time T1 contrast enhancement in MRI and the absence of intra abdominal collection were predictive factors of response to medical treatment (respectively p = 0.034, p = 0.027, p = 0.03).

Discussion/Conclusion: Digestive strictures in Crohn's disease may well evolve under medical treatment if the indication is well posed. Determining the predictive response factors would guide therapeutic indications.
The mean platelet volume: Which relationship with the Crohn’s disease activity?

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Introduction: The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are closely correlated with the clinical activity of Crohn’s disease (CD). The ESR is influenced by various factors unrelated to inflammation, such as age, sex, and the presence of anemia or kidney failure. The mean platelet volume (MPV) is provided by the automatic apparatus for determining the blood count. It correlates with the function and platelet activation and decreases during inflammation.

The objective of this study is to look for correlations between mean platelet volume (MPV) and indices that reflect the activity of the CD.

Methods: This is a comparative retrospective study of 122 cases of CD (66 men and 56 women with a sex-ratio of 1.17) with a mean age of 39 years (18–83 years). We used as a control group, 70 patients consulting for Helicobacter pylori gastritis (HP) (43 women and 37 men) whose average age was 42 years.

Results: We collected 122 patients followed for CD, the median follow-up was 16 months, 57% of patients were smokers, 12% had a family history of CD, 42% had an ileal disease, 30% a colonic disease and 28% an ileocecal location. The CD was inflammatory in 25% of cases, stenotising in 40% of cases, fistulizing in 23% of cases and both stenosing and fistulizing in 12% of cases. Thirty-six patients have resorted to surgical treatment.

The average value of CRP was 28 mg/l (15–213), the average index of Best was 167 (120–412), the average number of outbreaks was 3 (1–7). The average value of MPV in patients with CD was 8.2 and it was significantly lower in this group compared to the group of HP gastritis (8.2 vs. 11.8, p = 0.04) and we found a significant inverse association between disease activity markers (an index of Best > 250; CRP > 30 mg/l) and the MPV.

Discussion/Conclusion: We believe that the MPV is an interesting consideration for an initial assessment of disease activity and to confirm the values of ESR, CRP and the CADI score in CD. Further studies are needed to determine its validity for assessing the activity of the CD.
Distal ulcerative colitis – Pancolic ulcerative colitis: A comparative study

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Introduction: Ulcerative colitis is an inflammatory disease which affects rectum and spread. Some factors distinguish between distal UC and pancolic UC. The aim of the study was to compare between epidemiological, clinical and therapeutical characteristics in distal UC and pancolic one.

Methods: Retrospective study in gastroenterology department of Mohamed Taher Maamouri Hospital during 5 years.

Results: Forty-five cases of UC were colliged: 18 cases of distal UC (group 1) and 27 cases of pancolic UC (group 2). Both of groups were comparable in age, sex, smoking and age at diagnosis. Initial symptoms were significantly different in the 2 groups (p = 0.032), especially rectal syndrome (27.7% in group 1 vs. 3.7% in group 2) and abdominal pain (5.5% in group 1 vs. 14.8% in group 2). Severe colitis was more frequent in group 2. Extraintestinal manifestations were more frequent too in group 2 (44.4% vs. 70%, p = 0.045). Treatment by 5-ASA was essentially prescribed in distal UC (94.4% vs. 59.2%) whereas 33% of patients with pancolic UC were treated by azathioprine with different indications in the 2 groups (p = 0.015); the main indication was salicylate intolerance in distal UC and chronic active UC and corticosteroid resistance in group 2. The moment of introduction of Azathioprine and side effects were not significantly different between the 2 groups. Remission was similar in both of groups but its duration was significantly longer in group 2 (0.026). Surgical treatment was realised in 5 patients with pancolic UC and anti-TNF-α was prescribed in 1 case. One patient of group 2 presented a colic cancer.

Discussion/Conclusion: Pancolic UC is associated to an increased risk of acute severe colitis, more extraintestinal manifestations and need of immunosuppressive therapy and surgery.
Cholelithiasis associated with Crohn’s disease: Prevalence and risk factors

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Introduction: Many published studies have reported a significantly high rate of gallstones in Crohn’s disease (CD) compared to the general population. Nevertheless, literature data are conflicting and often dependent on the characteristics of the disease. The aim of the study was to determine the prevalence of symptomatic or asymptomatic cholelithiasis in a cohort of patients treated for CD and to identify the predisposing risk factors.

Methods: This is a retrospective study which included the patients followed for CD between January 2005 and December 2015. The main epidemiological and clinical features of the disease were identified in all patients. The diagnosis of gallstones was done through an abdominal ultrasound performed systematically or in emergency in case of clinical symptoms of acute cholecystitis.

Results: One hundred eighteen patients were included in this study. The average age at the time of CD diagnosis was 37.5 years [14–37 years]. The sex-ratio was 1.17. Body mass index (BMI) was on average equal to 26.41 kg/m² and 27% of patients were overweight with a BMI > 25 kg/m². The localization of CD was ileal or ileocecal in 78% of cases and ileal involvement was considered extensive in 19% of patients. High intestinal lesions (gastric or duodenal) were described in 16% of patients. The disease phenotype was stenosing in 41% of cases and fistulizing in 24% of cases. Perianal lesions were associated in 28% of cases. The disease was complicated by intra-abdominal abscess in 17% of cases and parenteral supply was indicated in all patients. Surgical resection was indicated in 31% of patients. In the majority of cases (89%), it was an ileocecal or ileal resection. Ileal resection carried more than 50 cm in 30% of cases. Cholelithiasis was diagnosed in 10% of patients. It was symptomatic, operated in an emergency situation or not, in 33% of cases. In multivariate analysis, female sex, age > 50 years, BMI > 25 kg/m², the fistulizing or stenosing phenotype disease, extensive ileal involvement, the presence of perianal manifestations, surgical indication and extensive ileal resection were significantly correlated with the occurrence of symptomatic or asymptomatic cholelithiasis (p < 0.05).

In univariate analysis, only female sex, older age, BMI > 25 kg/m², the fistulizing phenotype or stenosing disease, extent ileal involvement and ileal resection of 50 cm or more were identified as risk factors for gallstones. The duration of disease progression, the number and gravity of thrust, corticotherapy, use of immunosuppressant or biotherapy and parenteral supply were not correlated with the occurrence of gallstones (p > 0.05). Thus, in addition to common risk factors in the general population such as age, gender and overweight, cholelithiasis was diagnosed mostly in case of ileal localization of CD
and of ileal resection extent. This is explained by the reduction of the absorption of bile acids in the terminal ileum. Other factors characterizing the evolving profile of CD have not been identified as risk factors for occurrence of gallstones.

**Discussion/Conclusion:** In this study, among the clinical characteristics and the clinical course of CD, only the phenotype of the disease, the location and extensive ileal resection were identified as independent risk factors for developing gallstones.
Ulcerative colitis in the elderly: A descriptive analysis of disease in a gastroenterology department

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Introduction: The presence of an ageing population combined with an increase in the incidence of inflammatory bowel disease (IBD) may mean that the burden of elderly-onset ulcerative colitis (UC) will become more apparent. Relatively limited information is available about the disease process in this group.

Methods: We aimed to describe demographics, therapies and outcomes in a cohort of Tunisian patients with elderly-onset UC (diagnosis confirmed after 50th birthday) during the period between 2007 and 2016.

Results: Over the study period, 40 patients (52.5% male) with elderly-onset UC were identified, with a mean follow-up of 3.6 years. Mean age at diagnosis was 55.4 years. The proportion of current, none, and ex-smokers were 27.5% (n = 11), 50% (n = 20) and 22.5% (n = 9) respectively. Eighty percent (n = 32) of patients had received at least one prescription of 5-aminosalicylate therapy. Thirty-five percent (n = 14) had received a course of oral steroids during follow up with 42.8% (n = 6) prescribed corticosteroid therapy within the first year after diagnosis. 12.5% of patients were classified as steroid dependent. 25% had a prescription of thiopurine (TP) therapy. 5% of elderly onset UC patients underwent colectomy during follow up versus 7.1% in patients aged less than 50 years (p = 0.009). In multivariate logistic regression, risk factors associated with need for colectomy in elderly patients were thiopurine use (p = 0.0001) and steroid dependency (p = 0.001).

Discussion/Conclusion: Although colectomy rates appear comparatively lower than in younger populations, suggesting a more benign disease course, there is a concerning level of steroid dependency in this cohort of elderly patients who will be at particular risk from the many side effects of corticosteroid treatment. The low TP use in this group may reflect a less aggressive disease course, but may also indicate cautious prescribing in this age group.
Ionizing radiation in patients with Crohn’s disease

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Introduction: Crohn’s disease (CD) patients usually require along their monitoring multiple imaging. The aim of our study was to establish the effective radiation dose for patients and study factors that are correlated to it.

Methods: This is a retrospective study including patients hospitalized for CD between 2007 and 2015, followed for at least 2 years. The epidemiological, clinical characteristics and different radiological examinations were recorded. We used mSv reported in the literature by type of radiological examination to calculate effective doses.

Results: One hundred patients were included, with a median age of 38.9 ± 15.5 years. The type was ileal in 35% of cases, ileocolitis in 36% of cases and colitis in 22% of cases.

The overall effective radiation dose per patient averaged 20.26 ± 11 mSv (2.28 to 45.36). Twenty percent of patients were exposed to high radiation (30 mSv). In univariate analysis, the stenosing phenotype (with or without associated fistula) and male gender were the risk factors for high exposure with respectively odds ratio (OR) 17.6 (p = 0.001) and 3.1 (p < 10^-3). In multivariate analysis, only the stenosing phenotype was a risk factor with an OR of 18.02 (p = 0.001). Since exploration by MRI enterography was not realized in first intention, it was not identified as a protective factor of radiation. However, replacing the CT-enteroclysis and barium small bowel transits by MRI-enterography, the median radiation gain per patient over two years reached 45.4% ± 33.7.

Discussion/Conclusion: Ionizing radiation is necessary in CD, abdominal CT in emergency is essential for complications. But exploration with MRI enterography should be preferred whenever a lesion mapping is needed to minimize the irradiation of patients.
Azathioprine and chronic inflammatory bowel diseases: Efficacy and side effects

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Introduction: Immunosuppressive therapy is used at one time or another in nearly three quarters of patients with Crohn’s disease (CD) and a lower portion of patients with ulcerative colitis (UC). Among the immunosuppressive treatments, the place of azathioprine is well recognized. The objective of our study was to investigate the efficacy of azathioprine in chronic inflammatory bowel disease (IBD) and the prevalence of its adverse effects and risk factors for their occurrence.

Methods: This is a retrospective study conducted between January 2000 and March 2016 that included all patients with IBD put under azathioprine at a dose of 2 to 2.5 mg/kg/day and in whom we were interested in evaluating the efficacy and adverse effects.

Results: Ninety-seven cases of IBD receiving azathioprine were collected of which 78 cases of CD and 19 cases of UC. They were 48 men and 49 women. The sex-ratio was 0.97. The mean age was 41 years (18–88 years). Indications were respectively maintenance treatment after a severe relapse in 10 cases (10.2%) or severe acute colitis in 30 cases (31%), active chronic forms in 15 cases (15.5%), 8 patients before corticosteroid (8.2%), a preventive treatment for postoperative recurrence in 23 patients (23.7%), after a postoperative recurrence in 3 patients (3.1%), intolerance to aminosalicylates in 5 cases (5.2%), one case of upper gastric damage and in combination with anti-TNF-alpha in 19 patients (20%). The median onset time was 3 months (1–5 months). We observed a remission rate of 73%. The prevalence of adverse events was 19%, requiring azathioprine discontinuation in 7% of cases. The median time of occurrence of these side effects was one month (1 day–96 months). The two most common adverse reactions observed in 6 patients were gastrointestinal intolerance and haematological toxicity, including leukopenia in 4 patients, liver toxicity was noted in 4 patients, rash in 2 patients. No cases of acute pancreatitis have been observed. We found no significant correlation between the presence of adverse effects and the following factors: age, sex, type of IBD, IBD topography and corticosteroid.

Discussion/Conclusion: Azathioprine has an important place among the therapeutic arsenal of IBD. However, its use is not devoid of side effects that can be severe and requiring discontinuation of the treatment, hence the importance of a careful monitoring.
Crohn’s disease first diagnosed on surgical complications versus Crohn’s disease operated during follow-up: Does the timing of surgery change the outcome of the disease?

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Introduction: Surgical treatment remains the cornerstone in Crohn’s disease. Surgical complications (perforation, abscess formation, severe colitis resistant to steroids) and refractory disease to immunosuppressive therapy are its main indications.

The aim of this study is to compare clinical features and treatment outcomes between 2 groups of Crohn’s diseases patients: those diagnosed after first surgery versus patients followed for Crohn’s disease before having their first surgery.

Methods: A retrospective descriptive study, including all patients with Crohn’s disease in Mohamed Taher Maamouri Hospital, who had surgery during a follow-up of ten years from January 2005 to December 2014. Surgery for ano perineal lesions was excluded from the study.

Results: Thirty seven patients were included, divided into 2 groups: G1 Including 17 patients who were not followed-up for Crohn’s disease before their first surgery and G2 including 20 patients having surgery during follow-up. The mean age was 40.1 years (17–84 years) with a sex-ratio of 1.05. Epidemiological characteristics were comparable in the two groups (sex, smoking and family history of inflammatory bowel disease). G2 patients were significantly younger (p = 0.005). The phenotype and localization of the disease were also comparable. Ileal disease was seen more frequently than ileocolonic or colonic disease (52.9% in G1 and 70% in G2). In G1, disease was rather stricturing and fistulizing (35.2%) and most frequently stricturing in G2 (45%). There was no significant difference between the 2 groups concerning anoperineal complications and extraintestinal manifestations.

Surgical treatment was mostly indicated for bowel obstruction (41.1% in G1 and 45% in G2) and abscess (17.6% in G1 and 25% in G2). Ileocoecal resection was the most practiced intervention in our patients in the two groups. Colectomy was significantly more practiced in patients who have been firstly diagnosed by surgery (G1) (p = 0.04). The mean extent of bowel resection was also more significant in this group (p = 0.04). Maintenance therapy was used in almost 70% of patients in the two groups. Immunosuppressive treatment was prescribed to 8.3% of patients in G1 and 20% in G2.

The outcomes of surgery were comparable in the two groups; we did not note significant difference in terms of remission rate (p = 0.22), the mean duration between surgery and first flare of the disease (p = 0.47), the number of flares after surgery (p = 0.13) and the need for a second surgery during follow-up (p = 0.46).

Discussion/Conclusion: Surgical bowel resection remains inevitable in most Crohn’s patients and it should induce long-term remission if it is practiced early in the course of the disease, as it is published in some series. In our study, the time of surgery did not significantly influence the course of the disease.
Azathioprine in the treatment of inflammatory bowel disease: Efficacy and safety

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Introduction: Immunosuppresssive drug therapy is used in nearly three quarters of patients with Crohn’s disease (CD) and a lower proportion of patients with ulcerative colitis (UC). The aim of our study was to evaluate the efficacy of azathioprine in inflammatory bowel disease (IBD) and the prevalence of its adverse effects and risk factors for their occurrence.

Methods: This is a retrospective study conducted between January 2000 and March 2016 that included all patients with IBD treated by azathioprine at a dose of 2 to 2.5 mg/kg/day and in which we have evaluated the effectiveness and side effects of this drug.

Results: Four ninety-seven cases of IBD were treated by azathioprine: 78 patients with CD and 19 cases of UC. They were 48 men and 49 women. The sex-ratio was 0.97. The median age was 41 years (18–88 years). Indications of treatment were respectively maintenance therapy after a severe relapse in 10 cases (10.2%) or severe acute colitis in 30 cases (31%), in active chronic forms in 15 cases (15.5%), eight patients with steroid dependance (8.2%), prevention of postoperative CD recurrence in 23 patients (23.7%), treatment of postoperative recurrence in 3 patients (3.1%) after intolerance of aminosalicylates in 5 cases (5.2%), one case of upper GI localisation and combotherapy in with anti-TNF-alpha in 19 patients (20%). Remission was observed in 73% of cases. The prevalence of adverse events was 19%, requiring discontinuation in 7% of cases. The median time of occurrence of side effects was one month (1 day–96 months). The two most common adverse effects, observed in 6 patients, were gastrointestinal intolerance and haematological toxicity, including leukopenia in 4 patients; liver toxicity was noted in 4 patients, rash in 2 patients. No cases of acute pancreatitis have been observed. There was no significant correlation between the presence of adverse effects and the following factors: age, sex, type of IBD, IBD topography and steroid dependance.

Discussion/Conclusion: Azathioprine has an important place in the treatment of IBD. However, it has risks and side effects that can be severe, requiring sometimes discontinuation of treatment.
Loss of PTPN2 in dendritic cells results in systemic inflammation

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Introduction: Variants within the gene locus encoding protein tyrosine phosphatase non-receptor type 2 (PTPN2) are associated with the development of several inflammatory disorders. The role of PTPN2 in T cells and intestinal epithelial cells has been investigated previously but its role in dendritic cells (DCs) remains unclear. This study addresses how loss of PTPN2 in DCs affects inflammatory signaling cascades and intestinal inflammation.

Methods: For this aim, we generated mice lacking PTPN2 specifically in DCs (PTPN2-CD11cCre mice). Acute colitis was induced in 10–12 week old females by administration of 2.5% DSS for 7 days.

Results: Interestingly, PTPN2-CD11cCre mice show symptoms of splenomegaly and dermatitis. In addition, we observed inflammatory infiltrations in the liver and the lung in some PTPN2-CD11cCre mice. These symptoms start to develop around the age of 10 weeks, but onset and severity of the inflammation varies between individuals, and results in sudden, spontaneous death in some mice. Further, PTPN2-CD11cCre mice show increased numbers of effector/memory CD4+ and CD8+ T cells. On the other hand, severity of chemically-induced acute colitis was not affected in PTPN2-CD11cCre mice. Ex vivo, PTPN2-deficient BMDCs, differentiated from bone marrow cells, treated with LPS show increased phosphorylation of nuclear factor (NFκB) p65, as well as enhanced expression levels of co-stimulatory molecules CD80 and CD86. Upon treatment with IFN-gamma, phosphorylation of signal transducer and activator of transcription 1 (STAT1) and mRNA expression of TNF was enhanced.

Discussion/Conclusion: In conclusion, our results show that PTPN2 has an important anti-inflammatory role in DCs but it seems to be dispensable in the setting of acute colitis. Loss of PTPN2 in DCs promotes T cell activation, increased expression of co-stimulatory molecules, and results in skin, lung and liver inflammation. Therefore, we will further study the effect of a loss of PTPN2 in DCs in more chronic and T cell mediated colitis models.
Characterization of intestinal stromal stem cells for its future use in the treatment of inflammatory bowel disease

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Introduction: Mesenchymal stromal cells (MSCs) from the colon play an important role in the maintenance of gut homeostasis. However, when they are in a chronic inflammatory environment, like in IBD, the expression of HLA-DR is highly increased and may contribute to the development of the disease. Moreover, since the intestinal barrier function may be comprised, they could be exposed to different bacteria and their products that could modify their immunomodulatory properties. The aim of the study is to better characterize colonic human MSCs to develop new strategies for the treatment of IBD.

Methods: Colonic MSCs were isolated from resections of human colon from patients suffering from colon cancer or intestinal obstruction. After culturing, their phenotype was checked by flow cytometry and by the capacity to be differentiated into adipocytes, chondrocytes and osteocytes. The expression of different TLRs and immune mediators was analyzed by RT-qPCR, and polarization towards MSC1 and MSC2 phenotypes was performed.

Results: The cells isolated from the colonic resections that adhered to the plastic showed a fibroblastic morphology and expressed the typical membrane markers (CD90, CD73 y CD105). When TLRs expressions were analyzed, colonic MSCs showed high expression of TLR3, TLR5 and TLR7, while TLR4 was low expressed. When the polarization assay was carried out, cells stimulated with poly(I:C) showed an increased expression of IDO, which indicates a polarization the MSC2 phenotype; however, LPS did not induce the expression of IL-6 or IL-8 so the polarization to the MSC1 phenotype did not occur.

Discussion/Conclusion: Colonic MSCs express low TLR4 and can be polarized toward an MSC2 anti-inflammatory phenotype. These properties could be used to either design a cellular therapy for IBD or directly modulating colonic MSC phenotype to improve their capacity to maintain gut homeostasis.
MDR1-deficiency unmasks mitochondrial dysfunction as a pathogenic mechanism in human inflammatory bowel diseases

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Background: The multidrug-resistance-1 (MDR1) gene encodes an ATP-dependent efflux transporter that is highly expressed in the colon. In mice, loss of MDR1 function results in colitis with similarities to human IBD. Recently, we observed a marked accumulation of dysmorphic mitochondria within the mdr1a-deficient colonic epithelium using electron microscopy (EM). We hypothesise that loss of MDR1 results in intestinal mitochondrial dysfunction, a relevant process that drives the development of colitis in IBD.

Methods: We characterised mitochondrial function in mdr1a-deficiency mouse model and in shRNA-knockdown of MDR1 in T84 CECs. In vivo, we tested if induced gut mitochondrial dysfunction can potentiate colitis, by using direct colonic administration of rotenone and MitoQ\textsubscript{10} (mtROS inducer and inhibitor respectively) in mdr1a\textsuperscript{-/-}; and in acute + recovery DSS-colitis models. Furthermore, we generated a novel mouse model with intestinal-epithelial specific deletion (IEC-\Delta) of superoxide dismutase-2 (SOD2) gene responsible for mtROS detoxification to directly test the role of mitochondria. Finally, we analysed current GWA datasets (42,992 IBD/53,536 controls) to determine the clinical significance of mitochondrial homoestasis in IBD.

Results: Damaged mitochondria accumulate in mdr1a\textsuperscript{-/-} CECs vs. ileum/liver/lung; and vs. WT and il-10\textsuperscript{-/-} CECs. Mdr1a\textsuperscript{-/-} CECs have increased expression of p62, LC3 (general autophagy), PINK (specific mitophagy) and SOD2 protein expressions and impaired cellular energetics with reduced baseline respiration. Isolated Mdr1a\textsuperscript{-/-} mitochondria have lower threshold to induced damage and produced more mtROS, which are replicated in vitro in T84 shMDR1 CECs. In vivo, colonic rotenone accelerated spontaneous mdr1a\textsuperscript{-/-} colitis, increased the severity of acute DSS-colitis in mdr1a\textsuperscript{-/-} and in WT mice. Inhibition of mROS using MitoQ\textsubscript{10} attenuated the severity and promoted the recovery from DSS colitis. SOD2-IEC-\Delta mice displayed analogous dysmorphic mitochondria in CECs and are highly susceptible to DSS colitis. We showed that 29 (5.0\%) of 574 IBD susceptibility genes (p < 5 x 10\textsuperscript{-8}) have direct roles in mitochondria function (GO term:0005739). MDR1 and SOD2 genes showed associations with p = 3.19 x 10\textsuperscript{-3} and 3.04 x 10\textsuperscript{-3} respectively.

Conclusions: MDR1 has an important protective role for the mitochondria in the colon. Given that many IBD susceptibility genes are involved in the regulation of mitochondrial health, our findings suggest that mitochondrial toxin + genetic susceptibility interaction leading to mitochondrial dysfunction is a novel pathogenic mechanism that could offer many new therapeutic opportunities for IBD.

MtROS – mitochondrial reactive species, CECs – colonic epithelial cells, WT – wild-type
Validation of the CUCQ questionnaire with stoma extension in patients with acute ulcerative colitis in the CONSTRUCT trial

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

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

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

Discussion/Conclusion: The CUCQ is a useful tool for assessing quality of life in patients with acute severe colitis.
Comparative evaluation of the effect of combined therapy on morphological indicators in irritable bowel syndrome

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In order to adequately assess the effectiveness of the therapy prospectively analyzed results of treatment of 101 patients in patients with irritable bowel syndrome (IBS). Depending on the treatment, the patients were divided into 3 groups:

34 patients in Group 1, received probiotic chilak forte 40–60 drops 3 times a day, and rectal administration of ozonated mineral water in a volume of 200 ml/day on a daily basis; 34 patients in group 2 against the background of traditional therapy took chilak forte of 40–60 drops 3 times a day; 33 patients of the 3rd group on the background of traditional therapy was performed daily rectal ozonated mineral water in a volume of 200 ml/day.

After treatment, significant changes were observed morphological parameters. Normal secretory form of morphological changes in group 1 was detected in 17 (50%), in the 2nd – in 12 (35.3%), in the 3rd – group, 10 (30.3%) patients. I.e. the number of patients with normal secretory in group 1 increased by 29.4%, in the 2nd – 17.7%, in the third at 12.1%.

