Abstracts of Invited Lectures
Poster Abstracts

Symposium 206

FROM THE NEW AND COMPLEX CONCEPTS TO THE REAL PATIENT: SCIENCE AND CLINIC IN IBD

Madrid, Spain
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Scientific Organization:
S. Danese, Milan (Italy)
A. Dignass, Frankfurt (Germany)
J.P. Gisbert, Madrid (Spain)
F. Gomollón, Zaragoza (Spain)
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Session I

From basic to clinic
Genes: So complex

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The study of the genetic underpinnings of inflammatory bowel disease (IBD) has made great progress since the identification of NOD2 as a major susceptibility gene. Genotyping and sequencing technologies led to the discovery of over 240 common susceptibility loci, highlighting some major disease-associated pathways (innate immunity, autophagy, intestinal barrier function...). This knowledge provided new insights in the continuum of CD and UC, the genetic overlap with other immune-mediated diseases and genetic architecture of IBD. Part of the susceptibility loci (45) have been fine-mapped to the statistically conclusive causal variant(s). However, many causal genes/variants have yet to be identified, and there is still a large proportion of missing heritability to be accounted for. Besides common variants, rare variants associated with the disease are increasingly being identified. The main conclusion of these studies however appears to be that the overall contribution of these low frequency high-risk variants to IBD risk is likely to be only modest.

We will discuss these different points, and will finish by some suggestions how we can use genetics in the clinic, and topics for future research in the field of IBD genetics to fully harness the power of the genetic discoveries.
Epigenetics in IBD

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Epigenetic modifications can regulate nucleosomal arrangement around DNA and thus determine patterns of gene activity. They typically arise from environmental influence on slowly evolving genomic DNA and have the capability to induce specific long-term phenotypic consequences. While some of these modifications are inheritable others may subsist the causative environmental influences only by a short time frame.

The concept of epigenetics has been brought to life in simple model organisms such as flies, plants, worms, yeast or ciliated protozoans, which however in many aspects are not reflecting human biology. In human disease the epigenetic machinery has become a popular concept to explain the endurance of tumor cells and some of the concert of dysregulated gene silencing and activation seen in such cells. While epigenetic mechanisms are most frequently discussed as synonymous with DNA methylation many more epigenetic targets exist including methyl-CpG-binding proteins, transcriptional repression complexes, histone modifications that mediate gene repression/relaxation, core stability or linker flexibility, and alterations in nucleosomal remodeling complexes, HP1 and nuclear lamins.

In theory, IBD should represent a condition in which epigenetic modifications could play an important role in disease pathogenesis. The epithelial interface to the gut lumen is the point of interaction with aggressive molecules that are introduced directly (e.g. smoking) or result from processing by the microbiome. However, the large variance in disease pathophysiology on the background of both human diversity and an extremely polygenic disease etiology makes it difficult to detect clear epigenetic signatures. In addition it may be important to restrict the epigenetic interpretation to specific cells and not the summary of events and tissues represented in biopsies. In studies in human discordant, monozygotic twins it became clear that such epigenetic signature exists. Interestingly disease associated epigenetic variations affect many pathways that regulate epithelial cell renewal and differentiation. Moreover, many epigenetic target genes in disease overlap with genes identified as genetically associated disease genes demonstrating the crucial importance of the originating pathways in maintenance of an intact barrier function. A crosstalk between patterns of epigenetic modifications and microbiome patterns exist suggesting a closed feedback loop between these components of susceptibility.
Microbiome: Much more complex

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Humans are associated with complex microbial communities that live on body surfaces or within cavities connected with the external environment. The gastrointestinal tract harbors the largest microbial burden with around 40 trillion microbial cells, most of them belonging to the domain Bacteria.

Large-scale research projects provide novel insights on the structure and function of the human gut microbial ecosystem. The field progresses rapidly owing to the availability of high-throughput sequencing techniques, combined with powerful bioinformatics for taxonomic identification and comparative analysis of datasets. Whole-genome sequencing of DNA extracts from human fecal samples reveals the collective genetic content of the ecosystem from which functional and metabolic networks can be inferred. Up to 10 million non-redundant microbial genes were identified in samples from 1300 individuals from Europe, US and China. The gene catalog includes information about nonbacterial members (viruses, yeasts and protists). Each human individual carries an average of 600,000 non-redundant microbial genes in the gastrointestinal tract. A set of 300,000 genes was found to represent a common core prevailing in most of the cohort. Functional screening relies on matching sequences to known functional modules. The extensive catalogue of microbial genes encodes groups of proteins engaged in up to 20,000 biological functions related with life in the intestinal habitat. Of them, 5,000 functions are common to more than 50% of samples in the cohort.