Patients with hyper secretory form of morphological changes of the colon in group 1 before treatment was 17 (50%), after treatment with the remaining 11 (32.4%) in group 2 – respectively, 16 (47.1%) and 13 (38.2%), 3rd – 16 (48.5%) and 13 (39.4%), i.e. respectively decreased by 17.6, 8.9% and 9.1%. Patients with hyposekretory form of morphological changes and improvements have taken place: so, the number of patients with hyposecretion in group 1 decreased to 6 (17.6%), in the 2nd – 9 (26.5%), 3rd – up to 10 (30.3%), i.e. respectively 11.8, 8.8 and 3%.

The same pattern was observed in the analysis of the results of the morphometric study of biopsy specimens colonies. The lumen of glands, regardless of morphological variant remained within the normal range.

After treatment the lumen of the glands in normal secretory form was 3.0 ± 0.1%, with hypersecretory – 3.1 ± 0.2%, with hyposecretory – 3.0 0.1%. The epithelium of the glands after treatment in the form normalsecretory average was 33.2 ± 0.3%, and in the form of hypersecretory increased to 51.5 ± 0.2%; when hyposecretory form, on the contrary, decreased to 21.8 ± 0.3%. The epithelium goblet cells in hypersecretory form does not differ from that in normalsecretory form, while the form of several hyposecretory much decreased.

The epithelium goblet cells at rates of secretory form was 17 ± 0.3%, with hypersecretory – 43.9 ± 0.4%, with hyposecretory – 5.7 0.6%. The stroma of the lamina propria at hyposecretory form thickened, while hypersecretory contrast, flat out. The stroma of the lamina propria at normosecretory was equal to 56.2 ± 0.5%, with hypersecretion – 46.1 2.2% at hyposecretion 72.7 ± 0.4% (Table 4.8). Lymphoid – plasmocytic infiltrate after treatment at normosekretsi was 4.2 ± 0.2%, with hypersecretion – 5.4 ± 0.2%, with hyposecretion – 2.3 ± 0.2%. Plasma cells normally is 4.4 ± 0.6%, with hypersecretion – 6.4 ± 0.8%, with hyposecretion – 0.5 0.6%.
The results of morphological studies suggest that the positive effect of the treatment was observed in almost all groups. Using of probiotics and ozone therapy normalization of morphological parameters were more pronounced. And although each of the components of the treatment positively affects all intestinal morphological picture indices, but acting in the complex, the probiotic and ozone have a more pronounced beneficial effect on the organism, that leads to better results.
Correlation analysis of urinary homocysteine level with prostacyclin E2 and leukotriene E4 in IBD

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Introduction: To investigate the changes of urinary homocysteine (Hcy), prostacyclin E2 (PGE2) and leukotriene E4 (LTE4) in patients with inflammatory bowel disease, and to explore the correlation between urinary Hcy and LTE4 and PGE2 levels in patients with IBD, respectively.

Methods: 33 cases of ulcerative colitis (UC) (8 cases of mild, 11 cases of moderate, 14 cases of severe), 66 cases of Crohn’s disease (CD) (36 cases of mild, 20 cases of moderate, 10 cases of severe). Urine Hcy, LTE4 and PGE2 levels in CD and UC were measured by ELISA.

Results: In CD patients, the levels of Hcy, LTE4 and PGE2 in the urine had no significant difference in disease activity (F = 1.916, p > 0.05). In UC patients, Hcy, LTE4 and PGE2 had no significant difference in disease activity (F = 0.917, p > 0.05). In patients with IBD, urine Hcy and LTE4 have a certain related-trend, but no significant difference (r = 0.113, p > 0.05); similarly, there was no significant difference between urinary Hcy and PGE2 (r = 0.103, p > 0.05). In CD patients, urine Hcy and LTE4 have a certain related-trend, but no significant difference (r = 0.065, p > 0.05); similarly, there was no significant difference between urinary Hcy and PGE2 (r = 0.146, p > 0.05). In patients with UC, urine Hcy and LTE4 have a certain related-trend, but no significant difference (r = 0.194, p > 0.05); similarly, there was no significant difference between urinary Hcy and PGE2 (r = 0.118, p > 0.05).

Discussion/Conclusion: In this study, the levels of Hcy, LTE4 and PGE2 in the urine can not reflect the severity of the disease in IBD, and there is no significant linear correlation between urinary Hcy, LTE4 and PGE2 in IBD, CD or UC.
Appendicitis and Crohn’s disease

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**Introduction**: Clinical and laboratory examination results of the two groups (Appendicitis and Crohn’s disease) were analyzed with to determine independent diagnostic predictive factors for CD initially misdiagnosed as appendicitis.

**Methods**: Retrospectively were analysed all patients with complication appendicitis (175 cases), operating in Department of Surgery in both University Hospitals between May 2010 and May 2017. If our doubts persist due to the atypical clinical course or inadequate response to the therapy performed, the early laparotomy should be considered for an ex-diagnosis. We illuminate some practical points in the preoperative evaluation of these patients and deal with the question of whether appendectomy should be performed in these patients (US, CT, endoscopy and laboratory results).

**Results**: Fifteen patients (between 17 and 68 years old) who underwent laparotomy for suspected acute appendicitis were found to have Crohn’s disease of the terminal ileum. Appendectomy was performed in all although in only five patients were the appendix grossly inflamed. Postoperative complications, either abscess or fistula, developed in four patients (33%). Careful investigation of the records revealed some preoperative diagnostic symptoms: recurrent abdominal pain and/or diarrhoea (79%), normal temperature (49%), and laboratory results compatible with a microcytic anaemia (33%) and hypoproteinemia (49%). As the differential diagnosis between Crohn’s disease and appendicitis is difficult and the surgical approach to the appendix in the presence of Crohn’s disease is controversial.

**Discussion/Conclusion**: The current definition of CD characterizes it as an idiopathic granulomatous inflammation of the intestine with a tendency to erosions, ulcers, abscesses and fistulas affecting the entire intestinal wall and the adjacent mesentery. His clinical manifestations are varied and their differentiation from other diseases is sometimes very difficult, even in patho-histological studies. CD should be considered in cases initially diagnosed as appendicitis with change of bowel emptying habit and stool consistency, medical history of chronic abdominal pain or diarrhoea, anaemia, and increased platelet count. If our doubts persist due to the atypical clinical course or inadequate response to the therapy performed, the early laparotomy should be considered for an ex-diagnosis.

We suggest that Crohn’s disease be included in the preoperative differential diagnosis and that extensive intraoperative examination of the gastrointestinal tract be made in any case of suspected appendicitis that has had a protracted preoperative course.
HDAC7 is an important regulator for CD8+ T cell memory formation

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Introduction: Posttranslational modifications play a major role in fine tuning and homeostasis of T cell dependent memory responses. Acetylation and deacetylation exerted by a multitude of histone acetyltransferases and histone deacetylases regulating cell function and differentiation via altering biochemical properties of many proteins.

Methods: To identify the role of histone deacetylase 7 (HDAC7) in T cells, we crossed HDAC7flox/flox CD4-Cre mice (HDAC7ko) lacking HDAC7 expression in CD4+ and CD8+ T cells.

Results: Despite no obvious changes in their microscopic phenotype under steady state conditions, an in depth characterization of the immune cell compartment by mass cytometry analysis, revealed a highly pre-activated central-memory like phenotype of the CD8+ T cells. Due to this memory like phenotype we hypothesized that HDAC7 might be a central regulator of CD8+ T cell dependent memory responses. Upon infection with lymphocytic choriomeningitis virus (LCMV) HDAC7ko mice showed only minor differences in the acute phase of the infection. However, 30 and 60 days p.i. HDAC7ko mice showed decreased amounts of CD8+KLRG1-CD127+ memory precursor effector cells. In addition the lineage defining transcription factor Eomesodermin is significantly downregulated in LCMV-specific CD8+ T cells lacking HDAC7 suggesting a defect in CD8+ T cell memory maintenance and transcriptional programming. To explore the impact of HDAC7 on memory recall responses HDAC7ko mice previously infected with LCMV Armstrong were rechallenged with LCMV Clone 13 60 days p.i. In contrast to the primary infection, LCMV-specific CD8+ T cells didn’t expand properly after reinfection. Investigating the regulatory role of HDAC7 for the described defects we analyzed the store-operated calcium entry (SOCE) which regulates intracellular Ca²⁺ concentrations because lymphocyte function strongly depends on calcium signaling. Analysis of SOCE of the CD8+ T cell compartment revealed a disturbed Ca²⁺ influx which might explain partially the observed phenotype.

Discussion/Conclusion: Taken together our data disclose HDAC7 as an important regulator for CD8+ T cell activation and memory formation.
Extraintestinal manifestation prevalence in patients with inflammatory bowel disease

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Introduction: The aim of our study was to evaluate the prevalence of extraintestinal manifestations in inflammatory bowel disease (IBD) patients as in Crohn’s disease (CD) group as ulcerative colitis (UC) also, treated with 5ASA, 5ASA + steroids and biological therapy. We have shown our 3 years observation results from our IBD patients’ database.

Methods: 94 patients were included in the study (64 female, 30 male, mean age 37.5; range 29–45 years). They were divided into two groups: IBD – UC patients (n = 70) and IBD – CD patients (n = 24). Total colonoscopy with intubation in terminal ileum was performed to all patients and diagnosis was confirmed morphologically. Any other chronic diagnosis was absent in all cases of patients.

Results:

<table>
<thead>
<tr>
<th>Extraintestinal manifestations</th>
<th>IBD (n = 94) = UC (n = 70) + CD (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aphthous stomatitis</td>
<td>11 (11.7%)</td>
</tr>
<tr>
<td>Pioderma gangrenoso</td>
<td>4 (4.3%)</td>
</tr>
<tr>
<td>Peripheral arthropathy</td>
<td>19 (20.2%)</td>
</tr>
<tr>
<td>Nephrolithiasis</td>
<td>15 (16%)</td>
</tr>
<tr>
<td>Episcleritis, uveitis, iritis</td>
<td>3 (3.2%)</td>
</tr>
<tr>
<td>Nodal erythema</td>
<td>15 (16%)</td>
</tr>
<tr>
<td>Primary sclerosing cholangitis</td>
<td>6 (6.4%)</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>4 (4.3%)</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>1 (1.1%)</td>
</tr>
</tbody>
</table>

It should consider that in 17 cases of IBD patients we have mentioned the overlap of various extraintestinal manifestations.

Discussion/Conclusion: According to our study – the peripheral arthropathy, nodal erythema and nephrolithiasis as extraintestinal manifestations occurred in a significantly higher proportion of inflammatory bowel disease patients. Multivariable analyzes revealed, that female sex and steroid usage were significantly associated with the presence of extraintestinal manifestations.
Comparison of depression level in patients group with inflammatory bowel disease and irritable bowel syndrome

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Introduction: All of the gut diseases have a great influence on human quality of life and emotional status. The aim of our study was to investigate the depression level in patients with inflammatory bowel disease (IBD), as in case of ulcerative colitis (UC) also in Crohn’s disease (CD) patients and compare their psychoemotional status with irritable bowel syndrome (IBS) patients’ condition.

Methods: 195 patients were included in the study (112 female, 83 male, mean age 37.5; range 29–45 years). There were divided into two groups. IBS (n = 101 – include type 1, 2 & 3) and IBD (n = 94 – include CD and UC cases) patients’ groups. IBS was diagnosed according to the Rome Criteria IV. Total colonoscopy was performed to all IBD patients with morphologically conformation of diagnosis. Psychoemotional status was estimated by hospital anxiety and depression scale (HADS). The any other chronic diagnosis was absent in all cases of patients.

Results: All patients from IBS group got HADS score 11 and above, which entirely estimated as a clinical expressed depression. IBD patients had HADS score from 0 to 10, which is corresponded to normal (11 cases) and depression (83 cases) subscale, exactly subclinical expressed depression. Average HADS score for IBS patients was 15.7 ± 0.35; which is significantly higher (p = 0.004) than average HADS score for IBD patients – 7.16 ± 0.28.

Discussion/Conclusion: According to study, in case of IBD patients there is no evidence of depression or there is its’ mild expression. But in cases of IBS patients we had a real picture of clinical expressed depression. So the patients with functional intestinal disorders (IBS) clearly need more psychological support, compare with the organic intestinal pathology (IBD) patients. We may consider in our country the creation of special support groups for such patients.
Laboratory predictors of ineffectiveness of conservative therapy of Crohn’s disease

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Crohn’s disease (CD) in the form of terminal ileitis occurs in approximately 1/3 of patients with CD and often complicated by stricture formation ileum. When identifying stricture after first course of conservative treatment as the first stage of treatment shows abnormal bowel resection rather than a second course of conservative therapy. The operation of choice is a division of ileecolic resection.

Objective: to identify predictors of the ineffectiveness of laboratory course conservative therapy glucocorticosteroids (GCS)/immunesuppressive (IS) and the risk of operative treatment of patients with CD in the form of the terminal ileitis.

Materials and methods. 40 patients of CD in the form of terminal ileitis with narrowing the lumen of terminal ileum without signs of intestinal obstruction was held a course of conservative treatment (application of GCS). Evaluate the effectiveness of therapy carried out through the 3, 6, 12 and 24 months. The effectiveness of the therapy was assessed on Crohn’s disease activity index (CDAI), endoscopic and/or CT-enterography, level CRP, fecal calprotectin (FCP). From 24 months 12 patients 12 patients had ileocecal resection. Thus patients were divided into two groups: 1st group patients without surgical treatment, 2nd group patients who had ileocecal resection. The first group of patients aged 19 to 58 years (Me-29) (n = 28). The 2nd group of patients aged 20 to 68 years (Me-36) (n = 12). The baseline level CRP in 1st group – 29.5 ± 3.2 mg/l, in 2nd – 27.75 ± 3.0 (p = 0.73), the level FCP in the 1st group – 1019.4 ± 97.2 mcg/g, in 2nd – 998.8 ± 127.3 mcg/g (p = 0.9).

Results. After 12 weeks from start of therapy among patients of 1st group the average level of CRP decreased to 4.7 ± 0.4 mg/l, in 2nd – 6.5 ± 0.8 mg/l (p = 0.03). Level of FCP in 1st group had dropped to 1019.4 ± 97.2 mcg/g, in 2nd – 998.8 ± 127.3 mcg/g (p = 0.9).
After 6 months in the 1st group the average level of CRP – 7.2 ± 1.1 mg/l, in 2nd – 10.0 ± 2.1 mg/l (p = 0.2). Level of FCP in 1st group 87.2 ± 13.7 mcg/g, in 2nd – 149.2 ± 24.9 mcg/g (p = 0.025).
After 12 months in the 1st group the average level of CRP amounted to 10.76 ± 2.1 mg/l, in 2nd – 19.2 ± 3.5 mg/l (p = 0.039). Level of FCP in 1st group 100.4 ± 13.7 mcg/g, in 2nd – 191.7 ± 24.9 mcg/g (p = 0.002).
After 24 months in the 1st group the average level of CRP amounted to 9.5 ± 1.9 mg/l, in 2nd – 17.8 ± 3.3 mg/l (p = 0.027). Level of FCP in 1st group 98.0 ± 12.1 mcg/g, in 2nd – 121.7 ± 14.2 mcg/g (p = 0.27).

Conclusion. Elevated levels of CRP and FCP treatment of patients in the form of terminal ileitis of CD may be a factor in the progression of the disease and an increased risk of surgical intervention.
Barriers to IBD treatment dependent on the age of patients

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Introduction: Inflammatory bowel diseases (IBD) are chronic inflammatory diseases that usually manifest themselves at a younger age. However, the age of the patients at the time of diagnosis varies; the incidence of the first detection of IBD shows a bimodal age distribution in the third and sixth decades of the patient’s life.

Methods: In the period 2002–2016, the 2nd Internal Clinic admitted 168 patients (with a mean age of 28.7 years) with recent incidence of IBD. The patients were divided into groups according to their age when IBD was diagnosed and we monitored different types of drug therapy (aminosalicylates, corticosteroids, immunosuppressives, and biologicals) and serious adverse effects of therapy in patients in the following age groups: 18–29 years (group A), 30–49 years (B), and older than 50 years (C). The data obtained were statistically analyzed using standard descriptive methods for continuous data.

Results: For the use of aminosalicylates (87.8%, 92.4%, and 91.1% respectively), and corticosteroids (69.2%, 70.1%, and 66.8% respectively), no statistically significant difference (p = 0.11 and p = 0.8, respectively) was found for the above age categories. On the other hand, a statistically significant difference (p < 0.001) was found between groups A and C (59.7% and 33.9%, respectively) in the use of immunosuppressive drugs and between groups A, B, and C (28.1%, 12.5%, and 6.9% respectively) in the use of biological therapy. The incidence of serious adverse effects of IBD treatment did not exceed 3% in any age group and the difference was statistically insignificant (p = 0.3 and p = 0.6, respectively).

Discussion/Conclusion: The treatment of IBD with drugs is relatively safe for all age groups; the incidence of adverse effects is below 3%. Immunosuppressives and biological therapy are used primarily in younger patients when the course of the disease is more severe, with frequent relapses.
Evaluation of vitamin D status in patients with inflammatory bowel disease – Preliminary results

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Introduction: Vitamin D (VD) has several important actions beyond bone health maintenance, including various effects on the immune system. Data suggests association between VD deficiency and the development of inflammatory bowel disease (IBD). The aim of this study was to evaluate the relationship between IBD and VD and between IBD severity and VD.

Methods: Study encompassed 33 patients: 23 with IBD (14 – Crohn’s disease [CD], 9 – ulcerative colitis [UC]: 10 males, aged 40.25 ± 1.41 years), and 10 patients with irritable bowel syndrome (IBS) without organic bowel disorders as control group. 25-hydroxyvitamin-D determination (25OHD, sum of 25OHD3 and 25OHD2) was performed by LC-MS/MS method. VD status was assessed as deficiency (VD < 25 nmol/l), severe insufficiency (25–50 nmol/l), mild insufficiency (50–80 nmol/l), sufficiency (> 80 nmol/l). Disease activity was assessed by Crohn’s Disease Activity Index (CDAI) and Mayo score for UC. IBD duration, activity and CRP were assessed with respect to VD status. Statistical analysis was performed via SPSSv.22.

Results: Total 25OHD for all IBD patients was 36.96 nmol/l (range 10.4–75.5 nmol/l); 7 patients (30.43%) had deficiency; 43.47% profound insufficiency; 26.08% mild insufficiency, and no one was in sufficiency status. Mean ± SD VD values for CD were 37.65 ± 17.74 nmol/l and for UC – 35.9 ± 17.54 nmol/l. Mean ± SD VD values for IBS (63.8 ± 30.3 nmol/l) were significantly higher than those for CD and UC, p < 0.05. We observed lower VD levels in IBD females than males (33.3 ± 17.04 vs. 41.7 ± 18.06, p > 0.05). VD levels were lower with increasing the disease activity (Mayo score), p < 0.01. CD patients had relative risk (RR) = 1.29 (95% CI: 0.54–3.101) for VD levels under 50 nmol/l. Patients after surgery had RR = 1.76 (95% CI: 0.255–12.217) for severe VD insufficiency and deficiency. There was negative correlation between CRP and VD (r = -0.422, p < 0.05). Mean disease duration was 6.9 years (range 1–26 years) with lowest VD at disease’s onset.

Discussion/Conclusion: IBD patients develop VD deficiency/insufficiency regardless disease activity or duration, so VD screening should be considered as a substantial part of IBD management.
Wegener’s granulomatosis mimicking inflammatory bowel disease

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Introduction: Granulomatosis with polyangiitis (GPA) formerly known as Wegener’s granulomatosis is a small to medium vessel vasculitis, which mainly affects the upper respiratory tract, lungs and kidneys. Most patients are positive for anti-neutrophil cytoplasmic antibodies (ANCA) with proteinase 3 (PR3) specificity. Gastrointestinal involvement and colitis is rare in GPA. We report two male adolescents with GPA first presenting with symptoms and signs of inflammatory bowel disease (IBD).

Results: The first patient, a 15-year-old boy presented with weight loss, bloody diarrhea, leg pain, fatigue and very raised markers for inflammation. Colonoscopy revealed severe pancolitis with multiple ulcers. He was positive for xANCA and anti-PR3 antibodies. Additional investigation uncovered renal and pulmonary involvement. Diagnosis of GPA was made and therapy with corticosteroids and cyclophosphamide was started. The boy is now in remission with maintenance therapy of methotrexate and prednisolone.

The second patient, a 17-year-old boy, was referred to our hospital with watery and bloody diarrhea, 30 to 40 times a day, and severe weight loss. Colonoscopy showed severe pancolitis with extensive involvement of the terminal ileum. The colitis proved to be refractory to prednisolone, methylprednisolone pulse therapy, azathioprine and infliximab. Further investigation showed nasal granulomatous inflammation, pulmonary (ground glass infiltrates) and renal involvement (immune-complex nephritis) and positivity for anti-PR3 antibodies. Cyclophosphamide therapy was started and all, especially gastrointestinal, symptoms improved continuously.

Discussion: GPA should be considered as differential diagnosis of IBD. In a previous study of a large cohort of children and adolescents with IBD we found a significant proportion positive for anti-PR3 antibodies. Future research is needed to reveal the pathogenic relationship of IBD and vasculitis. Since most treatment used for IBD is also effective for vasculitis GPA may be overlooked. GPA should be considered as a cause for colitis in unusual cases of IBD or when standard treatment fails.
Efficacy of anti-TNF-alpha in the treatment of fistulizing perianal Crohn’s disease

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Introduction: Perianal fistulas are a major problem of patients with Crohn’s disease (CD) and occur in about 35% of patients. The treatment of fistulizing perianal CD has evolved. Especially the use of anti-TNF-alpha has been proven as the most effective therapy of fistulizing CD. We aimed to evaluate efficacy of anti-TNF-alpha in the treatment of fistulizing perianal CD.

Methods: Retrospective study including patients with fistulizing perianal CD referred to our department between 2006 and 2016. Clinical and therapeutic data were recorded. The efficacy of both infliximab (IFX) and adalimumab (ADA) was evaluated.

Results: We enrolled 32 CD patients with perianal fistulas. Fourteen patients received anti-TNF: 8 men and 6 women with mean age of 43.2 ± 7.8 years [27–59]. Localization was ileocolic, colonic and ileal respectively in 43%, 36% and 14%. Perianal disease was the exclusive location of CD in one patient (7%). IFX was prescribed in first intention in all patients, associated to azathioprine. Closure of over 50% of fistulas was achieved by 71.4% patients after induction therapy with IFX. Long term remission evaluated after 52 weeks of treatment, was observed in 4 out of the 10 patients (40%). Switch to ADA was indicated in 1 patient because of allergic reaction to IFX and in 4 patients with failure to treatment with IFX. Two out of 5 patients (40%) reached complete cessation of fistula drainage.

Discussion/Conclusion: In our study, results of anti-TNF-alpha therapy for fistulizing perianal CD were similar to those reported in the literature.
The effect of GC-C signaling pathway on intestinal barrier and inflammation in ulcerative colitis

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Introduction: Ulcerative colitis (UC) belongs to a group of chronic idiopathic inflammatory disorders that primarily affects the colon and is a major type of inflammatory bowel disease (IBD). Guanylate cyclase-C (GC-C) is a transmembrane receptor that is expressed primarily on intestinal epithelial cells. The peptides guanylin (Gn) and uroguanylin (Ugn) are the endogenous ligands for GC-C. The binding of Gn/Ugn to GC-C results in the activation of GC-C signaling pathway by the increase of cGMP. This physiological activation of GC-C regulates intestinal fluid and electrolyte homeostasis.

Methods: We explored the role of GC-C signaling pathway in intestinal barrier and inflammation using the colonic mucosa of UC patients, the barrier model of Caco-2 monolayers, and the DSS-induced UC mice.

Results: We found that the expressions of GC-C, Gn and Ugn in colonic mucosa of UC patients were significantly decreased and this decrease was more significant with the increase of disease activity. IL-1β-treated cells transfected with Gn overexpression vector had significantly increased levels of cell viability, SOD activity, Gn, GC-C, cGMP, claudin-1 and ZO-1 as well as decreased levels of permeability, IL-8 and TNF-α. Conversely, GC-C-silencing cells had more significantly decreased levels of cell viability, SOD activity, claudin-1 and ZO-1 as well as increased levels of permeability, IL-8 and TNF-α induced by IL-1β. After injection with the lentiviral of Gn overexpression, the intestinal permeability and histologic score of UC mice were reduced. The expressions of GC-C, Gn, Ugn, cGMP, claudin-1 and ZO-1 were increased, and the levels of IL-8 and TNF-α were decreased in colon and serum.