In patients with ulcerative colitis or Crohn’s disease, loss of species diversity and defective gene richness is commonly observed, even during periods of remission. From a functional point of view, low diversity is associated with reduction in butyrate-producing bacteria, increased mucus degradation potential, reduced hydrogen and methane production and increased hydrogen sulfide generation. Whether such microbial changes are cause or consequence of the underlying disease is still unresolved, since there is clear evidence for bidirectional influences between host and microbes. However, some changes are likely to play a pathogenetic role in the perpetuation of disease, since cohort studies show higher risk of relapse in patients with lower gene counts upon remission. Targeted interventions aimed at restoring the ecosystem (fecal microbiota transplantation, bacteriotherapy) are currently being explored for their ability to restore microbial gene richness and prevent relapse.
Session II

Diagnosis
The concepts are changing

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Ulcerative colitis (UC) and Crohn’s disease (CD) are lifelong idiopathic diseases. There is no single test to establish the diagnosis of IBD. The diagnosis and differential diagnosis is based on critical evaluation of clinical symptoms, appropriate inflammatory biomarkers, Imaging procedures, endoscopic and histologic findings in association with a chronic relapsing remitting or continuously active course of disease.

In recent years, innovative imaging (MRI and dynamic US) and endoscopic techniques (including capsule endoscopy) have allowed us not only make a correct but also a precise diagnosis at disease onset. Thus, we are able to map precisely the location and extent of disease in the gastrointestinal tract, assess the severity and activity of the intestinal inflammation, estimate the degree of structural and functional tissue damage and record the type and severity of extraintestinal involvement. We can therefore identify patients with potential optimal outcome of disease who need minimal therapeutic interventions but also patients with poor prognosis and risk factors predicting a disabling course of CD (such as young age at disease onset, complex perianal fistulizing disease, deep ulcers, severe ileitis or extensive small bowel or proximal involvement etc.) or UC (such as extensive colitis, poor response to corticosteroids etc.). The latter patients need early and ‘aggressive’ treatment to prevent serious and occasionally life-threatening complications necessitating hospitalizations and surgeries which impact tremendously on quality of life and cause severe or permanent disability. This ‘personalized diagnosis’ offers a clear view of global physical and psychological burden of the disease and forms the basis to build a highly individualized treatment that targets the multifactorial nature and complexity of IBD for the particular patient, that is treatment beyond symptoms, treatment of a lifelong disease and not a flare and avoiding over-treatment but also under-treatment.
Establishing a diagnosis of inflammatory bowel disease (IBD) relies upon typical findings of chronic active inflammation on endoscopy, histology and imaging. Given the expense and invasiveness of these diagnostic modalities, diagnostic biomarkers would be highly desirable. To date, however, no biomarker possesses adequate test characteristics to confer a definitive diagnosis of IBD, or to differentiate between Crohn’s disease (CD) and ulcerative colitis (UC). Beyond establishing a diagnosis, biomarkers may fulfill other important purposes. Tracking the state of inflammation in the course of treatment with biomarkers of inflammation may be helpful in a number of scenarios, including categorizing the disease as mild, moderate or severe when benchmarked against endoscopic severity; predicting clinical relapse of disease that is in medically or surgically-induced remission, and in predicting response to treatment. Among the best-studied biomarkers of inflammation are serum C-reactive protein and fecal calprotectin. While neither of these commonly used biomarkers have perfect sensitivity or specificity, both may be useful adjuncts to a treat-to-target strategy of disease management in IBD. Other investigational biomarkers of inflammation are in development. A second, broad category of biomarkers in IBD includes predictive biomarkers. These may be further characterized as those predicting the course of the disease, and those that predict response to specific therapies. A variety serologic biomarkers, generally reactive against microbial antigens, may help to predict the development of complications of CD, while pANCA may be useful in predicting specific features related to UC. A final category of predictive markers may predict the likelihood of response to specific therapeutic agents in relation to their mechanism of action. In summary, biomarkers are increasingly useful in the management of IBD, and may be especially beneficial in maintaining a treat-to-target paradigm to improve disease outcomes.
Imaging