Discussion/Conclusion: We revealed that the GC-C signaling pathway played a key role in the pathogenesis of UC. These observations suggest that the clinical therapeutic potential of GC-C agonists in UC and provide the important experimental basis of new treatment strategies for IBD.
Baicalin alleviates TNBS-induced colitis via inhibiting PI3K/AKT and NF-κB pathway activation

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Introduction: Inflammatory bowel diseases (IBDs) are chronic immunological disorders in intestinal tract characterized by persistent inflammation. Baicalin, isolated from the root of the Chinese herb, exhibits a wide range of pharmacological activities including immunomodulation and anti-inflammation. However, little is known about the therapeutic role of baicalin in IBD. The study was to ascertain whether or not baicalin could be a therapeutic flavonoid of IBD, furthermore, investigate the specific mechanisms underlying baicalin use.

Methods: In vivo, 2,4,6-trinitrobenzene sulfonic acid (TNBS) was used to induce the rat colitis model. Baicalin alone or with IGF-1 was administrated for 15 days, paralleled with the use of PI3K inhibitor LY294002. In vitro, HT-29 cells were stimulated with LPS and TNF-α to induce robust inflammation, then baicalin were used to evaluate the therapeutic effect, during the course, PI3K signaling pathway blockade or activation was operated by LY294002 or IGF-1.

Results: Our results showed that baicalin not only significantly alleviated TNBS-induced colitis by reducing the inflammation cytokines IL-6 and TNF-α release, attenuating apoptosis and injury of intestinal mucosa, but promoted the expression of tight-junction proteins Zo-1 and β-catenin to restore the injury of the intestine, moreover, we found the therapeutic role of baicalin were PI3K/AKT signaling pathway dependent.

Discussion/Conclusion: Our research reveals for the first time that the traditional Chinese herb constituent-baicalin acts as a therapeutic flavonoid in colitis and functions on the suppression of PI3K/AKT signaling pathway.
Long-term risk of infection in patients with Crohn’s disease on anti-TNF treatment: A prospective single center cohort study in China

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Introduction: Studies showed infections were the most concerned complications of anti-TNF treatment. Data from clinical practice in East Asia is limited. The aim of this study is to explore the long-term infection risk of infliximab (IFX) in treating patients with Crohn’s disease (CD) from an IBD center in China.

Methods: All patients with CD and on IFX (n = 70) were consecutively recruited from January 2008 to December 2015. Demographic and clinical characteristics, infectious events since IFX initiation were prospectively collected.

Results: During a median of 15 months (interquartile range [IQR] 10–23) on IFX, 15 (21.4%) cases had 17 infectious events, at a median time of 21 (IQR 4–46) weeks from IFX initiation. Infectious events included 8 viral infections, 6 bacterial infections, and 3 fungal infections, leading to IFX discontinuation in 6 (40%) cases. Compared with patients without infections (n = 55), patients with infectious events (n = 15) were more likely to be of Montreal B1 behavior, with concomitant systemic corticosteroids, more failure of steroids withdrawal and less mucosal healing (p < 0.05). By Cox regression, patients of B1 behavior had a higher risk of developing infections (HR = 4.897; 95% CI: 1.468–16.333; p = 0.010). Patients with successful corticosteroids withdrawal (HR = 0.275; 95% CI: 0.083–0.914; p = 0.035) and patients with mucosal healing (HR = 0.155; 95% CI: 0.049–0.492; p = 0.002) was associated with a lower risk of developing infections.

Discussion/Conclusion: Long-term IFX treatment in CD patients has a high occurrence rate of infections. Being not able to achieve mucosal healing and concomitant systemic corticosteroids treatment were independent risk factors of infectious events during IFX maintenance therapy.
Incidence of and risk factors for *Clostridium difficile* infection in patients with Crohn’s disease: A case-control study in a tertiary IBD center in China

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**Background:** A considerable number of studies conducted in western countries support a substantial increase in incidence of *Clostridium difficile* infection (CDI) in inflammatory bowel disease (IBD). However, there is little information on the incidence of CDI and risk factors in Chinese patients with IBD. The aim of this study was to investigate the incidence of and potential risk factors of CDI in Chinese patients with Crohn’s disease (CD).

**Methods:** We conducted a retrospective, case-control study within Peking Union Medical College Hospital from January 2010 to December 2015. CDI was diagnosed using enzyme immunoassay for detection of *Clostridium difficile* toxin A and toxin B (CDAB). Patients with CD and CDI were identified; controls were identified by matching age, gender, and the period of CDAB tests at 1:2 to 3 ratio. Demographic, clinical, and pharmacologic information for CDI cases and controls were collected.

**Results:** A total of 26 (6.1%) cases of CDI were identified among 429 patients with Crohn’s disease. Between 2010 and 2014, we could find an increasing trend of CDI cases in Crohn’s disease while a drop-down in year 2015 (Figure 1). A total of 69 controls (CD patients without CDI) were identified for comparison. On univariate analysis, CD patients with CDI had higher disease activity (measured by Harvey-Bradshaw index, median [IQR], 7 [6, 10] vs. 6 [3, 9], *p* = 0.013) than controls. Concurrent administration of steroids (53.8% vs. 31.9%, *p* = 0.049) was higher in CDI patients, while that of immunomodulators was lower (11.5% vs. 31.9%, *p* = 0.045) compared with controls. Patients with CDI had higher hospitalization rate (69.2% vs. 17.4%, *p* < 0.001) within 1 month and higher use of PPI within both 3 months (19.2% vs. 8.7%, *p* < 0.001) and 1 month (30.8% vs. 5.8%, *p* < 0.001) prior to CDI. BMI, disease duration from diagnosis, disease behaviors, concurrent biologics and 5-ASA treatments, previous bowel resection history, and antibiotics use within 3 months was not found different between CDI patients and controls. On Logistic regression, disease activity (OR = 1.286, 95% CI: 1.028, 1.610; *p* = 0.028) and hospitalization 1 month prior to CDI (OR = 5.751, 95% CI: 1.313, 25.196; *p* = 0.020) were found to be potential risk factors for CDI.

**Conclusion:** CDI is an emerging problem in patients with IBD in China. Although it is not news in western countries, but this should draw more attentions within Chinese IBD specialists. Patients with more active disease and recent hospitalization are at higher risk of *Clostridium difficile* infection in Crohn’s disease patients.
Figure 1: The incidence of *Clostridium difficile* infection in patients with Crhon’s disease changes over time from year 2010 to year 2015.
Surgery management of complex internal fistulas in Crohn’s disease

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Introduction: The transmural inflammation characteristic of Crohn’s disease predisposes patients to the formation of fistulas. Complex internal fistulas are internal fistulas joining a “diseased” organ to any intra-abdominal “victim” organ, with the exception of simply ileoileal fistulas.

Methods: A retrospective review of patients with Crohn’s disease undergoing surgery for complex internal fistulae between 2013 and 2017 was performed.

Results: 90 patients presenting with 120 complex internal fistulas were included. 79 (87.8%) patients were suspected with fistulas based on image, 11 (12.2%) patients were accidently founded during surgery. The types of fistulas were ileoileal with abscesses and inflammatory masses (51), ileocolonic (45), colocolonic (3), ileoduodenal (2), ileovesical (9), cologastric (4), ileoanastomotic (6). 9 patients received percutaneous drainage and 41 patients received enteral nutrition before surgery. Internal fistula with abscesses and inflammatory masses was the most common indication for surgery. 59 patients received laparoscopic surgery and 18 (30.5%) were converted. The duration of disease ≥ 36 months (OR = 3.7, p = 0.03) was the risk factor for conversion. Stoma was placed in 56 patients. 22 (24.4%) patients developed complications. The duration of disease ≥ 36 months (OR = 5.8, p = 0.01), laparotomy (OR = 3.3, p = 0.01) and previous intestinal surgery (OR = 2.6, p = 0.04) were the risk factors for complication.

Conclusion: ‘SNAP’, which represents sepsis control, nutritional support, definition of intestinal anatomy and surgical procedure is the useful management of complex internal fistulas. Preoperative optimization, evaluation and some surgical techniques can improve the outcome.
The frequencies of IgA- and IgG-coating fecal microbiota and clinical relevance to patients with IBD

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Introduction: Gut microbiota plays a crucial role in regulation of the intestinal homeostasis. The proportion of intestinal bacteria coated with IgA has been reported to be increased in patients with inflammatory bowel disease (IBD). The aim of this study was to determine the IgA- and IgG-coating bacteria in Chinese patients with IBD, and explore how the microbiota metabolite short chain fatty acid regulates intestinal IgA and IgG response.

Methods: Fecal samples were freshly collected from patients with active Crohn’s disease (CD, n = 63), active ulcerative colitis (UC, n = 55), CD patients at remission (n = 82), UC patients at remission (n = 6), and healthy donors (n = 26). The frequencies of IgA- and IgG-coating bacteria were analyzed in feces using flow cytometry. The levels of free IgA and IgG in feces were determined using ELISA.

Results: The frequencies of IgA- and IgG-coating fecal bacteria were found to be significantly increased in feces of patients with active IBD compared with those from IBD patients at remission and healthy controls. The numbers of IgA-coating bacteria were markedly increased in ileal Crohn’s disease (CD) patients compared with controls, and IgG-coating bacteria were significantly increased in colonic CD patients compared with controls. Compared with healthy controls, the frequencies of IgA-coating fecal bacteria were increased in CD patients without obstruction and penetration. Moreover, the numbers of IgG-coating fecal bacteria and IgA/IgG double-coating fecal bacteria were not dependently associated with C-reactive protein in CD patients (r = 0.2886, p = 0.0007; r = 0.2857, p = 0.0008). In ulcerative colitis (UC) patients, the numbers of IgA-coating bacteria were significantly increased in proctitis and left-sided colitis compared with controls. No clear association was found between the numbers of IgA- and IgG-coating fecal microbiota with disease activity index (CDAI, Mayo), age, gender of CD and UC patients. The levels of free IgA and IgG were also markedly increased in feces from active CD and UC patients as compared to healthy controls.

Discussion/Conclusion: Our data indicate that the frequencies of IgA- and IgG-coating of microbiota and the levels of free IgA and IgG in feces increase in patients with active IBD, and that the function and clinical relevance to the pathogenesis of IBD need to be further studied.
Reaction rates in patients transferred from biologic to bio-similar treatment for IBD

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Introduction: Biologic medication, (Infliximab) for patients with inflammatory bowel disease has been available in the UK since the late 1990’s. The cost implications for health authorities for patients receiving biologic treatment is high, however the enhanced quality of life for patients is described by many as priceless. In recent years, a cost effective alternative drug called a bio-similar has become available in the form of Inflectra. A bio-similar is drug designed to have active properties similar to one that has previously been licensed. The clinical data shows that the effects of the bio-similar family of medication should be on par with that of the biologic group – however do patients react to the bio-similar medication when changing from a biologic to bio-similar.

Methods: A retrospective review was carried out of all IBD biologic patients within the Royal Gwent Hospital who were transferred to bio-similar. The patients were looked after in the gastroenterology day-case unit by the same infusion nurse who had administered the biologic therapy. Medication was administered and patients were monitored in accordance with local polices for biologic and now bio-similar administration. In total 70 patients were transferred from biologic to bio-similar.

Results: During the retrospective review of the above patient group it was found that of the 70 patients, 22% of patients (n = 15) suffered a reaction. Most were minor with patients suffering hives, a mild wheeze or a feeling of being unwell, whilst the patient’s observations remained stable. 6% of the 70 (n = 4), had more severe reactions such as respiratory distress, widespread wheeze and tachycardia. In all cases symptoms resolved with stopping the infusion and administration of Hydrocortisone and Chlorphenamine. Of the 70, 12% (n = 8) had the bio-similar discontinued. Of the 70 patients transferred to bio-similar therapy, only 3% (n = 2) had experienced reactions to biologic previously.

Discussion/Conclusion: It is unclear as to why these patients reacted to the bio-similar. It could be suggested that the revisiting of symptoms of reaction prior to administration of the bio-similar produced a subconscious response. This could be linked to those who showed some anxiety towards the change in medication. One could suggest that further investigation into the responses noted would be appropriate.
Olive leaf extract exhibits immunomodulatory activity in human ex-vivo organ culture

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Introduction: Extracts from olive (Olea europea) leaves have been widely used as traditional remedies in Mediterranean countries. In fact, and based on their antioxidant properties, they have reported to exert beneficial effects in inflammatory conditions in humans, and this could be the case of inflammatory bowel disease. The aim of the study was to evaluate the immunomodulatory properties of an olive leaf extract in colonic biopsy specimens obtained from Crohn’s disease (CD) patients.

Methods: Surgical specimens were taken from patients with colonic CD undergoing surgery for a chronic active disease, who were poorly responsive to medical treatment, or from patients with ileal CD undergoing surgery due to stricturing. Samples were placed on iron grids with the mucosal face upward in the central well of an organ culture dish and incubated at 37°C in the presence or absence of olive leaf extract (0.1–100 μg/ml) and/or LPS (100 ng/ml). After 24 h, mucosal samples were homogenized and total RNA was extracted. In parallel, culture supernatants were collected and assessed for production of cytokines TNF-α, IL-1β, IL-6 and IL-8 by ELISA. In addition, in vitro immunomodulatory properties of the extract were determined when incubated (0.1–100 μg/ml) with intestinal epithelial cells (Caco-2 and CMT-93) and macrophages (RAW264), two cell types involved in the intestinal immune response.

Results: The olive leaf extract significantly reduced the expression of IL-1β, IL-6 and IL-8 in colonic explants from CD patients when stimulated with LPS. Similarly, the production of these cytokines was significantly reduced by the extract. However, no clear dose-effect relationship could be established, probably due to the complex composition of the extract. In addition, the extract inhibited LPS-induced nitrite production in RAW cells and reduced IL-1β-induced IL8 production in Caco-2 cells and LPS-induced IL-6 release in CMT-93 cells.

Discussion/Conclusion: The intestinal antiinflammatory effect of the olive leaf extract could be associated with a down-regulation of the altered immune response that characterizes the intestinal condition in inflammatory bowel disease, showing a direct effect on immune cells, as demonstrated in the ex-vivo and in vitro studies.
Histologic grading of disease activity in pediatric ulcerative colitis – Preliminary study

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Introduction: Inflammatory bowel disease (IBD, including ulcerative colitis (UC), Crohn’s disease and IBD unclassified (IBDU), are chronic immunologically mediated lifelong conditions that often begin in childhood. The main pathological feature of IBD is transmural infiltration of polymorphonuclear neutrophils and mononuclear cells. The major objective of the study was to determine of degree of inflammation in each biopsy specimens obtained from 38 UC pediatric patients underwent surveillance colonoscopy (in total 183 examinations), using the histologic activity index (HAI), according to Gupta RB et al (2007).

Methods: The degree of inflammation at each biopsied segment of colon was scored as follows: 0, inactive/absence; 1, mild (neutrophil infiltration of \( \leq 50\% \) of sampled crypts or cross sections; no ulcers or erosions); 2, moderate (neutrophil infiltration of \( \geq 50\% \) of sampled crypts or cross sections; no ulcers or erosions); 3, severe (erosion or ulceration, irrespective of other features). Histopathological assessment of colonoscopic specimens was performed in the Department of Medical Pathomorphology, Medical University of Bialystok.

Results: On the basis of the conducted assessment of the AIH, it was observed that in 183 surveillance examinations, most exhibited mildly active colitis, the second most exhibited was inactive colitis with no cryptitis or crypt abscesses, followed by moderately active colitis with cryptitis involving \( \geq 50\% \) of crypts, with the least exhibited severity active colitis with ulceration.

Discussion/Conclusion: The currently used relatively simple histologic activity index i.e. histologic scoring system to determine the severity of inflammation in biopsy colonoscopic specimens has allowed for a better understanding of the dynamics of CU in pediatric patients. The obtained results may also constitute interesting comparative material for similar findings.
Fecal microbial dysbiosis in Chinese patients with inflammatory bowel disease

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Introduction: Microbial dysbiosis in the gut has been suggested to play an important role in the pathogenesis of inflammatory bowel disease (IBD). Although the microbial community is gaining increasing attention for its influence on IBD, there is a lack of data on global alteration of microbiota in Chinese patients. In this study, we aimed to analyze the fecal microbiota in Chinese IBD patients.

Methods: Fecal samples from 15 patients with Crohn’s disease (CD) and 14 patients with ulcerative colitis (UC) were subjected to 16S rDNA sequencing. The V4 hyper-variable regions of 16S rDNA were sequenced by the Illumina MiSeq2500 platform. Quality control and operational taxonomic units were calculated with QIIME software.

Results: The community abundances and microbial structure of fecal microbiota were significantly decreased in IBD. At phylum level, analysis of the microbial compositions revealed that the abundance of Proteobacteria was significantly higher in IBD than in controls. At genus level, the abundances of 8 genera in CD and 23 genera in UC, particular the Escherichia genus, were significantly different as compared to controls. The abundance of Bacteroidetes was markedly decreased in active CD compared with inactive CD. However, Proteobacteria was only nominally increased in active CD relative to inactive CD. Furthermore, the relative abundance of Bacteroidetes, especially Bacteroides, was negatively correlated with the calculated Crohn’s disease activity index (CDAI) scores of patients.

Discussion/Conclusion: Our findings showed the specific characteristics and dysbiosis of fecal microbiota in Chinese patients with IBD, which were different from that of the normal controls. Alterations in the abundance of Bacteroidetes might be associated with the disease activity of CD.
**Duodenum bulb involvement of Crohn’s disease**

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**Introduction**: The duodenum bulb involvement of Crohn’s disease (CD) has not been established. The aim of the present study was to evaluate the prevalence of duodenum bulb involvement in CD patients, and to compare the differences between CD patients with duodenum bulb involvement and without upper gastrointestinal (UGI) involvement (non-L4), and the differences between endoscopic findings.

**Methods**: This was a retrospective study that finally included 104 CD patients between January 2015 and December 2016 at the first affiliated hospital of Nanjing medical university. Demographic data, clinical characteristics and endoscopic findings were compared between duodenum bulb involvement group (L4-duo bulb) and non-L4 group. Characteristics of three types of macroscopic findings were also evaluated. Independent samples t test, Kruskal Wallis ANOVA single factor analysis and chi square test were performed.

**Results**: Of 104 CD patients, 56 (53.8%) had non-L4 disease, while 48 (46.2%) had L4 disease. The detection of Crohn’s specific lesions in the esophagus, stomach, duodenal bulb, and 2nd portion of the duodenum to jejunum were 2 (4.2%), 4 (8.3%), 38 (79.2%), and 12 (25.0%), respectively. Patients with L4-duo bulb disease were more likely to have UGI symptoms (28.9% vs. 1.8%, $p = 0.000$) and extraintestinal manifestations (13.2% vs. 0, $p = 0.020$). Nodular lesions induced stricture (6, 15.8%), notched signs and BJA (8, 21.1%) and longitudinal arranged erosions and ulcers (24.63.1%) were observed as representative endoscopic findings in duodenum bulb in CD patients. UGI symptoms were more common, while BMI and CRP levels decreased significantly in L4-duo bulb stenosis group compared with L4-BJA and L4-erosive and ulcer groups.

**Discussion/Conclusion**: The proportion of duodenum bulb involvement in CD patients is high. Nodular lesions induced stenosis, BJA and notched signs and longitudinal arranged erosions and ulcers are considered as the representative findings under EGD, which are beneficial for the diagnosis of CD. Patients with duodenum bulb stenosis have more UGI symptoms and lower BMI and CRP levels which indicates poorer effect of medicine therapy.
The impact of innate immunity factors on developing kidney disease in patients with Crohn’s disease

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Introduction: The prevalence of renal pathology in patients with inflammatory bowel diseases (IBD) is 4–23%, while the mechanisms of its development not clear. Kidney damage in IBD can be a manifestation of systemic inflammation, autoimmune susceptibility, metabolic and nutritional disorders, or result from toxic effects of drugs.

Methods: We analyzed 55 patients with CD. Among these patients, 9 (15%) had kidney disease. In six cases (11%) nephrobiopsy was performed to clarify the diagnosis.

Results: The examined patients had the following renal pathology: drug-induced tubulointerstitial nephritis was verified in 4 cases (7.3%), IgA-nephropathy – in 2 cases (3.6%), nephrolithiasis – in 3 cases (5.5%). In patients with IgA-nephropathy, a higher level of expression of TLR-2 (84.2 ± 1.3) and TLR-4 (11.9 ± 0.4) on the surface of monocytes (%) was noted (p < 0.05). In 4 out of 15 patients (26.7%) who received long-term 5-ASA drugs, drug-induced tubulointerstitial nephritis was identified.

Discussion/Conclusion: The prevalence of chronic kidney disease (CKD) in patients with CD was 15%. The relationship between CD and IgA-nephropathy may indicate a general mechanism of development with the involvement of innate immunity factors in the pathological process. Long-term therapy with 5-ASA drugs is a known risk factor for the development of tubulointerstitial nephritis. Identification of additional risk factors and methods of prevention, as well as further study of the general mechanisms of the pathogenesis of CKD in patients with CD require further study.
**Helicobacter pylori** prevalence and risk factors among children with celiac disease

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**Introduction**: The relationship between *Helicobacter pylori* (Hp) and celiac disease (CD) remains controversial. Whether Hp triggers CD or protects against CD is currently the subject of research. We aimed to determine the prevalence of Hp and risk factors among Romanian children with CD.

**Methods**: We have performed a prospective observational study that included 70 consecutive patients diagnosed with CD hospitalized at "St. Maria" Children's Hospital in Iasi, Romania between January 2014 and December 2016. Multivariable logistic regression was used to identify independent predictors of Hp. A weighted risk score system was then generated for the independent predictors, and a risk score was calculated for each individual.

**Results**: Seventy children with CD were enrolled in this study; 37 (52.9%) were female and 33 (47.1%) were male, mean age was 4.04 ± 3.26 years. Hp infection prevalence was 21.7%. Statistical analysis of patient characteristics found Hp to be more common in patients older than 5 years (p = 0.010) and from single parent families (p < 0.0001). Using logistic regression analyses, the development of Hp infection was noted to be independently related to single parent family (OR = 9.04, 95% CI: 1.29–62.898, p = 0.006), houses without toilets or sanitary (OR = 3.88, 95% CI: 1.274–14.227, p = 0.016), low family income (OR = 8.52, 95% CI: 2.526–71.395, p = 0.002), and parent’s prior history of gastritis or ulcers (OR = 2.68, 95% CI: 1.495–14.509, p = 0.042) and were identified as independent predictors associated with HP infection. This risk score showed good prediction, with a c-statistic of 0.794 (95% CI: 0.612–0.976), p = 0.008.

**Discussion/Conclusion**: Overall, the prevalence of Hp among pediatric patients was similar to other studies. We developed a risk score that was able to significantly stratify individuals into low, moderate and high risk. The scoring system serves as a pragmatic and easy to use tool in clinical practice.
Expression of potassium channel and NLRP3 in platelets of ulcerative colitis

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Introduction: Platelets are important inflammatory cells, involved in inflammation and immune pathophysiology, while Kv1.3 channels are the main voltage gated potassium channels that affect platelet activation. In addition, platelets also have Kca3.1. Simultaneously, in the inflammatory response, there are increased platelet reactivity and abnormal expression of Nod-like receptor family, pyrin domain containing 3 (NLRP3). NLRP3 inflammasome is an important part of inflammatory corpuscles, and its genes are associated with susceptibility to ulcerative colitis (UC). These two potassium channels can regulate the concentration of intracellular potassium and calcium. Potassium and calcium are the key mediators of different agonists that activate NLRP3 inflammatory bodies.

Methods: 11 healthy volunteers (control group) and 17 UC patients (3 cases of mild, 9 cases of moderate, 5 cases of severe) participated in the trial. The platelets in the whole blood of the subjects were extracted, and the levels of KV1.3, Kca3.1 and NLRP3 were detected by RT-PCR and Western-blot.

Results: Compared with control group, the expression of KV1.3, Kca3.1 and NLRP3 in platelets from the UC patients were increased significantly at the mRNA levels (p < 0.05), which were not related to the severity of the disease (p > 0.05). The expression of Kca3.1, Kv1.3 and NLRP3 protein in platelets of UC patients was significantly higher than that of the control group (p < 0.05). And there was no significant correlation between their expression and the severity of the disease (light, medium and heavy (p > 0.05). Correlation analysis showed that the expression of Kca3.1 and NLRP3 protein in platelets of UC was significantly correlated (r = 0.877, p < 0.05). There was a general correlation between Kv3.1 and NLRP3 expression at protein level (r = 0.478), but there was no significant difference (p > 0.05).