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The role of imaging techniques, such as magnetic resonance imaging (MRI), computerized tomography (CT) and small bowel ultrasound (US), is well established for the detection and assessment of disease activity and complications in Crohn’s disease. Recent studies clearly demonstrate that imaging techniques are able to monitor also therapeutic response and bowel damage progression, and also can play a role in guiding therapeutic strategies and partially discriminating inflammation from fibrosis.

The presentation will make a brief overview of the most relevant data on the role of imaging techniques in the management of Crohn’s disease and will explore future perspectives for non-invasive monitoring of IBD patients.
A step further: Individual prediction

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The traditional classification system of inflammatory bowel disease includes Crohn’s disease and ulcerative colitis, but it is now fully appreciated that these two conditions are quite heterogeneous in their clinical presentation, clinical phenotypes, disease behaviors, responses to therapy, and immune and genetic markers. In addition to the challenge of primary nonresponse to many therapies, we are faced with the clinical challenge of secondary loss of response over time. This is because patients change in their age and presumably in their physiology, they are exposed to environmental triggers and the disease pathogenesis may change as well. Therefore, with the development of multiple new therapies that have novel mechanisms of action, there is an urgent priority to better characterize patients and select those who may respond preferentially to specific therapies. Such a selection process also requires better disease monitoring strategies which will incorporate a stratified approach to the patient’s prognosis and allow for adjustments in management that precede clinical deterioration or complications. In this presentation I will review traditional prognostic markers, that suggest a pathway towards differentiation of patient types based on likelihood of responding to therapy, and provide a glimpse into the near term future use of disease severity indices, personalized medicine approaches to treatment options, and a proposed strategy for incorporation of a modified treat-to-target approach to more sustained disease control and improved clinical outcomes.
Session III

The complex patient
Ready to use cells?

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Crohn’s disease (CD) is characterized by chronic inflammation in segments of the digestive tract and tissue damages. A significant progress has been made over the two last decades in the management of CD. However, a fraction of CD patients experiences severe disease, refractory to all available therapies. Autologous hematopoietic stem cell transplantation (HSCT) has been considered as an option for those patients. Other cell therapies using mesenchymal stem cells are in development.

Evidence for the feasibility and efficacy of HSCT has been reported in several types of severe treatment-resistant immune mediated inflammatory diseases, including multiple sclerosis and systemic sclerosis. Analyses of the EBMT database provided evidence for the feasibility and the toxicity of the HSCT procedures in immune mediated diseases. Despite long-term benefits, it is associated with a high morbidity and 2–10% mortality rate, making it an acceptable option for only highly refractory patients. The effect of HSCT on the disease is probably associated with a resetting of specific immune responses.

The first evidence of effectiveness of HSCT in IBD was observed in patients who underwent allogeneic or autologous HSCT for hematological or solid malignancy. The ASTIC trial, an international investigator-initiated randomized study, evaluated the early and late effects of autologous unselected HSCT on CD over 5 years. All cases suitable for the trial were discussed by a steering committee, which made suggestions for alternative management in a significant proportion of cases. We recently reported the outcome at one year. Forty-eight patients underwent mobilization of stem cells, and 45 patients were randomized to transplantation at one month (n = 23) or one year after (control arm, n = 22). Few patients in either arm achieved the primary endpoint of sustained disease regression (clinical remission off immunosuppressive drugs for 3 months with no evidence of intestinal inflammation on endoscopy and radiology). However, more HSCT patients were able to come off all immunosuppressive therapy than control patients and there was a clear trend for more HSCT patients being in clinical remission and free of active disease (endoscopy and imaging). HSCT was associated with a high burden of serious adverse events, and one patient died after the start of conditioning. An analysis of one-year outcome in the whole cohort (n = 40) was recently reported. At one year, HSCT was associated with significant improvement in clinical disease activity, quality of life and endoscopic disease activity. At one year, 43% of patients were in clinical remission, and mucosal healing was observed in half of patients. Anti TNF therapy was required in 7 (18%) patients after 18 (14–39) weeks. In anti TNF re-treated patients, CDAI fell from 319 (55) to 174 (39) (p = 0.016) and 71.4% patients experienced a clinical response (CDAI fall > 70 points).