Discussion/Conclusion: The expression of NLRP3 in platelets of UC was associated with potassium channel. And they were highly expressed in platelets of UC patients, disturbing normal physiological function of platelets and aggravating the inflammatory response, which may be related to the occurrence and development of the disease, and could be another breakthrough point in the diagnosis and treatment of inflammatory bowel disease.
Changes of mitochondrial membrane potential and reactive oxygen species in platelets of ulcerative colitis

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Introduction: Platelets are seedless and readily available, and in recent years have become a biological marker that is widely used in mitochondrial mechanisms and inflammatory related diseases. We aim to understand the changes of platelet mitochondrial membrane potential (MMP) and mitochondrial reactive oxygen species (ROS) in ulcerative colitis, and to explore its relationship with the severity of UC.

Methods: Subjects were collected for anticoagulation of whole blood, which were isolated and purified to obtain platelets. The platelets were labeled with fluorescent probes JC-1 and MitoSOX™. Finally, flow cytometry was used to detect the changes of these two fluorescence intensities.

Results: In the normal control group, the MMP of platelet was higher, JC-1 formed the polymer and emit red fluorescence, and the ROS in the platelet was lower, and MitoSOX™ into the platelet mitochondria can not be mostly oxidized to the state without fluorescence. UC platelet MMP decreased, JC-1 decomposition into monomer and produce green fluorescence; the same time, platelet mitochondria ROS is higher, MitoSOX™ is oxidized to produce red fluorescence. The changes in the fluorescence intensity of the two fluorophores are related to the severity of the disease.

Discussion/Conclusion: The decrease of MMP and the increase of ROS in UC platelets have disturbed the normal physiological function of platelets, exacerbated the inflammatory response of UC and provided new clues for the further diagnosis and treatment of UC.
Platelet indices in the course of infliximab induction regimen in ulcerative colitis patients

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Introduction: Biological treatment (BT) became one of the most common pharmacological strategies in inflammatory bowel diseases (IBD). The aim of the study was to assess the correlation between platelet (PLT) indices: MPV (mean platelet volume), PCT (plateletcrit), PDW (platelet distribution width), C-reactive protein (CRP) and endoscopic picture in the course of infliximab induction regimen in ulcerative colitis (UC) patients.

Methods: 46 patients with UC, 32 men and 16 women, were enrolled to the study. They were administered infliximab (standard induction therapy). Laboratory tests (CRP and PLT indices) and colonoscopy were performed in all patients during induction regimen – at 0, 2, and 6 weeks and in follow-up six weeks after finished induction therapy.

Results: The study revealed statistically significant (p < 0.05) decrease in CRP and PLT together with improvement of endoscopic picture (MAYO score) in all patients. Mean MAYO score prior to BT and after finished induction therapy were 9.84 and 2.8, respectively. PCT values were higher prior to BT and normalized after induction therapy (p < 0.05). On the other hand, MPV measurements were under normal range during qualification to BT and obtained adequate values after BT (p < 0.05). Subsequently, CRP and PCT significantly correlated with each other before the introduction of BT. The correlations between PDW and PLT and PCT and PLT were noticed before infliximab induction regimen and in follow-up after finished therapy, too.

Discussion/Conclusion: Chronic inflammatory process in patients with IBD is connected with elevated platelet count and changes in PLT activation and morphological parameters. Our data suggest that PLT indices might be useful biomarkers for determining active UC and for assessing the efficacy of BT. However, further studies are required to establish a correlation between platelet functions and BT in IBD patients.
The efficacy of biological treatment in the course of inflammatory bowel disease – The analysis of Polish patients’ group

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Introduction: Biological treatment (BT) became one of the most common pharmacological strategies in inflammatory bowel disease (IBD). The aim of the study was to assess the efficacy of BT in patients with Crohn’s disease (CD) and ulcerative colitis (UC) and to find out if there is any correlation between selected inflammatory markers and endoscopic picture in the course of BT.

Methods: 74 patients were enrolled to the study, 25 with CD and 49 with UC. 15 patients with CD were treated with infliximab and 10 patients with adalimumab (standard treatment regimen; one year of therapy). Patients with UC were administered infliximab (standard induction therapy). Laboratory tests (CRP and PLT) and colonoscopy were performed in all patients during BT.

Results: The study revealed statistically significant (p < 0.05) decrease in CRP and PLT together with improvement of endoscopic picture (SES-CD, MAYO) in all patients. Regardless of used TNF inhibitor, there were no statistically significant differences in results of CD group. A correlation between CRP and PLT in CD patients during both qualification and follow-up after finished BT was observed. A correlation between PLT and SES-CD score prior to the first dose was noticed too. Mean final SES-CD score after finished annual therapy was 5.48. CRP and MAYO score correlated with each other in UC group before the first dose of BT and in follow-up after finished induction therapy. There also was a correlation between MAYO score and MAYO endoscopic subscore during both qualification and follow-up. Mean final MAYO and MAYO endoscopic subscores after finished induction regimen were 2.76 and 1.84, respectively.

Discussion/Conclusion: According to the results of the presented study, a clinical and endoscopic remission of IBD was not achieved, although BT lowered levels of CRP and PLT and improved endoscopic picture in observed IBD patients.
Abdominal pain an important symptom in IBD or IBS

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Inflammatory bowel disease (IBD) and irritable bowell syndrome (IBS) seem to share similar symptoms, but these are two conditions with very different treatment requirements. Abdominal pain is a common symptom related to IBD and IBS. Aim of our study was to evaluate the impact of abdominal pain on general quality of life in patients with IBD or IBS.

Methods: We included 36 patients with IBS (26 females) and 34 patients with IBD (19 females). Mean age in IBS group was 42.3 years and in IBD group was 39.8 years. 14 patients from IBD group had UC and 20 with Crohn’s disease. All patients from IBD group had mild activity disease (CDAI 150–219 and UCDAI 3–8) and any patient was not in remission period. All patients received a questionnaire regarding abdominal pain intensity, character, period, localization and impact of pain on daily life and social activities.

Results: 28 patients from IBS group (20 females) and 22 patients from IBD group (17 females) considered that abdominal pain is a daily problem. From IBS group 21 patients had constant pain with slight fluctuation daily, with no/ little improvement to treatment, 3 patients accused constant pain with strong fluctuation and 4 patients declared pain attacks with free intervals. The impact on daily life is different so the patients with pain attacks and free intervals considered that their life isn’t influence very much. On the other side all females with constant pain considered that the symptom have a major impact on their life. From IBD group 16 patients had pain attacks with free intervals, 4 patients declared constant pain with slight fluctuation and 2 patients had constant pain with strong fluctuation. The negative impact on daily life was greater in patients with constant pain +/- slight or strong fluctuation than in patients with pain attacks.

Conclusion: Abdominal pain is a major problem in both diseases, especially in females. Constant pain is more difficult tolerate than pain attacks and have an worse impact on daily life. In our study quality of life was more affected in IBS group than in IBD group because most of the patients had constant abdominal pain.
The involvement of leptin and hs-CRP in osteoporosis in females with IBD

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IBD are associated with increased bone resorption inducing low bone density and increased fracture risk especially in Crohn’s disease (CD), but also in ulcerative colitis (UC). Leptin is a peptide hormone, mainly secreted by white adipose tissue and its effects on bone metabolism or intestinal inflammation are partly contradictory. High-sensitivity C-reactive protein (hs-CRP) is also, a marker of inflammation. Aim of our study was to correlate leptin and hs-CRP level with BMD in females with or without IBD.

Methods: We studied 2 groups of females, age and weight matched; first group included 23 females with UC and CD, mean age 48.3 ± 1.6 years and BMI 24.6 ± 1.3 and control group included 25 females with osteopenia or osteoporosis in postmenopausal period for at least 1 year, mean age 50.1 ± 2 years and BMI 25.4 ± 1.2. We excluded the patients with obesity, diabetes mellitus, cardiovascular disease, thyroid dysfunction. In all patients we measured bone mineral density (BMD) by DEXA (Dual energy X-ray absorptiometry) at femoral neck. T-score > -1.0 was considered as normal, between -1.0 and -2.5 indicated osteopenia and < -2.5 suggested osteoporosis. Serum samples were collected at baseline for both groups. A p value of less than 0.05 was accepted as significant.

Results: In group with IBD we had 9 females active and 14 females in postmenopausal period. Mean value of leptin for active subgroup was 13.1 ng/ml and for postmenopausal subgroup was 7.5 ± 2.8 ng/ml, p value between these subgroups was significant statistical (p < 0.05). Mean value of leptin level for control group was 5.5 ± 3.3 ng/ml, p value between postmenopausal subgroup and control group was > 0.05, without statistic significance. In IBD group we found 4 patients with normal value of T score, 10 with osteopenia and 9 with osteoporosis. In the other group we found 13 patients with osteopenia and 11 with osteoporosis. Hs-CRP had high level in IBD group and we found a significant independent association of hs-CRP with BMD scores in this group and no relationship in the other group, supporting the role of an inflammatory state which may accelerate loss of bone mass in patients with IBD.

Conclusion: Leptin level was significantly lower in patients with osteopenia or osteoporosis in postmenopausal period even the patients belonged to IBD group or control group, probably because estrogen may have an effect on leptin secretion. Leptin was normal in IBD group in active females. High hs-CRP level was an independent significant factor for osteopenia/osteoporosis in IBD group.
Characteristics and outcomes of acute colitis presenting via the Emergency Department in an Irish Academic Medical Centre

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Introduction: A significant proportion of Emergency Department presentations with gastrointestinal symptoms, resulting in the performance of cross-sectional imaging, receive a radiological diagnosis of colitis. Data are few on the demographics and natural history of this patient cohort. We aimed to review the characteristics, outcomes and final diagnoses of new emergency department presentations with colitis diagnosed on cross-sectional imaging.

Methods: An institutional radiology database was interrogated to identify cross-sectional imaging, which demonstrated a colitis, performed on patients admitted in 2015 via the Emergency Department of St. James’s Hospital. Radiology reports were reviewed to confirm the presence of colitis and exclude patients with known diagnoses of gastrointestinal disease. Baseline demographic data, information on inpatient investigations, final diagnoses and outcomes were recorded.

Results: N = 118 subjects were deemed eligible for inclusion: Age [median, range] 64 years [16.9–101.2]; 67% female. Proportions admitted under medical, surgical, gastroenterology and other services were 33%, 34%, 9% and 25% respectively. Median [range] admission duration was 10 days [1–241]. Laboratory parameters (median [range]) at admission were WCC 9.7 x 10^-9/l [0.1–55], haemoglobin 11.8 g/dl [5.8–17.7], platelets 261 x 10^9/l [10–757], albumin 34 g/l [14–71], CRP 54 mg/l [1–307] and lactate 1.8 mmol/l [0.7–15]. Final colitis diagnoses were: undefined (35%), infectious (25%), reactive to other intra-abdominal pathology (13%), new IBD diagnosis (11%), ischaemic (9%), chemotherapy-associated (3%), diverticular (3%) and medication associated (1%). Colonic perforation, colectomy and mortality occurred in 1%, 5% and 13% of the cohort respectively. No clinical or laboratory variable associated significantly with mortality.

Discussion: There is a broad differential for patients presenting with an acute colitis via the Emergency Department with a significant proportion having no clearly defined aetiology following hospital admission. Considerable morbidity and mortality is observed in this patient cohort.
Factors affecting postoperative recurrence after ileocecal resection in Crohn’s disease

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Introduction: In spite of the important role of conservative treatment, up to 90% of all patients with Crohn’s disease require surgery during their lifetime. However, the factors that predict postoperative recurrence remain controversial.

Aim: This study was designed to identify the risk factors for postoperative recurrence after ileocecal resection in patients with Crohn’s disease and the influence of the primary operation.

Methods: During the study period, 33 patients affected by Crohn’s disease required ileocecal resection. All these patients underwent a primary procedure. There were 20 men and 13 women with a mean age of 33 years (extremes: 18–60). Recurrence was defined by the presence of clinical symptoms. Univariate and multivariate analysis were performed to find the predictors of recurrence.

Results: The disease’s localization was ileal in 60.6% and ileocolic in 39.4%. The most common indication for the surgical treatment was stenosis (45%). Active smoking was noted in 30% of the cases.

The mean length of the follow-up was 48 months. The overall recurrence rate was 57.5% after a mean period of 25 months.

Logistic regression analysis revealed that age at onset of disease (p = 0.01), age at surgery (p = 0.02), duration of Crohn’s disease before surgery > 10 years (p = 0.03), male gender (p = 0.04), smoking (p = 0.005), BMI < 20 kg/m² (p = 0.04), preoperative treatment (p = 0.04), urgent surgery (p = 0.03) and absence of prophylactic medical treatment (p = 0.00) were associated with the risk of recurrence.

Neither anatomical site of involvement, form of aggressiveness of the disease, type of anastomosis, nor microscopically affected resection margins and typical granulomas were found to predict the recurrence of the disease.

Discussion/Conclusion: In this study, the incidence of postoperative recurrence was high stressing the importance of identifying patients with high risk of recurrence in order to undertake the appropriate medical prophylaxis.
Cell therapy for perianal Crohn’s disease

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Perianal fistulas are the most widespread and 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 bowel resection. Despite the significant effect of anti-cytokine therapy fistulous forms of CD, treatment of these patients remains a difficult task with high risk of relapse of CD. Mesenchymal stromal cells have immunomodulatory properties and a large regenerative potential, at present also used for treatment of fistulous CD and perianal fistulas of different etiologies.

Objective: To compare the efficacy of combined therapy (local and systemic) mesenchymal stromal cells (MSCs) of bone marrow, infliximab (IFX) and antibiotics/immunosupression (IS) on the rate of healing of simple perianal fistulas in Crohn’s disease.

Materials and methods: 36 patients with Crohn’s disease with perianal lesions were divided into three groups depending on the method of therapy. The first group of patients aged from 19 to 58 years (Me-29) (n = 12) received culture of MSCS systemically via the scheme and locally: on the perimeter of the fistulous introduced 40 million MSCs – 4 point of inject and 1 ml of saline containing 10 million MSCs. Then after 4 and 8 weeks re-injected 40 million MSCs in the area of the fistula. The second group of patients with CD (n = 10) aged 20 to 68 years (Me-36) were receiving anti-cytokine therapy of IFX. The 3rd group of patients with CD (n = 14) aged 20 to 62 years (Me-28) received antibiotics and IS. In the dynamics evaluated the closure of the external opening of the fistula. Ano- and rectosigmoscopy carried out after 3, 6, 12 and 36 months from start of therapy.

Results: After 12 weeks among patients of the 1st group simple healing of fistulas was observed in 10/12 patients (83.3%), in the 2nd group healing simple fistulas have a 8/10 (80.0%) (OR = 0.83; 95% CI: 0.14–4.9; p = 0.72). In the 3rd group – in 5/14 patients (35.7%) (OR = 0.26; 95% CI: 0.07–0.97; p = 0.04 in comparison with the 1st group). After 6 months in the 1st group of patients receiving MSCs, healing of simple fistulas persisted in 8/12 (66.6%) with the 2nd group – 7/10 (70.0%) (OR = 1.11; 95% CI: 0.32–3.84; p = 0.76). In the 3rd group – patients 4/14 (28.6%) (OR = 0.47; 95% CI: 0.2–1.11; p = 0.12 in comparison with the 1st group). After 12 months in the 1st group receiving MSCs, healing of simple fistulas persisted in 7/12 (58.3%), in the 2nd group – in 6/10 (60.0%) (OR = 1.25, 95% CI: 0.48–3.22; p = 0.69). In the 3rd group – in 2/14 patients (14.3%) (OR = 0.49; 95% CI: 0.24 to about 0.98; p = 0.03 in comparison with the 1st group). After 36 months among the patients of the 1st group, the closure of the fistula was preserved in 5/12 patients (41.6%), in the 2nd group – 5/10 (50.0%) (OR = 1.17; 95% CI: 0.53–2.55; p = 0.96). In the 3rd group – in 0/14 patients (0.0%) of (OR = 0.58; 95% CI: 0.36–0.94; p = 0.01 in comparison with the 1st group).
Conclusion: Combined stem cell and anti-cytokine therapy of CD with perianal lesions significantly contributes to more frequent and prolonged closure of simple fistula, compared with antibiotics/immunosuppressant.
Use of steroids in adults and adolescents with inflammatory bowel disease in the biologics era

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Introduction: Corticosteroids have been effectively used for decades for the rapid induction of clinical remission in patients with inflammatory bowel disease (IBD). However, their adverse event profile is well-known, particularly with long-term use and in younger populations, and they have no role in maintenance of remission. Steroid-sparing agents and more recently biological therapy have reduced systemic steroid use but the true incidence of steroid prescriptions especially in the outpatient setting is not known.

Aim: The aim of this study was to capture real-life steroid use in both adult and adolescent populations older than 13 years old who attend a dedicated IBD clinic in a tertiary referral centre. We tried to identify risk factors associated with appropriate or excessive steroid use in the whole cohort and in the two subgroups separately.

Materials and methods: All consecutive IBD patients who were followed up for at least one year in the adult or adolescent clinic in UCLH and attended their IBD appointment during February and March 2017 were included in the study. A steroid assessment questionnaire was completed by the clinician during the visit for eligible patients using the ‘Steroid Assessment Tool’ developed by AbbVie. Use and type of steroids prescribed during the past year was recorded, as well as appropriate bone protection and disease activity based on Physician Global Assessment.

Results: 60 adolescents and 59 adults were included in the study. Two thirds of adolescents had Crohn’s disease while in the adult population Crohn’s and ulcerative colitis (UC) were equally distributed. 57 (95%) adolescents had been exposed to thiopurines and 47 (78%) to anti-TNFs as opposed to 69% (p = 0.002) and 39% (p < 0.001) of adults respectively. Vedolizumab exposure was similar in adults and adolescents. The percentage of patients with moderate to severe disease at last visit was comparable between two groups (18/60, 30% adolescents had moderate to severe disease vs. 18/59, 31% adults, p = n.s.).

27/119 (23%) of patients were offered steroids during the past year and the incidence was the same in the adult and adolescent populations. 4/27 (15%) received excessive steroids, ie > 2 courses within the preceding 12 months. Of the 27, 17 (62%) had prednisolone and the rest received budesonide, while the choice of steroid was associated with a diagnosis of Crohn’s disease and was not different between the two groups.

Steroid use was not associated with the age group or initial diagnosis but was expectedly associated with severity of disease (severe > moderate > mild, p < 0.001). The use of thiopurines or anti-TNFs did not affect steroid use, but interestingly the majority of vedolizumab users received steroids in contrast to vedolizumab naïve patients (7/9, 78% vs. 20/109, 18%, p < 0.001). This association remained significant even after adjustment for disease severity and other co-factors, suggesting possibly
the higher need for ‘bridging’ steroids due to the slow-acting effect of vedolizumab therapy (binary logistic regression showed naive to vedolizumab patients were protected against steroid use, OR = 0.043; 95% CI: 0.005–0.382; p = 0.005).

**Conclusion:** The use of steroids in an outpatient population with IBD is still common regardless of age group and use of anti-TNFs, as almost 1 in 4 patients received some type of oral steroid during a one year period. Newer biologics, such as vedolizumab, may predispose patients to higher steroid use, possibly due to slow induction of remission.
Very early-onset inflammatory bowel disease in a patient with a IL10 receptor deficiency due to a novel homozygous \textit{IL10RB} mutation

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Very early-onset inflammatory bowel disease (VEOIBD) refers to IBD presented in children before the 6\textsuperscript{th} year of life, with few cases have been reported occurring in the first year of life. These diseases share the clinical picture of Crohn’s and Ulcerative colitis clinical and endoscopic characteristics, such as deep intestinal mucosal ulcerations, perianal inflammation with abscess and fistula formation. Linkage and candidate gene approach found recently, that monogenic autosomal recessive mutations in IL10 receptor chains, alpha or beta, leads to a severe pancolitis with perianal inflammation. Since today few patients with alpha or beta (\textit{IL10RA} and \textit{IL10RB}) had been reported. We present a case of a VEOIBD in a patient with a novel homozygous novel mutation in IL10RB gene. The index patient was from Tabasco, Mexico, he is the second child of a young consanguineous parents. The first child present at 3 months with VEOIBD and recurrent pneumonias, at 3 years the patient dies secondary to intestinal perforation. The patient presented at the age of 1 month with perianal bleeding secondary to multiple perianal abscesses, colonoscopy revealed multiple ulcerations through the colon. Biopsy revealed cryptitis and crypt abscesses. At 2 months intestinal coinfection with CMV that is treated with valganciclovir. Peripheral plasma flow cytometry revealed a low concentration of NKs cells 0.63 (1–6%). Nowadays the patient was treated initially with mesalazine and then with azathioprine, and nowadays the patient 11 months and is in bone marrow HSCT protocol. Clinical picture suggests a monogenic form of VEOIBD, so molecular analysis was performed DNA peripheral blood was extracted using Maxwell 16 DNA purification \textsuperscript{©} and perform a NGS approach by Nextera Rapid Illumina Inc\textsuperscript{®}. Bioinformatic analysis was performed. The NGS revealed an homozygous variant c.49C>T (p.Ala17Pro). Mutation Taster and Polyphen 2 predicts the potential pathogenicity, the variant is absent in the, ClinVar, HGMG, ExAC and 1000 genomeS databases. Extensive literature review revealed approximately 18 cases of \textit{IL10RB} mutations reported in series of VEOIBD mainly in Caucasian and Asian patients with a severe clinical picture like our patient phenotype.
Mesenteric vessels endothelial dysfunction may alleviate therapeutic targeting colonic resistance in IBD

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

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

**Results**: The microbial overgrowth syndrome of II–IV degree detected in 95.1–95.9% of cases. CC- genotype carriers of AGTR1 gene had heavier dysbiosis of III-IV grades. Patients with A-allele, had lower frequency of dysbiosis (p = 0.004) and moderate severity (p = 0.037). CC genotype of AGTR1 gene characterized by elimination of obligate colonic indigenous constant microorganisms and contamination by pathogenic (E. coli Hly+) and opportunistic (Proteus), Enterobacteriaceae, Peptococci, Clostridium and Candida fungi. In patients with CC genotype of the AGTR1 gene a significant reduction of Bifidobacteria (35.7%, p < 0.001), Lactobacilli (24.1%, p < 0.01) and enterococci (1.5%) was found. On this background, significant increase of entero-pathogenic Escherichiae (8.94 ± 0.08 lg CFU/g), opportunistic Enterobacteriaceae (8.78 ± 0.11 lg CFU/g), Hafniae (8.69 ± 0.09 lg CFU/g), Proteus – by 55.2%, Staphyloccoci (5.92 ± 0.14 lg CFU/g), Candida fungi (5.60 ± 0.10 lg CFU/g) was observed.

**Discussion/Conclusion**: The CC genotype of AGTR1 gene is generally characterized by elimination of normal colonic autochthonous obligate microflora and contamination by pathogenic and conditionally pathogenic microorganisms. The mechanism possibly involves changes of mesenteric arteries and endothelial function and may predict failures of microbiota substitution therapies.
The connection of the ulcerative colitis with the diverticulosis and polyps

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The research objective: To find out the connection of the ulcerative colitis (UC) with the diverticulosis and polyps.

Methods: We have analysed 246 medical cases of the patients diagnosed with the UC (average age 42 ± 3). All the patients underwent through the large bowel endoscopy with the histology, the ultrasound examination of the large bowel and the measurement of calprotectin.

The results: among 246 patients with the UC 30 patients had large bowel diverticulosis and polyps of different location.

11 patients (4.8%) had the diverticulosis, 19 patients (7.7%) had the polyps. The patients older than 50 were diagnosed with the diverticulosis, the average age of the patients with the UC and the diverticulosis was 58. The location of diverticula: 6 patients – in sigmoid colon, 7 patients – megacolon. The level of calprotectin – 160 to 402 mcg/g, the average level was 243 mcg/g. The patients with the UC with polyps can be divided into two age groups: the first group (8) – the patients younger than 50, the second group – the patients older than 50. The location of the polyps: 9 patients – one part section of the large bowel, 10 patients – two sections. The level of calprotectin – 264 to 600 mcg/g, the average level – 405 mcg/g.

The Conclusion: The older patients with the UC have the diverticulosis, the polyps, are found in both age groups. The high level of calprotectin in the group of the patients with the UC and the polyps means that the polyps have a strong effect on the presentation of the UC, and as a result, these patients need special methods of treatment.
Psychotherapy efficacy in inflammatory bowel disease patients distress

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\textbf{Introduction}: Our aim was to evaluate the efficacy of psychotherapy sessions in diminishing inflammatory bowel disease (IBD) patients distress.

\textbf{Methods}: Our 12-weeks long prospective study included 12 cognitive-behavioural therapy group sessions. Ten patients with ulcerative colitis (UC) and ten with Crohn’s disease (CD) were selected. Patients were psychologically evaluated at the start of the treatment, at the end of the treatment and 3 months after the treatment ended.

\textbf{Results}: Patients in UC group shown a significant decrease of worries from the moment when the study started to when the study ended (p = 0.03) while patients in CD group didn’t show a significant improvement in their distress status at the end of the treatment (p = 0.18). Concerning the difference between the level of worries at the start of the treatment and at the 3 months follow-up, both groups significantly improved their distress status (p = 0.01 and p = 0.048 respectively). In what concerns the evolution of depression, women significantly improved their depressive status at 3 months after the treatment ended, while men did not (p = 0.039 and p = 0.15).

\textbf{Discussion/Conclusion}: Psychological interventions in IBD patients may significantly reduce the level of psychological distress, but a gender-specific therapy design must be considered when it comes to the treatment of depressive symptoms in IBD.
Prognostic significance of anemia in terms of treatment change in patients with Crohn’s disease (CD) in clinical remission – A study in a tertiary care center in Romania

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Introduction: Anemia is the most prevalent complication in patients with CD, with a negative impact on health-related quality of life, cognitive function and functional status. The aim of this study was to identify the prognostic significance of anemia in terms of treatment change in patients with CD in clinical remission.

Methods: We have conducted a single-center clinical retrospective study. 69 patients with CD in clinical remission (mean Harvey Bradshaw Index = 2.57) were included. Demographic, clinical characteristics and laboratory findings were collected from medical records. Exclusion criteria were: age under 18, pregnancy, active CD requiring hospitalization, current history of any type of malignancy (except cutaneous), gastrectomy, liver disease, kidney failure, systemic infections, alcohol abuse, drug addiction, replacement therapy with B12, folic acid and iron in the last six months. We analyzed changes in the treatment (surgery, the addition of a new therapy, switching or dose escalation of existent biologic therapy) over a period of 1 year.

Results: Of 69 patients (male/female: 37/32, mean age 50.53) with CD in clinical remission, 32 (46.37%) had anemia. 15 patients (46.87%) required a change in treatment. In a multivariate analysis performed by binary logistic regression, anemia was significantly correlated with the treatment change (p < 0.001). There was no significant correlation between treatment change and age (p = 0.04), gender (p = 0.1), disease duration (p = 0.03), disease extent (p = 0.09), treatment with immunomodulators (p = 0.05) or biologics (p = 0.03), haemoglobin (p = 0.02), erythrocyte sedimentation rate (p = 0.09) and C-reactive protein levels (p = 0.04).

Discussion/Conclusion: In CD, even in remission, anemia is a more potent predictor of treatment change than inflammatory markers. Further studies are required to determine the highest risk groups for developing severe anemia as well as the appropriate treatment regimens with the most beneficial effect.
Hematopoietic stem cells transplantation in patient with ulcerative colitis

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Introduction: Despite advances in treatment, a significant proportion of patients with inflammatory bowel diseases (IBD) is refractory to available therapeutic options or loses response to treatment. Hematopoietic stem cells (HSCs) transplantation seems to be a promising therapeutic option for severe refractory cases and in situations where surgery is not feasible. The basic idea behind HSC is to eliminate the ‘autoreactive’ immune cells responsible for disease chronicity, and to re-establish immune tolerance to gut microbes.

In this report we present a patient who suffered from ulcerative colitis and received allogeneic HSC transplantation due to acute monoblastic leukemia.

Case report: A male patient was treated successfully for ulcerative colitis since 2007 (aged 20) with aminosalicylates and azathioprine. In 2012, now aged 25, he came to our Emergency department due to acute tonsylopharingitis. A routine laboratory tests showed agranulocytosis and he was hospitalised for further workup. Bone marrow aspiration confirmed acute monoblastic leukemia. Patient received hematologic treatment and achieved remission. Because of significant risk of infections, azathioprine therapy was discontinued. During treatment patient suffered from exacerbation of ulcerative colitis on two occasions and was treated successfully with salicylates, short-term corticosteroids and broad spectrum antibiotics. In 2015 patient suffered relapse of leukemia and was treated again and achieved remission. In this situation he was accepted for allogeneic HSC transplantation which was done in May 2015. For ulcerative colitis patient used aminosalicylates continuously. After allogeneic HSC transplantation patient achieved complete remission of leukemia, but also ulcerative colitis. He stopped salicylate treatment and had no clinical symptoms of colitis. In 2016 we performed colonoscopy that showed complete remission and mucosal healing of colonic mucosa.

Conclusion: HSC transplantation is being intensively investigated as a treatment option for refractory IBD patients. Our patient received allogeneic HSC transplantation due to acute leukemia, but in treatment of IBD allogeneic transplantation is not indicated due to unacceptable high risk of complication. However, autologous transplantation is promising option.
Intestinal anti-inflammatory effect of olive leaf extract in the DNBS model of mouse colitis

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Introduction: Olive (Olea europea) leaf extract is used in Mediterranean traditional medicine as an anti-inflammatory remedy, most probably due to the presence of antioxidant phenolic compounds, like oleuropeoside. It would be interesting to validate its use for the treatment of inflammatory conditions associated with oxidative stress in humans, such as inflammatory bowel disease. The aim of the study was to evaluate the intestinal anti-inflammatory properties of an olive leaf extract in the dinitrobenzene sulfonic acid (DNBS) model of mouse colitis, which resembles human IBD.

Methods: Male CD1 mice were assigned into five groups: non-colitic, colitic control and colitic treated groups with olive leaf extract (1-10-25 mg/kg). Acute intestinal inflammation was induced by intrarectal administration of DNBS (3 mg) in 50% ethanol. The administration of the extract started two days before colitis induction and continued until the sacrifice, which took place five days after the induction of the colonic damage. Animal body weights, occurrence of diarrhea, and water and food intake were recorded daily throughout all the experiment. Once the animals were sacrificed, the colon was removed and scored macroscopically. The inflammatory status was also evaluated biochemically by determining the colonic expression of mediators involved in the inflammatory response or in the intestinal epithelial barrier function.

Results: Although no differences in body weight were observed over the treatment period, OLE showed intestinal anti-inflammatory effects as evidenced biochemically by a significant inhibition of the expression of IL-1β, IL-6, IL-17 and TNF-α. OLE also down-regulated the adhesion molecule ICAM-1 and the inducible enzymes iNOS and COX-2, at the mRNA level. The beneficial effect of OLE was associated with the normalization of the expression of MUC-2 and ZO-1, thus promoting the restoration of the altered epithelial integrity that contributes to the intestinal inflammatory response.

Discussion/Conclusion: OLE showed intestinal anti-inflammatory effects in the DNBS model of mouse colitis, through the amelioration of the altered immune response and improvement of the epithelial barrier function in the inflamed colon.
Impact of dietary antigens on the mucosal homeostasis and inflammation

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Introduction: Inflammatory bowel disease (IBD), as Crohn’s disease and Ulcerative Colitis, are dysregulations of the mucosal immune system. The combination of the genetic predisposition and environmental factors, as microbiota and dietary antigens, seems to provoke the development of the disease. Furthermore, the immune system is linked to the dietary antigens through the Peyer’s patches (PP) in the terminal ileum. Murine data show that dietary antigens lead to an activation and subsequent apoptosis of the CD4⁺ T cells in the PP.

Methods: T cells in the PP will be characterized for their activation, phenotype, survival and apoptosis between the patient groups. Besides, food antigen activated CD4⁺ T cells in the peripheral blood of these patients will be analyzed by a magnetic enrichment of CD154⁺ cells and a subsequent cytometric antigen-reactive T cell analysis.

Results: CD4⁺ T cells in the PP of IBD patients show a reduced apoptotic rate. Further characterization reveals an increased expression of the marker for regulatory T cells, FoxP3, in IBD patients. Differences in the expression of the activation marker Helios are also found. In addition, an increased expression of pro-inflammatory cytokines in the antigen-specific T cells in IBD patients has been observed.

Discussion/Conclusion: In depth characterization of the T cells of the PP will lead to a better comprehension of the pathogenesis of IBD. Additionally, together with the prior murine data, further analysis of the observed food antigen dependent hyperactivation of the CD4⁺ T cells in the PP of IBD patients offers the possibility for future nutrition based interventions.
**Immunomodulatory tetracyclines for IBD: Comparative pharmacological study in DNBS colitis**

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**Introduction:** Minocycline and doxycycline have shown immunomodulatory effects and intestinal anti-inflammatory activity that could be beneficial in IBD. However, the mechanisms underlying are not well understood. Micro-RNAs are important for intestinal homeostasis, maybe influenced by microbiota and pharmacological therapies. The aim of the study was to compare the effects of immunomodulatory tetracyclines with other antibiotics and dexamethasone in an experimental model of colitis induced by DNBS in mice, which resembles Crohn’s disease.

**Methods:** CD1 mice were induced colitis by DNBS intracolonic administration (4 mg). Then, mice were treated with rifaximin (250 mg/kg/day), tetracycline (200 mg/kg/day), doxycycline (25 mg/kg/day), minocycline (50 mg/kg/day), tigecycline (25 mg/kg/day) or dexamethasone (2.4 mg/kg/day). After 6 days, mice were sacrificed and the inflammatory status was evaluated macroscopically and determining different inflammatory markers by RT-qPCR. Microbiota was characterized by pyrosequencing.

**Results:** Immunomodulatory tetracyclines, doxycycline, minocycline and tigecycline, decreased DNBS-induced mortality and ameliorated weight loss. They reduced colonic shortening, and prompted mucosal architecture recovery and reduced fibrotic lesions. However, rifaximin and tetracycline, which lack immunomodulatory properties, displayed minor beneficial effects, and dexamethasone showed no efficacy. The microbial population presented three major clusters according to PCA: non-colitic group, non-antibiotic- and antibiotic-treated groups. Antibiotics induced changes in the microbiota although they did not restore the basal conditions. The immunomodulatory tetracyclines improved intestinal barrier integrity and the expression of inflammatory mediators, like CCL2. They also modulated microRNA expression, downregulated NF-κB-related miR-9 and upregulated miR-142 and miR-375, required for goblet cell differentiation.

**Discussion/Conclusion:** Immunomodulatory tetracyclines showed higher efficacy than the other drugs in controlling inflammation in DNBS colitis, by ameliorating the progression of intestinal inflammation into fibrotic lesions. Their antibiotic activity could contribute to their efficacy but this study confirmed the importance of their immunomodulatory properties and showed the potential of immunomodulatory tetracyclines in the treatment of IBD.
Intestinal anti-inflammatory effects of different probiotics on the DNBS-induced colitis: Impact on gut microbiota and miRNA modulation

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Introduction: Probiotics have been reported to exert beneficial effects in inflammatory bowel disease. Unfortunately the knowledge of the mechanisms of action involved are not completely elucidated. With this purpose, in this study we evaluated the intestinal anti-inflammatory effect of different probiotics (Lactobacillus fermentum CECT5716, Lactobacillus salivarius CECT5713, Escherichia coli Nissle 1917, Saccharomyces boulardii CNCMI-745) by comparing their preventative effects in the dinitrobenzene sulfonic acid (DNBS) model of mouse colitis, a well-established model of intestinal inflammation with some resemblance to human IBD. In addition, the relationship among modification in the intestine microbiota, miRNA expression profile and development of intestine inflammation was analyzed.

Methods: Male CD1 mice (20–25 g) were randomly allocated in different experimental groups (n = 10): non-colitic and control colitic, which received orally PBS solution (200 µl), and other four colitic groups that were treated with the different probiotics: Lactobacillus fermentum CECT5716, Lactobacillus salivarius CECT5713, Escherichia coli Nissle 1917 (5 x 10⁸ CFU/mice/day) and Saccharomyces boulardii CNCMI-745 (5 x 10⁹ CFU/mice/day). After 14 days of treatment, colitis was induced with DNBS (3 mg/mouse in 50% ethanol) instilled rectally. Daily, animal body weight, the presence of gross blood in the faeces and stool consistency were evaluated. Once the animals were sacrificed, colonic tissue was evaluated biochemically after RNA/miRNA isolation by qPCR. Also, colonic microbiota composition was analysed by pyrosequencing.

Results: The beneficial effects exerted by these probiotics in the DNBS model of mouse colitis were evidenced biochemically by a significant inhibition of the expression of pro-inflammatory factors such as IL-1β, TNF-α and MMP-2. Only Lactobacillus fermentum was able to significantly inhibit the expression of iNOS. These beneficial effects were associated with the normalization and/or increase of the expression of MUC-3 and occludin, which are involved in epithelial integrity. Also, probiotics promoted the recovery in different miRNA (miR 155, miR223, miR 375, miR 143) in colitic mice; however, not all of them showed the same profile, since only the expression of miR-150 was restored by all probiotics. Finally, both lactobacilli and E. coli Nissle 1917, but not with S. boulardii, increased the diversity of the microbiota, partially restoring the dysbiosis observed in DNBS-induced colitis.

Discussion/Conclusion: In conclusion, the probiotics showed anti-inflammatory effects probably due to their capacity to modify miRNA expression in DNBS colitic mice and to restore the dysbiosis-associated status that characterizes intestinal inflammation.
Effects of anti-tumor necrosis factor alpha on quality of life in patients with Crohn’s disease

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Introduction: Administration of anti-tumor necrosis factor alpha (anti-TNFα) appears to be highly effective in patients with moderate to severe inflammatory bowel disease (IBD).

Aim: To assess the effect of anti-TNFα on the quality of life in patients with active of fistulizing disease, as measured by the Crohn’s and ulcerative colitis questionnaire-8 (CUCQ-8) for organic dimension and the hospital anxiety and depression (HAD) scale for social and psychological dimension.

Methods: An observational study was conducted in 15 patients. Anti-TNFα were given first for induction treatment, than for sequential treatment. Changes from baseline in the total scores were calculated and compared before and after induction phase. Potential predictors of change in the quality of life were identified.

Results: At week 4, the mean total CUCQ-8 score improved compared to baseline (p < 0.05). No change was noted on HAD scale. At week 6, scores (CUCQ-8 and HAD) changed from baseline (p < 0.05). Improvement in the CUCQ-8 score correlated well with the improvement of the Crohn’s disease activity index. Organic score improved more than emotional score (p < 0.05).

Discussion/Conclusion: Anti-TNFα therapy improves all dimensions of the quality of life in patients with IBD.
Immunomodulatory effects of the probiotic *Lactobacillus paracasei* INIA P272 in DSS-colitis: Impact on immune cell populations

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Introduction: Probiotics have been reported to exert beneficial effects in inflammatory bowel disease through different mechanisms, including their immunomodulatory properties. The aim of the study was to evaluate the effect of the probiotic *Lactobacillus paracasei* INIA P272 in the DSS model of mice colitis, exploring its impact on immune cell activity located in the gut.

Methods: Male C57BL/6 mice were treated with *L. paracasei* INIA P272 (5 x 10⁸ UFC/mice/day) for 23 days. At day 14 colitis was induced by DSS administration (3% dissolved in drinking water for 5 days). Non-colitic and non-treated colitic groups were included as reference. The progress of the intestinal inflammation was evaluated daily by a disease activity index (DAI). At day 24 mice were sacrificed and the intestinal inflammatory status evaluated. Moreover, the expression of inflammatory markers in the inflamed tissue was evaluated by RT-qPCR and the leukocyte populations from colonic lamina propria were analyzed by multiparametric flow-cytometry.

Results: *L. paracasei* INIA P272 treatment produced an intestinal anti-inflammatory activity, since it reduced DAI values. Immunomodulatory effects were also evidenced by the ameliorated expression of inflammatory cytokines and chemokines, such as IL-1β, IL-6, MCP-1 and I-CAM, and the enzymes iNOS and MMP-9, involved in the inflammatory response and the tissue remodelling. When immune cell infiltration in colonic lamina propria was evaluated, the probiotic-treated group showed reduced neutrophil numbers while IL-10-producing FoxP3⁺ Tregs were increased.

Discussion/Conclusion: *L. paracasei* INIA P272 presented intestinal anti-inflammatory effects, by decreasing the susceptibility to DSS-induced colitis. The immunomodulatory activity exerted by this probiotic could be of great interest for its future development in the treatment of human IBD.
Common features of hepatic and pancreatic stellate cells in rat copper-deficient model of injury

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²Kazan (Volga Region) Federal University, Kazan, Russia

Introduction: The possibility of pancreatic cells transdifferentiation into hepatocyte-like cells in copper-deficient model of injury in rats was shown by M.S. Rao and D.G. Scarpelli. Considering that hepatic stellate cells (HSC) play an important role in hepatocytes' differentiation as well as common features of hepatic and pancreatic stellate cells (PSC) the aim of our work was to study HSC and PSC in this model of injury.

Methods: Wistar rats were maintained on copper-deficient diet containing copper-chelating agent for 8 weeks, and then were returned to normal rat chow for another 8 weeks. Liver and pancreas paraffin sections were stained with antibodies to desmin and alpha-smooth muscle actin (α-SMA).

Results: We observed increased number of desmin-positive HSC in periportal and pericentral areas of liver at all weeks of diet. Maximum α-SMA expression detected after 6 weeks of diet.

The Mallory staining revealed connective tissue fibers mainly in periportal areas with few porto-portal septa till the 6th week of diet.

The number of desmin-positive PSC in pancreatic acinar tissue and on periphery of islets increased by 8th week of diet. The number of PSC decreased, and few desmin-positive cells were found in islets and along the border of remaining islets and newly formed acinar tissue at the recovery phase.

Discussion/Conclusion: PSC and islet cells (possibly glucagon-producing cells as it was shown earlier in our lab) can be involved in pancreas regeneration including possible transdifferentiation into the hepatocyte-like cells in case of copper-deficient diet. The same pattern of changes in liver can be due to HSC response to liver injury reflecting common ways of pancreas and liver regeneration.
Impact of microbial colonisation on the immune cell composition and barrier function in the gut

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²Freie Universität Berlin, Fachbereich Biologie, Chemie, Pharmazie, Berlin
³German Institute of Human Nutrition Potsdam-Rehbruecke, Department of Gastrointestinal Microbiology, Nuthetal
⁴Max-Planck-Institute of Neurobiology, Neuroimmunology, Planegg-Martinsried, Germany

Introduction: Intestinal microbiota is influenced by the environment and central for mucosal homeostasis. Previous data indicate a pro-inflammatory role of natural killer T cells when intestinal colonisation occurred later in life. In this study we asked whether the time point of colonisation impacts the development and function of intestinal macrophages. Therefore we analysed germ-free (GF), specific pathogen-free (SPF) mice and GF mice colonised at age of 5 weeks with SPF-microbiota (COL) in health and intestinal inflammation.

Methods: The phenotype of lamina propria mononuclear cells (LPMC) was determined by flow cytometry and immunohistochemistry. LPMC were stimulated with lipopolysaccharides (LPS) in the presence of Brefeldin A to assess intracellular tumor necrosis factor α-expression by flow cytometry. Acute colitis was induced by dextran sodium sulfate (DSS). Barrier function of colon was analysed by electrophysiology using Ussing-chamber. Local cytokine production was assessed in supernatants of cultures ex vivo isolated colon tissue by Cytometric Bead Array. To confirm successful colonisation cecal content was sequenced for 16 S ribosomal RNA genes.

Results: GF mice revealed barrier defects attributed to a decrease in subepithelial resistance paralleled by an increased paracellular flux. Phenotypic differences of macrophages were observed in the ileum but not colon of GF mice versus SPF mice. 4 weeks after colonisation the macrophage compartment did not differ from that of SPF mice. Although GF mice died after exposure to DSS, no infiltrating macrophages were detected. Remarkably, COL mice presented with less inflammation when compared to SPF mice, suggesting a tolerance induction by colonisation at week 5.

Discussion/Conclusion: Our data emphasise the plasticity of macrophages by indicating that the numeric, phenotypic and functional development depends on the luminal microbiota but to a lesser extent on the time point of colonisation.
The value of serum antibody in hierarchical management of Crohn’s disease

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Introduction: Investigate the value of serum antibody in the hierarchical management of CD.

Methods: 100 patients with CD were enrolled in this study. According to disease behavior, they were divided into 3 groups (B2 group: narrow type, 28 cases; B3 group: penetrating type, 29 cases; B1 group: non-narrow and non-penetrating type, 43 cases). There were 54 cases of lesions involving the terminal ileum and not involving the colon. According to whether or not involving the gastrointestinal tract above the small intestine, they were divided into 2 groups (L1+L4 group: yes, 28 cases; L1 group: no, 26 cases). Single blind ELISA method was used to detect the level of ASCA IgG, ASCA IgA, AMCA, ACCA, anti-OmpC, anti-I2, anti-CBir1, pANCA, anti-PR3 in all subjects. The SEN, SPE, PPV and NPV in the diagnosis of CD disease phenotype by each antibody were calculated. And the diagnostic value was evaluated by ROC curve.

Results: In China, anti-I2 was associated with narrow CD (Table 1), while ACCA and anti-CBir1 were associated with penetrating CD (Table 2). ASCA IgA and AMCA were associated with the lesions involving the gastrointestinal tract above the small intestine (Table 3). Focusing on the diagnostic accuracy, anti-I2 was the highest in the diagnosis of narrow CD (figure 1), while anti-CBir1 was the highest in the diagnosis of penetrating CD (figure 2). AMCA was the highest in the diagnosis of the lesions involving the gastrointestinal tract above the small intestine (figure 3). Joint detection can effectively improve the accuracy. However, the expression level of these antibodies in Chinese CD population was too low, and the cutoff value should be adjusted reasonably to improve the positive detection rate.

Discussion/Conclusion: Serum antibody detection has important clinical value in the management of disease classification of Chinese CD population, which is worthy of further study.
Table 1. Regression analysis on the correlation between serum antibody and narrow CD (N=100)

<table>
<thead>
<tr>
<th>serum antibody</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCA IgG</td>
<td>0.223</td>
</tr>
<tr>
<td>ASCA IgA</td>
<td>0.447</td>
</tr>
<tr>
<td>AMCA</td>
<td>0.605</td>
</tr>
<tr>
<td>ACCA</td>
<td>0.820</td>
</tr>
<tr>
<td>anti-CBir1</td>
<td>0.149</td>
</tr>
<tr>
<td>anti-Ig</td>
<td>0.011</td>
</tr>
<tr>
<td>anti-OmpC</td>
<td>0.223</td>
</tr>
<tr>
<td>pANCA</td>
<td>0.096</td>
</tr>
<tr>
<td>anti-PR3</td>
<td>0.862</td>
</tr>
</tbody>
</table>

Figure 1. ROC curve of serum antibody detection in diagnosis of narrow CD

Table 2. Regression analysis on the correlation between serum antibody and penetrating CD (N=100)

<table>
<thead>
<tr>
<th>serum antibody</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCA IgG</td>
<td>0.790</td>
</tr>
<tr>
<td>ASCA IgA</td>
<td>0.719</td>
</tr>
<tr>
<td>AMCA</td>
<td>0.085</td>
</tr>
<tr>
<td>ACCA</td>
<td>0.027</td>
</tr>
<tr>
<td>anti-CBir1</td>
<td>0.021</td>
</tr>
<tr>
<td>anti-Ig</td>
<td>0.246</td>
</tr>
<tr>
<td>anti-OmpC</td>
<td>0.053</td>
</tr>
<tr>
<td>pANCA</td>
<td>0.213</td>
</tr>
<tr>
<td>anti-PR3</td>
<td>0.591</td>
</tr>
</tbody>
</table>

Figure 2. ROC curve of serum antibody detection in diagnosis of penetrating CD

Table 3. Regression analysis on the correlation between serum antibody and the lesions involving the gastrointestinal tract above the small intestine (N=64)

<table>
<thead>
<tr>
<th>serum antibody</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCA IgG</td>
<td>0.600</td>
</tr>
<tr>
<td>ASCA IgA</td>
<td>0.044</td>
</tr>
<tr>
<td>AMCA</td>
<td>0.013</td>
</tr>
<tr>
<td>ACCA</td>
<td>0.100</td>
</tr>
<tr>
<td>anti-CBir1</td>
<td>0.668</td>
</tr>
<tr>
<td>anti-Ig</td>
<td>0.850</td>
</tr>
<tr>
<td>anti-OmpC</td>
<td>0.925</td>
</tr>
<tr>
<td>pANCA</td>
<td>0.0500001</td>
</tr>
<tr>
<td>anti-PR3</td>
<td>0.363</td>
</tr>
</tbody>
</table>

Figure 3. ROC curve of serum antibody detection in diagnosis of the lesions involving the gastrointestinal tract above the small intestine
Roseburia intestinalis is an anti-inflammatory bacterium identified by fecal sequencing of Crohn’s disease patients

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Introduction: To elucidate the anti-inflammatory effect and mechanism of Roseburia intestinalis (R. intestinalis) in Crohn’s disease (CD).