The team of Barcelona recently published their experience on HSCT. Toxicity and complications during the procedure and within the first year following transplantation were reported. Viral infections were the most commonly observed complications, and one patient died due to systemic cytomegalovirus infection. Interestingly, changes in supportive care over the study, including antibiotic prophylaxis, and a reduction in cyclophosphamide dose, diminished the incidence of severe complications.
According to the EBMT guidelines, HSCT is considered a salvage therapy for patients with severe CD refractory to immunosuppressant and biologics, after consideration of all therapeutic options, and in whom surgery is not suitable including surgery. Autologous HSCT should be performed only in highly experienced centres.

Mesenchymal stem cells (MSCs) represent another option for the treatment of refractory diseases. Preclinical studies suggest the potential efficacy of MSCs in models of autoimmunity, inflammation, and tissue damage. Clinical trials using MSCs have been initiated in CD. Locally administered MSCs showed results in the treatment of perianal fistulae. MSCs (autologous or allogeneic bone marrow-derived), which have immunosuppressive properties, have also been tested though IV infusions in luminal disease. A randomized clinical trial assessed the efficacy of allogeneic, expanded, adipose-derived stem cells (Cx601) for the treatment of refractory complex perianal fistulas in CD. A significantly greater proportion of patients treated with Cx601 versus placebo achieved remission.

Tandem talk: Stenosis

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The stenosis is one of the consequences of the progressive destructive nature of inflammation of Crohn’s disease and may produce a permanent intestinal damage. Based on the Montreal classification, the presence of stenosis defines the stricturing pattern or B2 pattern. However, it is known that various disease behaviors can coexist and that pure fibrotic stenosis rarely exist. In fact, inflammation and fibrosis coexist in stenosis lesions and distal to the origin of internal fistulas there is some degree of stenosis or obstruction. Intensive medical treatment should be the first line if signs of inflammation are detected.

Before planning the treatment strategy, stenosis should be assessed by imaging techniques and by activity index. The presence of inflammation can be detected by the use of fecal and serum biological markers such as calprotectin and CRP. The endoscopy provides relevant information by detecting luminal narrowing impossible or difficult to pass with the endoscope and detecting mucosal activity at the site of stenosis. Cross sectional imaging has high accuracy for detection of stenosis and adds information relevant to clinical management (number of stenosis, location, length and also signs of inflammation). MRI avoids radiation exposure and for that reason is preferred to CT scan. The presence of wall thickness, enhancement, comb sign and lymphadenopathy detected in MRI favors the presence of inflammation.

Short stenosis accessible to the endoscope can be managed by endoscopic balloon dilatation (EBD) or by a stent placement. EBD can be repeated 2–3 times until the clinical success is achieved whereas the stent should be removed maximum at 4 weeks of placement if spontaneous migration does not occur. Surgical resection should be indicated in predominantly fibrotic stenosis or in stenosis resistant to medical treatment.
Tandem talk: Stenosis

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Within 20 years after diagnosis, about 50% of Crohn’s Disease (CD) patients will develop intestinal complications, such as strictures or fistulas and the majority will undergo surgery during their lifetime. Stricture may occur at the diseased segments and CT scan and MRI enterography are the preferred tools to phenotype the disease. The latter may be useful to differentiate between inflammation and fibrosis. However, once a stricture has been diagnosed, the management is not a clear-cut decision.

The widespread use of anti-TNF agents have shown clear effect on mucosal healing in the preoperative setting and in delaying recurrences. However, the picture is not clear when using anti-TNF agents in established stricture, especially when mostly related to fibrosis. Indeed, the rate of small bowel resection has remained unchanged over the years as well as the rate of bowel stricture.

In this scenario, the surgical management still retains a crucial role. Moreover, the minimally invasive techniques are able to produce a lower surgical impact on the patients in terms of functional recovery and cosmetic results in comparison to open surgery. Strictureplasty is also a potential option for CD stricture, especially after multiple resections, to preserve intestinal length. On the other hand, prolonged ineffective medical therapy and, in turn, delayed surgery may produce more complex disease presentation that increases operative time, conversion rate and postoperative complications.

In conclusion, the management of CD stricture should be tailored to the individual patients’ situation and a concerted decision between the gastroenterologist and the surgeon is advocate.
Chromoendoscopy

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Patients with longstanding inflammatory bowel disease (IBD), extensive or left ulcerative colitis (UC) or colonic Crohn’s disease (CD), have an increased risk for developing colorectal cancer, and surveillance colonoscopy is recommended to detect dysplasia. Stenosis or previous dysplasia lesions, extensive UC with severe activity, first-degree colorectal cancer (CRC) diagnosed earlier than 50 years old and primary sclerosing cholangitis are the most important risk factors for development CRC. According to a 1992 study, guidelines recommended obtaining at least 33 random biopsies from all the segments of the colon to detect dysplasia with a probability of 90%, but with newer endoscopic technologies most dysplasia lesions are visible. Prospective cross-sectional trials illustrate chromoendoscopy usefulness comparing with white light endoscopy or narrow band image (NBI) in the detection of dysplastic lesions. Comparing NBI and chromoendoscopy with high definition colonoscopy, NBI appears to be a less time-consuming and equally effective alternative to CE for the detection of dysplasia but a higher lesion miss rate, resulting in potential missing neoplastic lesions. Nowadays, ECCO guidelines and SCENIC consensus recommend, with a high evidence level (1B) and a recommendation grade of B, chromoendoscopy rather than white light endoscopy or NBI for surveillance in these IBD patients. Contrast agents such as indigo carmine (0.2–0.4%) highlight the architecture via the pooling of dye in the grooves between colonic crypts and within the colonic pits and ridges of polyps. The widely accepted Kudo pit pattern classification is used to differentiate five types of staining patterns to predict neoplastic lesions. Real life experience in screening programs with chromoendoscopy shows that many lesions are detected but most of them have not neoplastic potential; only about 10% are premalignant. However, negative predictive value is high, and could prevent biopsy of Kudo I–II pattern lesions. Surface guidelines must be followed to perform chromoendoscopy and morphology of lesions must be described with a variation of Paris classification as it’s recommended by SCENIC consensus. It is necessary studies to reveal the true clinical utility of adjunctive surveillance, whether with dye spray and chromoendoscopic techniques or with another emerging technique.
Treatment 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 promote carcinogenesis of melanomas. 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.
Infections in inflammatory bowel disease

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Current management of inflammatory bowel diseases (IBD) both Crohn’s disease (CD) and ulcerative colitis (UC) still rely on immunosuppressive drugs. Up to 50% of UC and 80% of CD patients will receive at least one course of corticosteroid therapy during their lives. 25% of UC patients and over 70% of CD patients will be treated with conventional immunomodulators (thiopurines and methotrexate), and 15% and 40%, respectively, will require biological therapies. Thus, a relevant proportion of IBD patients will be at risk to develop serious or opportunistic infections. Other factors beyond drug therapy may also impact on the risk of infections such as co-morbidities, age and IBD inflammatory activity.

For these reasons it is outstanding to carefully evaluate the risk of infection in every clinical scenario, for every individual patient and with every particular drug. Primary prevention, by assessing the serological status and vaccinating the patient when necessary, is the main tool to minimize the risk of infection. Surprisingly, this is still underused among IBD patients all over the world. Early recognition of infections is also important. From this perspective, it is relevant to know the spectrum of infections that are more prevalent with each drug in order to decrease the threshold of suspicion and actively rule out particular infections.