Methods: 16S-rRNA genome sequencing technique is used to detect the characteristics of intestinal flora in untreated CD patients and healthy controls. Then we investigate the effects of R. intestinalis on DAI score, intestinal pathology, the differentiation of Treg cells and the expressions of TSLP, TGF-β, IL-10 by using TNBS colitis models. At the cellular level, we use LPS to stimulate Caco-2 cells to conduct inflammation models, and then co-culture with R. intestinalis and detect changes of TSLP and TGF-β. Then use R. intestinalis to stimulate PBMCs and the change of Treg cells was detected.

Results: The abundance and diversity of intestinal flora in CD patients decreased. At the species level, it was found that the abundance of R. intestinalis was decreased obviously. R. intestinalis significantly decreased DAI scores, and played anti-inflammatory role by increasing the levels of Treg cells, TSLP, TGF-β and IL-10 (p < 0.05). The co-culture of R. intestinalis and Caco-2 cells increased the secretion of TSLP and TGF-β. R. intestinalis stimulates PBMCs to differentiate into Treg cells (p < 0.05).

Discussion/Conclusion: R. intestinalis promotes the secretion of TSLP and TGF-β, thus inducing the differentiation of the Treg cells so as to inhibit inflammation.
Patient’s consent for oesophagogastroduodenoscopy (OGD) in a district hospital

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³CMT year 2 at University Hospital of Wales, Cardiff, CF14 4XW, UK

Introduction: Informed consent is central to the relationship between all Health Professionals and their patients. There are no satisfactory data for the UK but in a review of 31 claims against endoscopists in England and Wales it appeared that in at least 12 instances patients consented to the procedure after little or no explanation. The aim of this study was to ensure valid consent is taken from patients having oesophagogastroduodenoscopy (OGD) in compliance with the Guidance.

Methods: Over 6 month period, data was gathered retrospectively on 62 patients (age range 24–93 years) who had OGD. The standards were: has the consent form specified the type of the procedure, was the writing legible, were medical terms used, was the procedure explained in lay man language, was this clearly documented, and has the consent form been filed in the case notes.

Results: Results showed that majority of the consent forms (84–87%) were legible and clearly specified the type of the procedure. However, only 45% of the consent forms were written in lay man words and medical abbreviations were used in 42% of them. Although 90% of the consent forms were filed in the case notes, only 13% of the consents were documented in the case notes.

Discussion/Conclusion: Out of the 62 consent forms studied, 13% did not specify the type of the procedure and many of them were written in medical terms. There was lack of documentation in the case notes that consent has been given by patient and required information was provided.
A rare cause of retroperitoneal fibrosis

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

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

Results: Ascitic tap revealed chylous ascites with high SAAG (serum ascites-albumin gradient) of > 1.1 g/dl indicating a non-peritoneal cause of ascites. Cytology revealed no evidence of malignancy. CT abdomen revealed a mildly enhancing soft tissue mass encasing the mesenteric and renal vessels and the upper abdominal aorta and also the left peritoneal space; appearances were suggestive of lympho-proliferative disorder. CT guided biopsy showed reactive changes consistent with retroperitoneal fibrosis. Immunohistochemistry done at University College of London showed no evidence of Ig4 disease. Patient was commenced on prednisolone and azathioprine. He failed to tolerate azathioprine which was then stopped. Treatment with prednisolone failed to slow the rate of reaccumulation of the ascites, and he continued to require frequent abdominal paracentesis.

Discussion/Conclusion: Chylous ascites has rarely been reported as a presenting feature of retroperitoneal fibrosis. [1] Retroperitoneal fibrosis may be an idiopathic in 70% of cases or secondary condition. The incidence of idiopathic form is 0.1 per 100,000 person-years with a prevalence of 1.4 per 100,000 population. [2] The primary modality used for diagnosis of retroperitoneal fibrosis is CT imaging, biopsies are performed in cases of unusual presentation and to exclude malignancy and IgG4-related pathology. Treatment of retroperitoneal fibrosis in most cases depends on whether it is idiopathic or secondary. The mainstay of treatment is corticosteroids and if no response, immunosuppressive therapy can be used. Case series data is present which has shown that high dose corticosteroids like prednisolone are effective in reducing the chronic inflammatory response caused by retroperitoneal fibrosis; however there is a high rate of recurrence once the steroids are withdrawn. Mycophenolate mofetil in addition to corticosteroids has shown reduced duration of steroid use without affecting the efficacy and reduces disease recurrence rate.
Matrix metalloproteinases in differential diagnosis of inflammatory bowel disease

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²Titu Maiorescu University, Faculty of Medicine, Bucharest, Romania

Introduction: The matrix metalloproteinases (MMPs) expression is altered in inflammatory bowel disease (IBD) but while their involvement is known, circulating concentrations of MMPs, a potential tool for diagnostic tests, have not been established. This paper aims serum quantitative investigation of MMP-3 and MMP-9 in patients with IBD compared with control group, for establishing their roles in the disease pathophysiology and as potential biomarkers in differential diagnosis.

Methods: The present study investigated levels of MMP-3, MMP-9 and CRP in serum samples of 67 patients, of which 46 with ulcerative colitis (UC) and 21 affected by Crohn's disease (CD). Parallel, we used a control group of 30 persons unaffected by CD or UC. For dosage of MMP-3, MMP-9 and CRP, were used Invitrogen Corporation and INOVA-ELISA kits. Clinical disease activity was evaluated using a Truelove-Witts severity index TWSI for UC and the Harvey-Bradshaw severity index (HBI) for CD.

Results: Serum levels of MMP-3, MMP-9 and CRP were significantly higher in IBD patients than in controls ($p < 0.0001$). In UC serum levels of MMP-9 showed significant correlation with TWI score ($r = 0.308$, $p = 0.037$) but MMP-3 levels were statistically correlated only with the number of points obtained in the evaluation of disease activity by TWI score ($r = 0.344$, $p = 0.029$). In CD patients, MMP-9 concentrations correlated positively with HBI ($r = 0.608$, $p = 0.039$); no significant correlations were between concentrations MMP-9 and CRP ($r = 0.246$, $p > 0.05$). Serum levels of MMP-3 in CD patients were correlated better with indices of disease evaluated for this entity.

Discussion/Conclusion: The data of our study indicate the presence of correlations between the activity of inflammatory bowel disease and serum levels of matrix metalloproteinases. In CD patients serum levels of MMP-3 were correlated better with indices of disease (HBI and CRP) evaluated, while in patients with UC, was achieved better correlation with MMP-9. We can notice that, MMP3 and MMP9 concentrations are important indicators of inflammatory disease, which can be used in differential diagnosis of IBD.
Reconsidering the prognostic value of traditional serologic antibodies in Crohn’s disease – Immunoglobulin classes to take the center stage

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Background: The most relevant scope of serologic antibodies in Crohn’s disease (CD) is to stratify the risk of complicated disease course. Significance of distinct antibody classes and their characterisation was rarely considered. We aimed to address these concerns.

Methods: Sera of 266 well-characterized CD patients (m/f: 112/154, median age: 25 years, B1: 80.1%, P1: 18.0%) and 155 controls were assayed for traditional antimicrobial antibodies (ASCA IgA/IgG, anti-OMP IgA). Endotoxin core IgA (EndoCAb) and a panel of non-specific immunoglobulin A (IgA) antibodies (IgA1, IgA2 and secretory[s] IgA) were also assessed by ELISA. An observational follow-up study (median, 143 months) was conducted to assess possible associations between serologic antibodies and the development of various complications and subsequent surgical interventions. A novel flow cytometry test system was established for characterisation of IgA type ASCA to reveal possible origin of the antibody.

A total of 65.7% and 46.2% of the CD patients were positive for ASCA IgA/IgG and anti-OMP antibodies. Both ASCA types occurred equally. EndoCAb IgA positivity was more frequent (15.4% vs. 5.4%, \( p < 0.01 \)) and slgA levels were increased (median, 51 vs. 29 \( \mu \)g/ml, \( p < 0.001 \)) in CD compared to controls. They were also associated with presence of IgA type anti-microbial antibodies. Contrary, ratio of IgA2/A1 in CD corresponded with the value of the controls. In Kaplan-Meier analysis, development of internal penetrating and/or stenosing (IP/S) complications and resective surgery (SR) was significantly associated with IgA type (pLogRank < 0.001 and pLogRank = 0.025 respectively), while development of perianal penetration (PP) with IgG type ASCA (pLogRank = 0.008).

Performance OMP IgA was equal to ASCA IgA, however slgA not. Antimicrobial antibodies remained independent predictors in multivariate Cox-regression analysis comprising relevant clinical factors. Without uncoupling of Ig antibody classes yielded clearly inferior performance.

ASCA IgA subtyping assays revealed marked increase in the proportion of IgA2 subtype (29%) and presence of the secretory component (89% of total ASCA IgA) concurrently.
**Results:** Consideration of antibody classes is an important novel parameter in serology-based prediction in CD. Involvement of gut mucosal immune system is in center of IgA type antibody formation reflecting sustained exposure and dysregulated immunresponse to bacterial constituents.
Optimization the clinical prediction of the manifestation severity in ulcerative colitis

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Ukrainian Medical Stomatological Academy, Poltava, Ukraine

Ulcerative colitis (UC) is chronic inflammatory disorder of gastrointestinal tract that is characterized by extraintestinal symptoms in addition to intestinal complaints. In active inflammatory phase endoscopy may be associated with high risk of iatrogenic complications. From this point, special attention should be paid to the evaluation of the effectiveness of non-invasive methods in prediction of the severity during UC relapse.

The aim – to provide comparative estimation of leucocytes, erythrocyte sedimentation rate (ESR), fecal calprotectin with endoscopic assessment to define the extent and severity of colon mucosal inflammation in UC patients.

Materials and methods: We examined 27 patients with relapse of UC, who were on gastroenterologist outpatient consultation in Poltava Regional Clinical Hospital n.a. M.V. Sklifosovsky, of which 12 women, 15 – men, age 25–49 years. Colonoscopy was conducted to all patients with estimation of extent and severity of inflammation by Mayo score. Serum C-reactive protein and fecal calprotectin were determined.

Results: According to colonoscopy distal colitis was found in 10 (37%) patients, proctitis – in 4 (14.8%), rectosigmoiditis – 6 (22.2%), left-sided colitis 8 – in (29.6%), total colitis – 9 (33.3%). In 7 (25.9%) patients was established degree I of endoscopic index of severity, in 17 (63.0%) – degree II, in 3 (11.1%) – degree III. Third degree endoscopic index was estimated only in patients with left-sided or pancolitis. The most frequent was II degree endoscopic index that was found in 60–66.7% in all forms. The distal ulcerative colitis in 40% patients was associated with minimal degree endoscopic activity.

Moderate leukocytosis was found in 16 (59.2%) patients with total and left-sided colitis, in 8 and 6 patients respectively, with degree II and III of endoscopic index and 4 patients with distal colitis and degree II of endoscopic index by Mayo. ESR > 30 mm/h was determined in 9 (33.3%) patients, in 8 with total colitis and degree II, III of endoscopic index and 1 with left-sided colitis and degree III endoscopic activity by Mayo. ESR above the normal but < 30 was detected in 11 (40.7%) patients with distal colitis and degree II of endoscopic index by Mayo. Fecal calprotectin was elevated in patients with relapse and was in 5.38 times above the normal with maximum elevation in patients with highest degree local activity.

Conclusion: Patients with extended forms of UC have high association with leukocytosis and high ESR, meanwhile the inflammation severity correlates with high levels of fecal calprotectin.
Corticosteroid therapy in patient with microscopic colitis and schizophrenia

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Introduction: Corticosteroid therapy has effective anti-inflammatory, immunosuppressive and anti-proliferative activity, but also numerous side effects, among others a worsening of psychical condition of a patient. Budesonide is an extremely strong corticosteroid of local activity, its action is limited to gastrointestinal tract. Owing to metabolism of a preparation, that passing through the liver, metabolites in steroids, which have significantly lesser activity than budesonide alone; with application of budesonide lesser side-effects can be expected.

Methods: Case presentation.

Results: 35-year-old male, regularly controled by psychiatrist under diagnosis of schizophrenia, in remission phase of the illness, comes in gastroenterological unit because of repeated watery diarrhoeas. Problems are lasting for a 20 years. Basic laboratory elaboration was performed, thyroid gland hormones, tTg antibodies. All the findings were within referal values. Microbiological analysis of the stool has not shown pathologic microorgasnisms. We decided to perform the colonoscopy, at which tidy mucous membrane of colon and terminal ileum were found; random biopsies accordingly to protocol for microscopic colitis were taken. Pathohistological finding is in concordance with collagen type of microscopic colitis. Loparamid was introduced in therapy, but without succes, so we decided to introduce budenosid in dosis of 9 mg daily. After 4 weeks of therapy good clinical response was noted, as well as, reduction in number of stools to twice daily, stool became formed. Psychical condidion of a patient remains unchanged, remission persisted. Patient was on budenosid therapy during 8 weeks; regarding clinical remission and periodic headaches therapy was stopped. Five months after termination of therapy with budenosid, exacerbation of schizophrenia occured, colitis is furthermore in remission. Two years after onset of a disease, control colonoscopy was performed. Again, normal macroscopic finding was noted, mild colitis without increase of collagen fibers was histologically described. Patient is free from therapy, disease is in remission, he is further under our supervision.

Discussion/Conclusion: Application of budesonide caused remission of colagen-type microscopic colitis without worsenings of psychical status of a patient.
Localization and protein levels of intestinal tissue kallikrein (ITK), kallistatin, and kinin receptors in colorectal cancer

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²Department of Proteomic, SPLMS in Sosnowiec, Medical University of Silesia, Katowice, Poland
³Section of Gastroenterology, and Department of Surgery, Endocrinology and Oncology, District Hospital, Jaworzno, Poland
⁴Department of Basic Biomedical Sciences, SPLMS in Sosnowiec, Medical University of Silesia, Katowice, Poland

Introduction: We investigate the expression and localization of ITK, its inhibitor kallistatin, and B1 and B2 kinin receptors (B1R, B2R) in intestinal tissue of patients with colorectal cancer.

Methods: The resected cancerous tissue samples were graded as grade G1, grade G2 or grade G3 (poor differentiation). ITK, kallistatin, B1R and B2R proteins were visualized by immunohistochemical staining and quantified by image analysis.

Results: In normal intestine ITK was localized in goblet cells, however it was mainly present in epithelial cells of G1 and G2 grades, and in G3 grade reaction was low. Kallistatin reaction intensity was higher in enterocytes of G1 and G2 grades, and weaker in grade G3. B2R increased in enterocytes of G1 grade, but was weaker in grades G2 and G3. B1R was found in the basal area of enterocytes in normal intestine, but in the apical portion of enterocytes in grades G1 and G2. The staining reaction for ITK protein in grade G1 (156.8 ± 11.7) was significantly (p < 0.05) higher as compared with controls (132.0 ± 10.3), but not in grade G2 (144.2 ± 11.2), and was lowest in grade G3 (108.0 ± 11.7). Kallistatin protein significantly increased in G1 (149.0 ± 11.0, p < 0.05), and in G2 (166.8 ± 9.9, p < 0.01), but not in G3 (111.8 ± 9.1). B1R protein level was significantly higher in G1 (151.7 ± 12.8, p < 0.01), and in G2 (167.5 ± 10.0, p < 0.01) than in controls (112.3 ± 10.9), whereas B2R protein level was higher in G1 (173.6 ± 11.9, p < 0.01), but nearly equal in G2, and G3 as compared to control (124.6 ± 12.1).

Discussion/Conclusion: Alterations of localization and increased protein levels of ITK, kallistatin, and kinin receptors indicate that the ITK-kinin system may play a role in malignant cellular transformation mainly in well and moderately differentiated grades of colorectal cancer.
The immunologic mechanism of interleukin-25 mediated mesenchymal stem cell in treatment of inflammatory bowel disease

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Introduction: To investigate the anti-inflammatory mechanism of IBD treatment with mesenchymal stem cells (MSC) mediated by IL-25 in DSS-induced rat colitis models.

Methods: We separated rat MSCs, used green fluorescent protein (GFP) to mark MSCs, and stimulated them with IL-25 for subsequent experiments. Experimental rats were divided into 5 groups: negative control group (rats fed with water), positive control group (rats fed with DSS solution), MSC group (DSS-treated rats injected intravenously with common GFP-MSCs), IL-25 primed-MSC group (DSS-treated rats injected intravenously with IL-25 primed GFP-MSCs), and positive drug group (DSS-treated rats fed with mesalazine). Inflammatory activity and histological changes were evaluated on day 8, and cytokine levels of peripheral blood CD4+ cells isolated from each group were determined with flow cytometry.

Results: Administration of DSS solution resulted in severe colitis that was characterized by weight loss and bloody diarrhea on day 3–8. Compared with positive control group, each treatment group showed a preventive effect on weight loss and bloody diarrhea, especially in IL-25 primed MSC group and positive drug group. H&E staining also revealed that IL-25 primed MSC group and positive drug group had fewer inflammatory infiltrates and less crypt structure damage compared with other groups. No definite GFP positive cells were observed in the colons of MSC-injected colitis rats. Flow cytometry analysis indicated that the expression of FOXP3 and IL-4 was decreased, and the expression of IL-17A and IFN-gamma was increased in peripheral blood CD4+ cells of DSS-treated only rats. This phenomenon was reversed by MSC injection or mesalazine treatment. In addition, only differences of IL-17A and FOXP3 levels were determined between MSC group and IL-25 primed-MSC group.

Discussion/Conclusion: Pretreatment with IL-25 could improve the therapeutic effect of MSC on intestinal inflammation of IBD. These data suggest that IL-25 may be an attractive candidate for MSC-based therapy of IBD.
Emphasizing microbiota and genetic predisposition in IBD: Changes of colonic resistance and ACE genes’ I/D polymorphism

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Introduction: The role of gut microbiota and genetic predisposition become more appreciated in recent years emphasizing the IBD etiology and pathogenesis. However, exact mechanisms of interaction between immune system and microbiota remain to some extend unclear and, exact mechanisms that determine and provoke changes of colonic microbiota remain insufficiently discovered. Genetic predisposition to IBD is extensively discussed emphasizing microbiomics, immunobiomics, proteomics and metabolomics as well as changes of colonic resistance and permeability but it is still unknown if human genomic mechanisms may influence microbiota, not directly limiting to immune and inflammatory response. We hypothesized that several polymorphisms of angiotensin-converting enzyme (ACE) gene may induce morbid changes of colonic microbiota through changes of intestinal vascularization.

Methods: Totally 104 individuals participated in the study. Among them 34 had proven IBD (UC/CD in remission not less than 30 days), others with at least three risk factors for IBD (family history, smoking, antibiotics, travel history, immune, etc.). Diagnosis and management provided according to ECCO Guidelines. Standard microbiology techniques and PCR for insertion/deletion (I/D) ACE polymorphisms were used. Mesenteric vascular changes determined by plasma nitric oxide, ultrasonography and morphologically.

Results: ACE genes’ DD genotype was found in 29 (27.9%), ID in 56 (53.8%) and II in 19 (18.3%) cases. Respectively, for DD, ID, and II groups following values of statistical parameters (%) in prediction of grades III–IV of dysbiosis were calculated: specificity – 80.0, 73.1, 46.1; sensitivity – 30.8, 62.8, 6.4; accuracy – 43.3, 65.4, 16.3; efficacy – 55.8, 67.9, 26.3; prognostic value – 82.8, 87.5, 26.4. For II genotype RR of extremely heavy dysbiosis was 0.21–3.55, OR – 0.04–12.6 (95% CI). For ID genotype, RR – 0.82–1.40, OR – 0.29–7.53 (95% CI). For DD genotype, RR – 1.09–2.16, OR – 0.78–60.1 (95% CI, p = 0.031). Vascular changes correlated with D allele.

Discussion/Conclusion: Good predictive values were found for colonic microbiota changes in IBD in relation to ACE (I/D) polymorphism: presence of D allele (ID, DD genotypes) increases chances for significant dysbiosis 4.75 i 3.38 fold (OR = 12.7 and OR = 5.6, 95% CI OR = 1.06–62.6, p ≤ 0.031–0.0004). DD genotype carriers have the highest risk of decompensated microbiota violations. Traditional understanding of genetic factors’ role in IBD is limited to immune and cytokines’ response. This study points another possible genetically determined mechanism of microbiota changes in IBD.
The role of different E. coli variants emphasizing colonic inflammation: Breaking the mucosal barrier

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Introduction: It is generally accepted that mucosal microbiota plays an important role in pathogenetic cascade leading to colonic inflammation and development of IBD. However, therapeutic outcome in relation to microbiota is comparatively poor. Existing studies point on possible peculiarities of microbiota as an integral part of colonic inflammation involving the linkages of genomic, microbiomic, proteomic, and metabolomic factors acting both synergically and opportunistically. E. coli is often considered as a primary target for research, currently focusing on microbiome and potential influence on metabolomics. E. coli is one of the most diverse bacterial species with only 20% of the genes in a typical E. coli genome shared. Following this idea, we aimed on studying various variants of E. coli at inflamed colon as an important component of colonic resistance and its failure.

Methods: Totally 95 (mean 38.66 ± 3.11 years) individuals with different forms of chronic colonic inflammation (37 [38.95%] clinically proven IBD) and 58 healthy donors participate in the study. Colonic resistance studied in mucosal bioplates. Standard aerobic and anaerobic microbiology techniques with nosology identification and quantity composition of microbiota were used. Immunotyping (0, K, H antigens) and PCR (genomic study) were used for identification of E. coli variants.

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

Discussion/Conclusion: E. coli plays an important role in modelling both colonic resistance and immune response in both healthy and inflammatory conditions. This study confirms the role of microbiota in development of IBD. However, selected genes cannot explain E. coli influence on the mucosal barrier and wider range of genomics must undergo further research.
Combined use of pre- and probiotics therapy influence on both colonic resistance and clinical course in IBD

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Introduction: Colonic mucosal microbiota i.e. colonic resistance plays a pivotal role for the development of colonic inflammation, being reinforced by an explosively growing database demonstrating that the abnormal presentation and recognition of microbiota’ antigens by the innate immune system is one of the earliest events in the pathogenesis of IBD. A thorough review of the available sources shows that the current database is comparatively small; the variety of symbiotics makes it difficult to draw clinically relevant recommendations. Therefore, the aim of the study was to clarify the effect of combined pre- and probiotic use in IBD.

Methods: 95 patients and 87 healthy donors participate in the study. Colonic resistance studied in mucosal biopates obtained endoscopically. Standard aerobic and anaerobic microbiology techniques with nosology identification and quantity composition of microbiota were used. T73 strain of Propionibacterium Shermani with high antagonistic/immunoregulatory potential was orally given with inulin/fiber twice daily basis during 150–180 days in a form of suspension containing 10–15 lg/CFU bacteria. Patients without pre-/probiotic treatment formed control. Both groups’ patients received mesalazine 1500–3000 mg daily as a basis therapy. Treatment efficacy evaluated according to WGO Global Guidelines and included CDAI, SF-36 and IBDQ scores.

Results: Dysbacteriosis was diagnosed in 57.90% patients, dysbiosis in 42.11%. 63.16% subjects had 3rd and 4th degrees dysbiosis, 1st and 2nd degrees dysbiosis in 36.84% ( ² = 13.16; p < 0.001). Among healthy individuals Normal flora dominates in control group over dysbiosis of 1st and 2nd degrees (89.66% vs. 10.34%, p < 0.001). There were 16.67% and 22.22% recurrences requiring hospitalization during the study period. CDAI score at the end of study was 49.37 ± 3.14 points lower in study group (p < 0.05). SF-36 score difference between groups became 11.8 ± 0.84%. Abdominal pain, stool, and drug use for symptomatic therapies improved in study group, too. However, pre-/probiotic treatment did not influence anemia and other extra-abdominal symptoms. Endoscopic picture and biopsies presented no specific differences between groups after treatment.

Discussion/Conclusion: Pre/probiotic treatment is often accepted as a “folk” therapy of IBD. Our study shows underestimation of this technology as well as insufficient understanding of particular mechanisms determining both its usefulness and failure.
**Atg16L1 orchestrates interleukin-22-signalling in the intestinal epithelium via cGAS/STING**

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**Introduction**: Coding variants of the inflammatory bowel disease (IBD) risk genes *XBP1* and *ATG16L1* have been associated with defective autophagy, deregulation of endoplasmic reticulum (ER) function and impaired pathogen clearance. IL-22 is a barrier protective cytokine by inducing regeneration and antimicrobial responses in the intestinal mucosa.

**Methods**: Mice deficient for *Atg16l1* and both *Atg16l1* and *Xbp1* in the intestinal epithelium were generated (*Atg16l1\(^\Delta\)IEC, Atg16l1\(^\Delta\)IEC/Xbp1\(^\Delta\)IEC*) and treated with IL-22 over the course of 6 days every day or 14 days every other day, respectively. Histopathological analysis of ileal sections was performed. Small intestinal organoids derived from wildtype, *Xbp1\(^\Delta\)IEC, Atg16l1\(^\Delta\)IEC, Atg16l1\(^\Delta\)IEC/Xbp1\(^\Delta\)IEC, Tmem173(Sting)\(^{gt}\), Mda5-ko, Ripk3 \(^{\Delta}\)IEC, Ripk1\(^{D138N}\) mice were generated, treated with IL-22 (with or without autophagy blocking bafilomycin A1) and ISG induction, TNF\(\alpha\) production and cell death induction were assessed.

**Results**: Here, we show that *XBP1* and *ATG16L1* critically orchestrate beneficial IL-22 signaling in intestinal epithelium. IL-22 stimulation physiologically leads to transient ER stress, intracellular release of dsDNA and subsequent activation of the cGAS-STING pathway. In pathogenic ER stress conditions (either chemically induced or by loss of *Xbp1*), IL-22 amplifies UPR downstream proinflammatory signaling. Loss of *ATG16L1* exacerbates IL-22-induced ER stress and augments STING-dependent IFN-I responses in IECs. IFN-I amplifies epithelial TNF\(\alpha\) production downstream of IL-22 and leads to necroptotic cell death. Necroptosis in *Atg16l1*-deficient organoids
was rescued after anti-TNFα treatment. *In vivo*, IL-22 treatment in $\text{Atg16l1}^{\text{IEC}}$ mono- and $\text{Atg16l1}^{\text{IEC}}/\text{Xbp1}^{\text{IEC}}$ double knock-out mice potentiates endogenous ileal inflammation and causes widespread necroptotic epithelial cell death.

**Discussion/Conclusion**: These data suggest an unexpected role of IBD risk genes related to autophagy and ER stress, in particular *XBP1* and *ATG16L1*, in coordinating the outcome of IL-22 signalling in the intestinal epithelium.
Infection with Clostridium difficile in inflammatory bowel disease

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Introduction: Clostridium difficile infections (CDI) are increasing, causing 2 million deaths annually. CDI in patients with inflammatory bowel disease (IBD) may be associated with a negative prognosis, including prolonged hospitalizations, disease recurrence and colectomy.

The objective of this study was to evaluate the frequency of CDI among patients with IBD and also to assess the response to standard therapy.

Material and method: We performed a retrospective study conducted over a period of 2 years (January 2015 to January 2017) which included 13 patients with ulcerative colitis and Crohn’s disease admitted for infection with Clostridium difficile in the Institute of Gastroenterology and Hepatology, Iasi.

Results: The average age was 38.86 years. The frequency of Clostridium difficile infection in patients with inflammatory bowel disease was 4%. Clostridium difficile infection was more frequent in patients with ulcerative colitis – 11 patients (84.61%) compared to patients with Crohn’s disease – 2 patients (15.39%). Metronidazole therapy with 1.5 g/day orally was sufficient in 5 patients (35% of cases). In 8 patients (65% of cases) vancomycin 1 g/day was also needed.

Conclusions: Inflammatory bowel disease is a risk factor in the development of Clostridium difficile infection. In addition, the association of ulcerative colitis with Clostridium difficile infection is more common compared to Crohn’s disease. The average age of patients with inflammatory disease and C. difficile infection is lower compared to general population. The exclusion of Clostridium difficile infection is mandatory in patients with acute activity of inflammatory bowel disease.
Prebiotic influence on ulcerative colitis – Remission

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Introduction: Clinical and endoscopic effects of prebiotics in inflammatory bowel disease are controversial. Prebiotic inulin containing administration could be beneficial in patients with ulcerative colitis (UC) remission.

Aim: Prebiotic assessing treatment effect on remission of ulcerative colitis.

Material and method: We performed a retrospective study in the Institute of Gastroenterology and Hepatology Iasi. The study included 30 patients (17 men and 13 women with a mean age 53.3 years) diagnosed with moderate activity UC who initiated therapy between January 2016 and June 2016. Patients were divided into 2 groups according to the treatment followed. Patients in group A were treated with standard mesalazine (2–3 g/day), and those in group B with mesalazine (3 g/day) in combination with a prebiotic that contains inulin enriched with oligofructose, 1 administration per day for 6 months. We evaluated the therapeutic response, as quantified by UCDAI score (ulcerative colitis disease activity index) before and 6 months after initiation of treatment.

Results: Before initiating the treatment, both groups of patients had similar scores. UCDAI medium in group A was 8.74. In group B score was 7.84. After 6 months UCDAI average was 5.12 points in group A, compared to 3.18 points in the group treated with prebiotics (p < 0.01).

Conclusions: Our results demonstrated the superiority association with prebiotics mesalazine for the treatment of ulcerative colitis compared to monotherapy with mesalazine. Both clinical and endoscopic remission induction and for maintaining them while further studies are needed to deepen this topic.
Th17 cytokines in patients with ulcerative colitis

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Introduction: Ulcerative colitis (UC) is one of the main clinical forms of inflammatory bowel diseases (IBD). IBD fall into the class of autoimmune diseases affects gastrointestinal tract. The pathogenesis of UC remains unclear. Nowadays the role of T-helpers type 17 (Th17) as well as cytokines they release is being discussed in pathogenesis of autoimmune inflammation in UC.

Objective: To analyze the serum levels of cytokines released by Th17: interleukin (IL)-17A and F, 21, 22 in UC patients both in the acute stage of disease and remission compared to healthy controls.

Methods: A total of sixty eight UC patients were included into the study: forty eight patients had an acute stage of the disease and twenty patients considered as in remission. Serum cytokine levels were analyzed using multiplex immunoassay for Th17 cytokines (Bio-Rad). Statistical analysis was performed using Statistica 6.0 Software Package. The control group consisted of 11 healthy volunteers.

Results: Statistically significant results were determined concerning IL-17A and IL-21 both in acute stage and remission. Statistically significant increase of IL-17A level (15 pg/ml [12.11; 23.38]); 14.68 pg/ml [11.29; 17.19], respectively) was observed in patients with UC both in acute stage and remission compared to controls (7.36 pg/ml [5.18; 8.06], p = 0.00007, p = 0.00029, respectively). The same trend was observed regarding IL-21, which median values were higher both in acute stage (156.51 pg/ml [133.44; 233.53]) and remission (144.02 pg/ml [133.44; 154.43]) compared to control group (98.31 pg/ml [89.14; 124.86]), and showed statistically significant differences (p = 0.00077, p = 0.0054, respectively). Our study didn’t show any statistically significant differences regarding IL-17F and IL-22. It was revealed that IL-17F and IL-22 were also higher in acute stage (136.5 pg/ml [68.25; 228.185] and 3.76 pg/ml [1.5; 5.83], respectively) compared to controls (48.7 pg/ml [38.7; 87.6]; and 2.6 pg/ml [1.7; 3.2], respectively), however differences were not statistically significant (p = 0.06; p = 0.172, respectively).

Discussion/Conclusion: Increase of described cytokines levels could be a sign of Th17 functional overactivity suggesting autoimmune type of inflammation in ulcerative colitis. Th17 could play essential role in pathogenesis of UC. Among all cytokines released by Th17 levels of IL-17A and IL-21 were significantly increased in patients both in acute stage and remission in our study. Thus IL-17A and IL-21 might be considered as markers of active autoimmune inflammation in UC patients.
Olive leaf extract exhibits immunomodulatory activity in human PBMCs and antiinflammatory effect in the DSS model of mouse colitis

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Introduction: Olive tree (Olea europaea L.) is one of the most relevant botanical drugs in traditional Mediterranean Medicine, and olive leaf extracts have been used to treat different conditions, including hypertension, atherogenesis, hyperglycemia and hypercholesterolemia, due to its bioactive compounds. However, only one study has investigated its intestinal antiinflammatory properties. The aim of this work is to evaluate the intestinal antiinflammatory properties of an olive leaf extract (OLE) in the dextran sodium sulfate (DSS) model of mouse colitis, which resembles human inflammatory bowel disease.

Methods: Male C57BL/6J mice were assigned into five groups: non-colitic, colitic control and colitic treated groups with OLE (0.5 – 1 – 10 mg/kg). Colitis was induced by incorporating DSS (3%) in the drinking water for 5 days. The treatment started the same day of colitis induction, and was maintained for 7 days after the establishment of the colitic process. The inflammatory status was evaluated macroscopically, assigning a disease activity index (DAI), and biochemically by determining the colonic expression of mediators involved in the inflammatory response or in the intestinal epithelial barrier integrity. In addition, in vitro immunomodulatory properties of the extract were determined when incubated (0.1–100 μg/ml) with peripheral blood mononuclear cells (PBMCs) obtained from healthy and Crohn’s disease patients.

Results: The treatment with the extract improved the recovery of the colitic mice, since a significant reduction in DAI values was observed. This effect was associated with a reduced expression of colonic pro-inflammatory mediators (IL-1β, IL-6, TNFα, ICAM-1 and MIP-2), and an increased expression of key players of the intestinal epithelial integrity (occludin, ZO-1 and MUC-3). Besides, it displayed immunomodulatory properties in vitro since it decreased pro-inflammatory cytokines production in LPS-stimulated human PBMCs.

Conclusion: The olive leaf extract showed intestinal antiinflammatory activity in the DSS model of mouse colitis, maybe related to its antioxidant properties, which may result in the downregulation of the immune response and the improvement of the intestinal epithelial barrier integrity. In addition, this extract has a direct effect on human immune cells, as demonstrated in the in vitro studies.
Effect of resolvin D1 on the autophagy in mice experimental acute pancreatitis

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Introduction: Precise mechanisms of pathophysiology of acute pancreatitis (AP) are still unknown. Increasing evidences indicated that autophagy is involved in the development of AP. Resolvin D1 (RvD1), an endogenous anti-inflammatory lipid mediator derived from ω-3 polyunsaturated fatty acids, protects mice from cerulein-induced AP and activates autophagy in macrophages. Therefore, we aim to investigate effect of RvD1 on autophagy in experimental AP mice.

Methods: Adult male C57/B6 mice were randomly divided into control group, AP group and RvD1 group. RvD1 was given intraperitoneally to mice at 1 hour before and 3.5 hours during the induction of AP by 7 hourly intraperitoneally cerulein, simultaneously, control group received normal saline. The mice were sacrificed after completion of AP induction. Then, pancreatic and lung tissue, as well as serum were harvested for analysis. Levels of amylase and lipase in serum were measured by colorimetric method, pathological changes in the lung and pancreas observed by H&E staining. Autophagic expression of pancreatic tissue were performed using transmission electron microscope, quantitative RT-PCR and Western Blot.

Results: Levels of amylase and lipase were significantly increased in RvD1 group than AP group (p < 0.05). In addition, pathological staining showed less inflammation response of pancreas and lung in RvD1 group than AP group. Transmission electron microscopy revealed that AP group induces more and dramatically larger vacuoles than RvD1 group. Moreover, RT-qPCR and Western Blot exhibit that LC3-II, P62, and Beclin1 expression in the pancreatic tissue were significantly reduced in RvD1 group, compared with AP group (p < 0.05).

Discussion/Conclusion: These features suggested that autphagic flux is impaired in pancreatitis, besides, resolvin D1 can ameliorated the severity of cerulein-Induced AP in mice, attenuating the impaired autophagy and restoring autophagic flux.
Clinical analysis the levels of urinary sCD14 in ulcerative colitis

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Introduction: Soluble CD14 (sCD14) are significantly associated with inflammatory disease activity, which present in the body’s blood and urine. Increased plasma sCD14 levels in patient with inflammatory bowel disease, but less research about urinary sCD14 level in ulcerative colitis (UC) even though high excretion in urine and urine easier to access and safe. The aim of study was to investigate the clinical significance of urinary sCD14 level in patients with UC.

Methods: Concentrations of urine and plasma level of sCD14 was measured in 48 ulcerative colitis patients and 30 healthy controls by ELISA assay, and were analysis with clinical features for correlation.

Results: Compared with healthy control (0.10 ± 0.05 ug/ml), elevated urine levels of sCD14 was detected in patients with UC (0.37 ± 0.14 ug/ml),which reach the difference (t = 12.592, p < 0.05). Urinary sCD14 levels in active UC patients were higher than those in remission, and increased with the severity and range of the lesion. Besides, Urinary sCD14 levels was positively correlated to the level of CRP (r = 0.562, p < 0.05), and was statistically reduced after treatment.

Discussion/Conclusion: These data indicated that the level of urinary sCD14 has a certain clinical value in the diagnosis and evaluation of ulcerative colitis.
Lymphoid follicular proctitis: A case report and literature review

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Introduction: Lymphoid follicular proctitis (LFP) is a rare rectal benign lymphoid disease. Patient with LFP shows a special clinical, endoscopic, and histological features. The therapy of LFP was not identified [1] and we herein present a case of LFP resolved with administration of mesalazine enemas.

Case report: A 35-year-old man was admitted to our hospital with complaints of intermittent rectal bleeding, without diarrhea, fever, weight loss, or other systemic symptoms. The patient denied a history of sexually transmitted diseases and surgery. Colonoscopy revealed nodular mucosa with top pinpoint-like ulcer from rectum to the border between the sigmoid flexure and rectum. The nodulars congested together on the Lower rectal segment and occupied 2/3 lumina of rectum (Fig. 1a). Indigo carmine staining showed Pit Pattern II type (Fig. 1b). There were no abnormal findings above the rectum. Endoscopic ultrasonography (EUS) showed a thickening of the first and second layer of the rectal wall (Fig. 1c). Biopsy specimens disclosed some dense, abnormal lymphoid infiltrate (Fig. 1d), but Immuno-histochemical staining showed no malignant changes. To identify the diagnosis, endoscopic submucosal dissection (ESD) was performed (Fig. 1e) and histologic examination marked lymphoid follicular hyperplasia with reactive germinal center and preserved mantle zone. The lamina propria of the mucosa was normal (Fig. 1f). Crypt abscesses, ulceration or granulomas were not identified. DNA tests for Chlamydia, ureaplasma, cytomegalovirus, EBV were negative. The patient was diagnosed as LFP. Treatment was started with mesalazine enemas 4 g q.d. in a rectal suppository. After 3 days, the patient was asymptomatic. A sigmoidoscopy performed one week after the start of sulfasalazine treatment showed a slightly improvement of endoscopic findings and only few aphthous ulcer left on rectum 20 days later using a total colonoscopy. All the lesions disappeared 2 month later and histological exam from biopsy showed no evidence of hyperplastic or atrophic changes, cell necrosis and lymphocytes infiltration in the epithelium.

Discussion/Conclusion: Mesalazine enemas could be a promising therapeutic option for LFP therapy.

Reference:
Fig. 1 (a) Nodulars congested together on the lower rectal segment by conventional endoscopy. (b) Variably sized nodules can be detected after Indigo carmine spray. (c) EUS showed a thickening of the first and second layer of the rectal wall. (d) Biopsy specimens shows dense, abnormal lymphoid infiltrate (HE,×40). (e) ESD was performed. (f) Histologic examination of ESD specimen (HE,×80).
Increase in body mass index paralleled increasing the risk of relapse in Crohn’s disease patients with deep remission: A retrospective study

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Introduction: The effect of nutrition status on the long-term complications in Crohn’s disease (CD) patients with deep remission (DR) is unknown.

Methods: The primary outcome was the recurrence, the secondary outcome was the hospitalization, steroid use and surgery. The logistic and Cox regression were used to identify the risk factors predicting relapse, and the receiver operating characteristic (ROC) curve to identify an optimum cutoff value of ∆BMI.

Results: At deep remission, 39.6% CD patients were still underweight. During the median follow-up period of 19.6 months, 49.0% subjects had relapsed. In logistic regression model, BMI at initial visit and ∆BMI were associated with earlier CD flare (odds ratio [OR] = 0.866 [p = 0.034] and 1.280 [p = 0.038], respectively). The independent predictors of relapse were C-reactive protein (CRP) > 5 mg/l at DR (hazard ratio [HR] = 2.194, p = 0.020) and per unit absolute increase in ∆BMI (HR = 1.267, p = 0.017).

Discussion/Conclusion: A high proportion of CD patients with DR were still malnourished. BMI increment and elevated CRP were associated with earlier relapse, and patients absolutely increasing by 0.32 kg/m² in BMI were at high risk for relapse.
Diagnostic accuracy of serological markers in Chinese patients with Crohn’s disease

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Introduction: Crohn’s disease (CD) is difficult to distinguish from other bowel diseases. This study is to evaluate the clinical value of detecting serological markers in the diagnosis of Chinese patients with Crohn’s disease (CD).

Methods: A total of 63 Chinese patients with CD were enrolled as CD group and 10 healthy volunteers as healthy control group. The serum samples of both groups were collected. The serological markers including ASCA, AYMA, AYCA, CBir1, I2, OMPC and pANCA were determined with enzyme linked immunosorbent assay (ELISA). The sensitivity, specificity and positive predictive value of both groups were calculated. Chi square test or Fisher test was performed for data analysis.

Results: The sensitivity of ASCA-IgG, ASCA-IgA, AYMA, AYCA, I2,OMPC and pANCA in CD group were 33.3% (21/63), 14.3% (9/63), 7.9% (5/63), 3.2% (2/63), 3.2% (2/63), 1.6% (1/63) and 3.2% (2/63), while no person in the healthy control group were detected. There were significant differences between two groups (p < 0.05). The specificities and positive predictive values of these seven serological markers were 100.0%. The sensitivities of CBir1 was 26.7% (17/63) in CD group, while only one person was detected in healthy control group. The specificities and positive predictive values of CBir1 were 90% and 94.4%. There was no significant difference in the sensitivities of these serological markers between the subgroups of CD group (all p > 0.05).

Conclusion: All these serological markers have a higher specificity and positive predictive value, but their sensitivities is relatively low. The serum ASCA-IgG and ASCA-IgA have a higher sensitivities than other serological markers in the diagnosis of CD. However, these data should be validated in a larger cohort.

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Keywords: Crohn’s disease, serological markers.
Stool and serum angiogenic growth factors in children with active Crohn’s disease during exclusive enteral nutrition therapy

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Introduction: Exclusive enteral nutrition (EEN) is effective method of treatment of active Crohn’s disease (CD) in children and its postulated mechanism of action is connected with its anti-inflammatory activity. Angiogenic growth factors as transforming growth factor beta 1 (TGF-beta 1), vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) play important roles in the early stage of inflammation, stimulating angiogenesis and healing processes. The aim of our study was to assess the influence of the EEN on stool and serum TGF-beta 1, VEGF and FGF concentrations in children with active CD.

Methods: Twenty children with CD and 18 healthy controls were enrolled into the study. Stool and serum TGF-beta 1, VEGF and FGF concentrations were assessed at the baseline and after 1, 2 and 3 weeks of EEN using ELISA immunoassays.

Results: We found increased serum VEGF concentrations in CD group at the baseline and after 1 and 2 weeks of EEN when compared to controls (p < 0.05) followed by a decrease after 3 weeks, while stool VEGF concentrations were comparable to controls during whole study. Assessing serum TGF-beta 1 and FGF concentrations in CD group, we found them comparable to controls at the baseline, increased after 1 and 2 weeks (p < 0.05) and decreased after 3 weeks. During EEN we observed higher increase of TGF-beta 1 and FGF concentrations after 1 and 2 weeks in stool (4-fold and 5-fold, respectively) than in serum (both 2-fold). We found correlation of serum VEGF and pediatric Crohn’s disease activity index (PCDAI) (R = 0.94; p < 0.05) and C-reactive protein (CRP) (R = 0.93; p < 0.05).

Discussion/Conclusion: TGF-beta 1 and FGF mainly showed local activity in inflamed intestine during EEN, while VEGF has more general activity. Differences of stool and serum angiogenic concentrations during EEN in active CD in children may reflect different mechanisms of action of EEN on the inflammatory process.
Association of Card9 gene polymorphisms and ulcerative colitis in Chinese Han and Uyghur population

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Introduction: CARD9, a caspase recruitment domain-containing signaling protein, is one of the central regulators of innate immunity. It has been reported as one of the candidate genes susceptibility loci associated with inflammatory bowel disease (IBD) in western country. The aim of this study was to assess the effect of genetic variants of Card9 on UC between Chinese Han and Uyghur population.

Methods: Sixty-two UC patients, 21 Uyghur and 41 Han population in Xinjiang province were recruited. Prevalence of polymorphisms of three Card9 SNPs (rs4077515, rs10781499 and rs10870077) was investigated by touch-down nested polymerase chain reaction amplification. The impacts of these SNPs on the patients' phenotype were assessed.

Results: A set of comparisons assessed the prevalence of CARD9 polymorphisms in Han and Uyghur patients with UC (Table1). A one-to-one correspondence was found between polymorphisms of rs4077515 and rs10781499 in each individual. The distributions of SNP rs4077515 and rs10781499 are exactly the same in both populations. No significant difference of the Card9 polymorphisms in ulcerative colitic patients between Han and Uyghur population was found.

Discussion/Conclusion: Although some risk genes polymorphisms associated with inflammatory bowel disease were different in different populations, Card9 polymorphisms in susceptibility to ulcerative colitis is same between Han and Uyghur population.
All-trans retinoic acid inhibits the development of murine colitis-associated colorectal cancer

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Introduction: Colitis-associated colorectal cancer (CACRC) is a serious complication of inflammatory bowel disease. Traditional chemopreventive agents are expensive and have obvious side effects. All-trans retinoic acid (ATRA) is a natural metabolite of vitamin A which plays roles in many physiological processes. Previous study indicated that ATRA not only ameliorated inflammation but rather inhibited cancers including colorectal cancer, while little was known about CACRC.

Methods: In this experiment we adopted classical AOM/DSS induced murine CACRC model. Mice were divided into four groups: control group, model group, ATRA200 group and ATRA500 group. ATRA was given by gavage from the use of AOM (10 mg/kg) to the end of the study (three times per week; single dose was 200 ug and 500 ug for ATRA200 group and ATRA500 group respectively). We determined the expressions of proinflammatory mediators and oncogenes in colonic neoplastic tissues by RT-qPCR. Several major retinoic acid receptors (RARs) were also determined through RT-qPCR and western blot analyses.

Results: Both ATRA groups had decreased tumor numbers, colonic disease activity index scores and increased colon length in comparison with the model group. Besides, ATRA reduced the levels of proinflammatory mediators (TNF-α, IL-1β, IL-6, IL-11, COX-2 and iNOS) and oncogenes (PCNA and β-catenin) compared with the model group. RARs (RARα, RARβ and RXRα) were downregulated in the model group, while upregulated in the two ATRA groups compared with the model group.

Discussion/Conclusion: These results suggested that ATRA could inhibit the development of murine CACRC through depressing the expressions of pro-inflammatory mediators and increasing the expressions of RARs.
Treatment strategies influence the bacterial microbiota in IBD patients

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Introduction: The microbial dysbiosis plays a pivotal role in the pathogenesis of inflammatory bowel disease (IBD). However, the effect of treatment strategy on microbiota was unclear. This study aimed to clarify the bacterial composition in IBD patients with different treatment strategies.

Methods: 73 IBD patients were divided into three different groups, untreatment (U, n = 21), antiinflammation (A, n = 43) and immunosuppression (I, n = 9). Antiinflammation was defined as treatment with 5-ASA/SASP and immunosuppression as treatment with GC, AZA, biologics and thalidomine. Non-inflamed (N) and inflamed (L) were acquired for 16S sequencing to investigate the bacterial composition.

Results: Treatment didn’t significantly alter the bacterial richness and evenness (Figure 1A). The beta diversity analysis showed a clustering according to sampling location and treatment strategy (Figure 1B). Three main phyla constituted the gut microbiota, Firmicutes, Bacteroidetes and Proteobacteria. We found an increase of Proteobacteria in untreated non-inflamed and inflamed mucosa (Figure 1C and 2). Compared with non-inflamed mucosa, the abundance of Firmicutes increased and Proteobacteria decreased in inflamed mucosa, while treatments increased Proteobacteria abundance to a level almost equal to non-inflamed mucosa. Thus we infer that non-inflamed mucosa was susceptible to colonize Proteobacteria, which triggered host immune reaction and induced mucosal inflammation. Adversely, activated immune system and inflammatory reaction suppressed Proteobacteria colonization at inflamed mucosa. Treatment suppressed immune system, which offered a shelter for Proteobacteria to colonize at “non-inflamed” mucosa (transformed from inflamed mucosa). Additionally, antiinflammation partially increased the abundance of Dorea and butyrate-producing bacteria, immunosuppression increased Bacteroides. Notably, Immunosuppression decreased Fusobacterium, Ruminococcus and Dorea in both non-inflamed and inflamed mucosae.

Discussion/Conclusion: Non-inflamed mucosa was susceptible to colonization of Proteobacteria, treatment altered the colonization of Proteobacteria. To some extend, immunosuppression aggravated gut microbial dysbiosis, while antiinflammation partially ameliorated it in IBD patients.
Figure 1: Treatment altered bacterial microbiota beta diversity and abundance.

Figure 2: Treatment changed bacterial composition
Results and predictors of outcome of endoscopic balloon dilation of colonic strictures in inflammatory bowel diseases

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Introduction: Endoscopic balloon dilation represents a therapeutic alternative in patients with inflammatory bowel disease that have colonic symptomatic strictures. The aim of this study was to analyze the outcomes and to identify the predictors of success of endoscopic colonic dilation.

Methods:
Inclusion criteria: Patients having inflammatory bowel disease with colonic stenosis treated by endoscopic balloon dilation from 2000 to 2015 were enrolled. Patients with a follow up lower than 6 months were excluded.

Criteria defining dilation failure: Failure of endoscopic balloon dilation was defined by the need to recourse to a second session or to surgery within six months after the first session of dilation.

Results: During the study period, 31 dilations have been performed among 18 patients (mean age 49.6 years old and sex ratio of 1,2). Three patients had ulcerative colitis while fifteen had Crohn’s disease since an average duration of 10 years.
Endoscopic treatment was successful in 72% in our cohort after a follow up of 18 months (6–48 months). Six patients needed more than one dilation (2–5 dilations), while 2 needed a surgical removal of the stricture. No complication occurred in our study.
In univariate analysis, predictors of outcome of endoscopic balloon dilation were: the age lower to 60 years, an inflammatory stricture, a disease that has been evolving for less than 5 years, a high balloon pressure, the association to a systemic treatment and an elevated level of the C reactive protein. In multivariate analysis, no factor was identified as an independent predictor of outcome of endoscopic balloon dilation.

Conclusion: Endoscopic balloon dilation of stricture during inflammatory bowel disease represents a safe alternative to surgery with a success rate of 72%. It should be privileged in young patients with an inflammatory stricture. It has a better outcome when done with a high balloon pressure and when associated to other therapeutic measures.
Diagnostic utility of the serological biomarkers in patients with Crohn’s disease in China

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Introduction: Yet, a conclusive plan of action cannot be devised from current findings which suffer from small sample sizes, particularly with studies conducted in China. Furthermore, studies examine only a limited range of serological markers and demonstrate a low positive response rate (such as ASCA) in clinical practice as opposed to trials. In light of these prevalent issues, the multi-center study presented herein discuss the utility of several blood-based markers in the proper diagnosis of CD.

Methods: The presence of antibodies against outer membrane porin C (anti-OmpC), Pseudomonas fluorescens bacterial sequence I2 (anti-I2), anti-laminarin (anti-L), anti-chitin (anti-C), anti-chitobioside (ACCA), anti-laminaribioside (ALCA), anti-mannnobioside (AMCA), and anti-Saccaromycescervisiae (ASCA) were tested in serum samples from 160 participants, of which 98 were diagnosed with CD, 33 with ulcerative colitis (UC) and 29 healthy controls by enzyme-linked immunosorbent assay (ELISA) in Eastern China.

Results: Anti-C, anti-L, ASCA-IgG and ALCA lack diagnostic value to differentiate CD in this study. ASCA-IgA remained the most accurate for the diagnosis of CD with an AUC of 0.777. When the five markers which offered significant diagnosing ably for CD were combined, the use of four markers was found to have the highest predictive accuracy for with a specificity and PPV of 87.3% and 85.1%, respectively, and an AUC of 0.754.

Discussion/Conclusion: Serological antibodies have a remarkable worth and four of the five markers ASCA-IgA, AMCA, ACCA, anti-OmpC and anti-I2 postive is the best combination in differential diagnosis of CD.
Infliximab therapy, tuberculosis disease burden, and latent tuberculosis infection among patients with inflammatory bowel disease in China: A retrospective multicenter study

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Introduction: The higher risk of tuberculosis (TB) after anti-tumor necrosis factor (TNF) therapy in TB high-prevalence countries have been reported. Whether the risk factors and the strategies for decrease the risk vary in different TB burden countries remain unclear. This study investigated the incidence of and risk factors for TB activation among inflammatory bowel disease (IBD) patients receiving IFX therapy in China, a country with high TB burden in the world, and assessed whether prophylaxis for TB reduces this risk.

Methods: The medical records of IBD patients receiving IFX between 2007 and 2017 at 22 tertiary referral hospitals were analyzed retrospectively. The incidence rates of active TB after IFX therapy were calculated. Factors analyzed included screening for latent TB infection (LTBI) and anti-TB prophylaxis.
Results: Of 1711 IBD patients receiving IFX, 1556 (90.9%) had Crohn’s disease and 155 (9.1%) had ulcerative colitis. Seventeen patients (0.99%) developed active TB (all pulmonary TB). The incidence of TB in the study population was 9 times that in the general Chinese population (691 vs. 67 per 100,000 person-years). Of the 1711 patients, 121 (7.07%) were positive for LTBI. The incidence of TB was significantly higher for LTBI-positive than for LTBI-negative patients (6.61% [8/121] vs. 0.57% [9/1590], p < 0.001) and LTBI was an independent risk factor for TB activation (OR = 11.89; 95% CI: 3.90–36.26; p < 0.001). Anti-TB prophylaxis reduced risk of active TB in patients with baseline LTBI positivity (18.52% [5/27] vs. 3.19% [3/94], p = 0.014), but not negativity (1.06% [4/376] vs. 0.41% [5/1209], p = 0.23).

Discussion/Conclusion: IFX increased the risk of TB for IBD patients in China. LTBI is an independent risk factor for active TB and anti-TB prophylaxis can reduce, but not eliminate such risk. LTBI screening and chemoprophylaxis for patients positive for LTBI prior to IFX are recommended for IBD patients in high TB burden areas. However, anti-TB prophylaxis may not benefit patients negative for LTBI prior to IFX.
Thiopurine S-methyltransferase activity analysis in patients with inflammatory bowel diseases

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Introduction: Inflammatory bowel diseases (IBD) nowadays are widely treated with thiopurines. Thiopurine S-methyltransferase (TPMT) and inter-individual variability of TPMT activity affects therapy efficiency and drug toxicity. Reduced TPMT activity is associated with thiopurines induced adverse effects like myelosuppression, hepatotoxicity and pancreatitis, which are leading to life threatening complications. The very high TPMT activity is showing decreased response on thiopurine therapy. The aim of the present study was to evaluate the pretreatment TPMT status in IBD patients as part of therapeutic drug monitoring.

Methods: A prospective pilot study included 20 patients (55% female n = 11 and 45% male n = 9) having an age ranging from 22 to 79 years. All participants where admitted to Pauls Stradins Clinical university hospital (Riga, Latvia) from January 2017 to May 2017. All included patients received standard treatment of 5-aminosalicylic acids, steroids or azathioprine. The expression of TPMT in each blood sample was analyzed using ELISA (MyBioSource, USA) method.

Results: All patients were previously diagnosed with IBD and were admitted to hospital due to of exacerbation of IBD. 70% of patients (n = 14) was diagnosed with ulcerative colitis (UC), 30% (n = 6) with Crohn’s disease (CD). 75% (n = 15) of patients had not previously received azathioprine. 15% (n = 3) had received azathioprine therapy, but stopped using it due to side effects like acute pancreatitis, rash or symptoms of exacerbation. 10% (n = 2) were still receiving azathioprine therapy. Activity of TPMT was low (< 5.5 U/ml) in 10% of patients (n = 2), average (5.6–15.5 U/ml) in 5% (n = 1), normal (15.6–29.9 U/ml) in 35% (n = 7) and too high (> 30.0 U/ml) in 50% (n = 10).

Discussion/Conclusion: The results of this study confirmed the important role of the TPMT enzyme activity in the therapeutic drug monitoring and managing life threatening complications. Further studies in combination with TPMT genotyping are necessary for additional evaluation of treatment risks.
Chronic circadian desynchronisation worsen DSS-induced colitis by decreasing colon mitochondrial energy metabolism in mice

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Introduction: The study aims to investigate the effect of chronic circadian desynchronization on colon mitochondrial energy metabolism and if circadian desynchronization worsen colitis by regulating mitochondrial energy metabolism.

Methods:
Part I: 6 week old male C57 bl/6J mice were randomly assigned to 2 groups: (1) normal-light-dark (LD) cycle (non-phase shift); (2) chronic-circadian-desynchronization (phase shift): 6-h advance of the LD cycle every 3 days and lasted 5 cycles. Mice in each group were separately sacrificed at ZT4, ZT10, ZT16, ZT22. HE staining of colon tissue was performed. Examined colon mRNA of TNF-α, IL-6, Bmal1, clock, Per1, Per2, Cry1, Cry2, Rev-erbα, Ogdh, Idh3b, Uqcrcl, Cox7b, Pgc-1α by RT-PCR. Mitochondrial total protein, NADH, NAD+ and ATP in colon tissue was detected.

Part II: C57 bl/6J mice were randomly assigned into 3 groups: (1) non-phase shift; (2) non-phase shift + DSS; (3) phase shift + DSS. Colitis was induced with 2.5% DSS from last 7 days, weight change and stool features were observed. ATP was detected.

Results:
Part I: (1) Both group exhibit no significant difference on body weight or colon histological damage. (2) Transcription of Bmal1, Clock, Per1, Per2, Cry1, Cry2, Rev-erbα exhibit rhythmicity in non-phase shift mice, whereas the rhythmicity changed in phase shift mice, transcription level of clock increased and Cry1, Cry2, Per2 reduced. (3) Transcription of Ogdh, Idh3b, Uqcrcl, Cox7b, Pgc-1α exhibit rhythmicity in non-phase shift mice, whereas the rhythmicity changed and transcription level decreased in phase shift mice. (4) Mitochondrial total protein, NADH, NAD+ and ATP reduced in non-phase shift mice.

Part II: (1) Body weight, DAI scores and histopathology scores indicate that circadian desynchronization worsen DSS-induced colitis in mice. (2) ATP reduced significantly in non-phase shift DSS mice and further decreased in phase shift DSS mice.

Discussion/Conclusion: Chronic circadian desynchronization decrease colon mitochondrial energy metabolism and worsen DSS-induced colitis by decreasing mitochondrial energy metabolism in mice.
The pathogenic mechanism of aryl hydrocarbon receptor-mediated abnormal differentiation of intestinal ILC3/ILC1 in Crohn’s disease

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Introduction: The abnormal differentiation of intestinal innate lymphoid cells ILC3 and ILC1 exist in autoimmune disease. ILC3 decreased and ILC1 increased in Crohn’s disease (CD) patients, suggesting that CD patients have abnormal intestinal ILC3/ILC1 alteration, but the mechanism of abnormal alteration of ILC3/ILC1 keep unclear. The present study investigated the aberrant colonic mucosal ILC3/ILC1 in active CD patients and 2,4,6-trinitrobenzene sulphonic acid (TNBS)-induced colitis mice.

Methods: The expressions of aryl hydrocarbon receptor (AhR) in colon of active and quiescent CD patients were detected by western blot and immunofluorescence. The ILC3/ILC1 were investigated in CD patients and TNBS-induced colitis mice (AhR−/−, AhR+/+).

Results: Compared to quiescent CD patients, the expression of aryl hydrocarbon receptor (AhR) in the intestinal tissue in active CD patients was decreased. Meanwhile, the number of ILC3 in active CD patients and AhR knockout mice was decreased while ILC1 increased. The intestinal inflammation in AhR knockout mice given TNBS was more severe than wild type mice.

Discussion/Conclusion: These findings suggest that AhR may mediate abnormal differentiation of ILC3/ILC1, and the production of inflammatory cytokines, finally, promotes the pathogenesis of CD.
The alterations of Th17/Treg cells in peripheral blood and serum inflammatory biomarkers in patients with Crohn’s disease and its clinical significance

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Introduction: The aim of our study is to investigate the alterations in frequency of regulatory T cells (Treg) and T helper 17 (Th17) cells in peripheral blood in patients with Crohn’s disease (CD) and the relationship between the proportion of Treg cells and clinical features of CD.

Methods: Forty-six patients with CD (31 quiescent and 15 active CD patients) were enrolled in our study. Eight cases who had their gastrointestinal polyps treated and will have gastrointestinal endoscopy to check as normal controls. The disease activity of CD was evaluated by crohn’s disease activity index (CDAI). Concurrently, blood platelet (PLT), mean platelet volume (MPV), platelet distribution width (PDW), erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) level were measured. The percentage of Treg and Th17 cells in peripheral blood from CD patients and control group were detected by flow cytometry.

Results: In peripheral blood, the proportion of Treg cells in active CD patients was significantly decreased compared with patients in remission and control group (p < 0.05). Compared with quiescent CD patients, active CD patients had higher percentage of Th17 cells in peripheral blood (p < 0.05). ESR and serum CRP levels increased and MPV obviously decreased in active CD patients compared to quiescent patients. Negative correlation was found between proportion of Treg cells and ESR, serum CRP levels as well as CDAI (p < 0.05). In addition, there was a positive correlation between the proportion of Treg cells and MPV (p < 0.05).

Discussion/Conclusion: The change of proportion of Treg and Th17 cells in peripheral blood and the relationship between the proportion of peripheral Treg and serum inflammatory biomarkers reflecting CD activities (e.g., CRP, ESR and MPV) indicated that the differentiation imbalance of Th17/Treg was involved in the pathogenesis of CD.
Introduction: Dendritic cells (DCs) failure to silence the immune system can lead to ulcerative colitis (UC). The type of immune response depends upon the maturity of DCs. Immature DCs have the function of inducing immune tolerance through promoting the balance of Th17/Treg. Th17 secretes proinflammatory cytokine IL-17. IL-10 is an immunosuppressive cytokine produced by Treg. Paeoniflorin (PF) is a monoterpenoid glucoside, which is the principal bioactive component of the paeony root. Paeony is widely used in Chinese clinics to treat UC. However, the mechanisms underlying the anti-inflammatory effect of PF remain unclear. The aim of this study was to explore the effect of PF on the maturation and immunostimulatory function of DCs.

Methods: Surface antigen expression of DCs (MHC II, CD80 and CD86) and cytokine (IL-12), as indicators of mature DCs after LPS stimulation in the absence or presence of PF at different doses, was detected. Then, the effect of PF-treated DCs on T cells and TNBS-induced colitis in mice was observed.

Results: PF inhibited the up-regulation of MHC II, CD80 and CD86, decreased IL-12 secretion, in vitro and in vivo. DCs exposed to PF had diminished capacity to stimulate Th17 proliferation and decreased expression of IL-17mRNA, while induced CD4⁺CD25⁺Foxp3⁺ Treg differentiation from naive CD4⁺ T cells and increased production of IL-10 mRNA. PF and PF-treated DCs reduced gene and protein expression levels of IL-17, IL-12; elevated IL-10, Foxp3 levels and lowered Th17 proportion in mice.

Discussion/Conclusion: These results suggest that PF can treat UC effectively through inhibiting maturation of DCs and thus decreasing the capacity of DCs to stimulate Th17/Treg differentiation.
Significantly decreased colonic ERβ in immune cells may contribute to the disease progression in a murine colitis model

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Introduction: The precise cause of inflammatory bowel diseases (IBD) has not yet been fully elucidated. Estrogen receptor beta (ERβ), is highly expressed in intestinal tract, has been suggested to exert anti-inflammatory effect. The aim of this study was to evaluate the role of ERβ in the pathogenesis of IBD by a murine colitis model.

Methods: Murine colitis was induced by administrating 3% DSS in the drinking water for seven days. Body weight and stool were recorded every day. Colon length, Inflammatory Disease Activity Index (DAI) and histology were detected. Colonic ERβ and its mRNA level were examined by western blot and quantitative real-time PCR respectively. CD4+ T cells, CD8+ T cells, B cells, macrophage and dendritic cells of the spleen, mesenteric lymph nodes, intestinal epithelium and lamina propria were examined by flow cytometry. ERβ expression in these immune cells was examined by flow cytometry.

Results:
1. Compared with normal mice, the body weight, colon length and DAI scores were significantly different in colitis mice (p < 0.05).
2. Significant decrease in the expression level of protein and mRNA of ERβ in the colitis colon were observed (p < 0.05).
3. The infiltrated CD4+ T cells and CD8+ T cells in lamina propria of colitis mice were dramatically increased (p < 0.05).
4. Various decline of the expression level of ERβ in CD4+ T cells, CD8+ T cells, macrophages and dendritic cells from spleen, mesenteric lymph nodes, intestinal epithelium and lamina propria in colitis mice were observed (p < 0.05).

Discussion/Conclusion: Our study suggests that significantly decreased colonic ERβ may contribute to the disease progression in a murine colitis model.
Estrogen receptor beta alleviates DSS-induced colitis by inhibiting the expression of phosphorylated mTOR

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Introduction: The aim of this study was to explore the possible protective mechanism of estrogen receptor beta on mice colitis by regulating the expression of phosphorylated mTOR (p-mTOR).

Methods: Six to eight weeks C57 mice were randomly divided into three groups. Group I was given normal drinking water; Group II received 2.5% DSS drinking water; Group III was given 2.5% DSS drinking water + ERB-041 10 mg/kg/day by gavage. The expression levels of RNA and protein were detected in colon tissues after sacrifice of mice.

Results: The body weight of group II decreased significantly, and group III was improved than group II. Group II had more serious blood stool than group III. After the mice were sacrificed, the colon length was found to be 7.6 ± 0.42 cm in group II, 5.95 ± 0.75 cm in group II and 6.86 ± 0.26 cm in group III, and the difference was statistically significant (p < 0.05). Group II had a higher degree of inflammation than the group III regarding to histological score of colon. The levels of estrogen receptor beta mRNA and protein, NDUFS mRNA and Occludin mRNA in group II were significantly decreased, and the expression of group III was higher than that of group II (p < 0.05). P-mTOR, STAT3 protein levels and PDH, LDH, ACC1, TNFα, IL-1β, IL-6, IL-10 mRNA levels in group II were significantly increased, group III decreased (p < 0.05).

Discussion/Conclusion: Estrogen receptor beta agonist alleviates DSS-induced colitis by reducing the expression of p-mTOR in colon of mice, which may increase the level of oxidative phosphorylation, decrease glycolysis and fatty acid oxidation to improve intestinal energy metabolism, increase energy production and protect the intestinal mucosal barrier.
GTS-21, α7 nicotinic acetylcholine receptor agonist, attenuate DSS-induced colitis by improving intestinal mucosal barrier function

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Introduction: In this study we investigate whether GTS-21 protects against DSS-induced colitis and its potential mechanism.

Methods: Male BABL/c mice (6–8 weeks old, n = 32) were randomly divided into 4 groups: DSS group was given final concentration of 3.5% DSS drinking water, the GTS-21 group was treated with GTS-21 (20 mg/kg i.p.) per day, α-BGT group was pre-treated with α-BGT (0.1 mg/kg/day, i.p.) for 30 min prior to GTS-21 injection and the control group received saline. Caco2 cells were divided into 4 groups: TNF-α group of Caco2 cells were exposed by 25 ng/ml TNF-α, GTS-21 group were given 100 ng/ml GTS-21 for 30 min prior to TNF-α; α-BGT group pre-treated with α-BGT (50 ng/ml) for 30 min prior to GTS-21 injection. DAI and HAI were determined. The intestinal permeability of mice was measured by FITC-Dextran method. Western blot was used to detect the tight junction protein and NF-κB associated protein expression.

Results:
1. Compared with DSS-induce mice, DAI score decreased and colon length improved after administration of GTS-21, HAI decreased. α-BGT can eliminate those protective effects.
2. The intestinal permeability improved after administration of GTS-21 compared with DSS-induced mice whereas α-BGT can block this protection.
3. The expressions and distribution of tight junction protein in DSS-induced mice were enhanced after treatment with GTS-21.
4. GTS-21 attenuated the NF-κB activation. α-BGT administration reversed the inhibitory effect of GTS-21.
5. GTS-21 improves the distribution of tight junction proteins in the intestinal epithelial cells induced by TNF-α.
6. GTS-21 reduces nuclear translocation of NF-κB in Caco2 cells induced by TNF-α.

Discussion/Conclusion: GTS-21 can attenuate the intestinal inflammation in DSS-induced mice, which may be due to improving intestinal mucosal barrier function by enhancing the expression of tight junction protein.
Modulation of immune cell composition and epithelial barrier function by leptin in a patient with acquired generalized lipodystrophy and combined Crohn’s disease

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Introduction: Leptin has been implicated in shaping inflammation in various animal models including colitis. The existence of creeping fat in IBD makes it likely to play a role in human disease as well. However, the immune-modulatory role of Leptin on human lymphocyte and epithelial barrier function in IBD is still unknown. We here investigated for the first time the in-vivo impact of recombinant Leptin treatment on immune cell composition and intestinal barrier function in a patient with acquired generalized lipodystrophy (AGL) and combined Crohn’s disease.

Methods: Multi-panel immune phenotyping of PBMCs and lamina propria cells of the AGL patient before and after leptin treatment was performed by CyTOF, FACS and CBA analysis and compared to healthy individuals and CD patients. Seahorse analysis and Ca²⁺ influx measurements assessed the metabolic capacity and activity of immune cells. Wound healing was investigated using a scratch assay.

Results: We found that leptin is required for the maintenance and expansion of natural killer cells and dendritic cells as we observed reduced frequencies of CD56⁺ NK cells and CD11c⁺ dendritic cells in the AGL patient before leptin substitution. Furthermore, CD8⁺ and monocytic cells accumulated lipid droplets metabolically impairing their function. Remarkably, treatment with recombinant leptin increased the amount of TNFalpha producing cells and induced expression of perforin in cytotoxic lymphocytes in-vivo. Additionally, leptin treatment increased serum levels of several cytokines required for epithelial barrier function and wound healing including TGFbeta and IL-8. Subsequently, we obtained first in-vitro evidence that leptin directly promotes wound healing of epithelial cells.

Discussion/Conclusion: Our results show that, in humans, leptin is important for NK and dendritic cell proliferation, development and function. Via TGFbeta and IL-8, it might also have an influence on mucosal healing and barrier function.
Usefulness of TNBS colitis in inflammatory bowel diseases

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Introduction: To establish a standard model of 2,4,6-trinitrobenzenesulfonic acid (TNBS) colitis in the rat miming inflammatory bowel diseases (IBD) lesions and used this model to investigate the anti-inflammatory effect of the Pistacia Lentiscus oil.

Methods: Forty male Wistar rats, weighing 320–400 g, were recruited and divided into 4 groups. Groups were categorized based on the delay between TNBS administration and the day of sacrifice: 3, 7, 15 or 30 days after ethanol or TNBS administration in groups 1, 2, 3 and 4 respectively. The second part of this study consist of induced TNBS colitis of 5 rats received Lentisc oil 2 months before colitis induction (preventive group), 5 rats received the oil on the day of colitis induction (curative group) and 5 control rats.

Results: In all TNBS groups, severe and intense transmural inflammation, epithelial change and ulceration were observed and the difference was significant compared to the control group. The comparison between TNBS treated rats was observed noticeable inflammation, erosion and extensive lesions in group 1 but mucosal architecture was normal. The chronic lesions with modifications of mucosal architecture were observable in groups 2, 3 and 4. The difference is more significant between groups 1 and 3 (p = 0.005).
Rats received lentisc oil had disappearance of erosion, decreased of cryptitis, irregular crypts and crypt loss and the difference was significant compared to the control group. There was an attenuation of inflammation in the preventive group compared to the curative group without statistically significant.

Discussion/Conclusion: With a single dose of TNBS, we demonstrate that the ideal experimental model to mimic IBD with chronic lesions would be the seventh and fifteenth day after TNBS administration. Lentisc oil administration could provide a protective effect on intestinal inflammation in TNBS colitis rats. This beneficial effect would involve a modification of arachidonic acid metabolism.
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