Regardless the widespread use of checking lists before starting immunosuppressants and biological agents, infections still remain one of the most common side-effects of these drugs. A clear example is anti-TNF-associated tuberculosis, which is still occurring despite adequate screening of latent infections. Moreover, with new drugs, new infectious risks will appear leading to changes in our clinical practice.
Session IV

Classic treatments: Do they really work?
Mesalazine

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In view of the current drug development in inflammatory bowel diseases and here in particular in ulcerative colitis (UC) the question arises whether or not the “classic” mesalazine still has a place in our treatment algorithms? To start with, the question do they really work? should be reversed and we should rather asked what should be considered before we decide that mesalazine is not working and as a consequence start escalating our therapy. Several points are worth discussing: i) Did the patient receive just a regular dose or was the mesalazine dose increased? ii) Along the same line, was the disease localization considered? A limited left-sided disease will primarily profit from local therapy that can even be improved once oral and local treatment is being combined. Alternatively, oral formulations that increase the drug release on the left side of the colon might offer an alternative strategy. Having optimized the route of application, the applied dose as well as introduced combined treatment are there still reasons why mesalazine can fail and we still should not switch the treatment strategy? iii) Adherence to therapy is the last point to take into account. Probably this is the most difficult to address objectively. However several studies performed with mesalazine have proven that the adherence to therapy improves by a once-daily strategy versus a qd or tid strategy. In parallel to an improved adherence those studies revealed and at least equal therapeutic effect.

In summary, yes, mesalazine is working and we should consider in our UC patients the above detailed three points, namely: appropriate dosage, local versus systemic therapy or even a combination and adherence to therapy. In clinical practice, a surprisingly high percentage of UC patients with mild to moderate disease will achieve clinical remission by applying this strategy.
Thiopurines versus methotrexate

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Thiopurines have been a mainstay of IBD therapy since the 1980. Present study of 83 patients with Crohn’s disease demonstrated steroid sparing and fistula healing effects, and methotrexate since the 1995 Feagan study of 141 patients with Crohn’s disease which demonstrated clinical remission and reduced steroid use. These therapies were clearly an improvement over sulfasalazine and 5-aminosalicylates, but have been overshadowed by the introduction of monoclonal antibody therapies in 1998. The effectiveness and utility of thiopurines have been questioned after the negative RAPID and AZTEC therapeutic studies. The safety of thiopurines is increasingly challenged by evidence from large cohorts of risks of shingles, lymphoma, and skin cancer. The utility of methotrexate is challenged by the difficulties of use in young women and by frequent side effects that limit persistence on therapy. However, the low costs of immunomodulators and extensive experience with these therapies make them attractive and support continued use, even with increasingly available monoclonal and biosimilar therapies. Several strategies for optimizing immunomodulator therapies have been developed, including metabolite assays, CD4 activation assays, and machine learning approaches. Several strategies for improving tolerability and adherence to these immunomodulators have been developed with increasing clinical experience. Both thiopurines and methotrexate can work very well for a minority of patients with IBD and can improve trough levels of and reduce antibody formation against monoclonal antibody therapies. Azathioprine can increase the efficacy of infliximab when used in combination therapy, and could be comparable to infliximab in ulcerative colitis in selected patients with low TPMT levels. Altering the metabolism of thiopurines with allopurinol can improve efficacy. Careful patient selection and dose optimization can improve outcomes for IBD patients on immunomodulators, and keep these low-cost therapies in our armamentarium.
Calcineurin inhibitors, still a role?

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Following mostly negative trials, calcineurin inhibitors have virtually no role in Crohn’s disease whereas clinical data are more positive in ulcerative colitis (UC). Here, steroids are unable to achieve a clinical response or remission in roughly one third in acute disease. Colectomy was mandatory in former times once steroid resistance in severe colitis was established. Anti-TNF antibodies, particularly infliximab, and calcineurin inhibitors emerged as effective therapeutic alternatives to avoid the surgical rescue. A recent randomized controlled trial in 115 patients with acute severe and steroid-refractory UC demonstrated the calcineurin inhibitor cyclosporine and infliximab to be equally effective. Although tacrolimus is considered to be similar to cyclosporine, a head to head comparison between tacrolimus and infliximab or between tacrolimus and cyclosporine is lacking in UC. In a recent retrospective study from our group, tacrolimus was found to prevent colectomy in 86% of 130 steroid-refractory UC patients after three month of treatment. Despite the lack of larger controlled trials, tacrolimus is recommended as a therapeutic option in present guidelines for the steroid-refractory UC.

However, on the long-term up to 50% of UC patients that initially benefit from rescue therapy will lose their colon. Rather than perpetuating calcineurin inhibitors for maintenance, the overlap use of purine analogues (PA) azathioprine and mercaptopurine is suggested for the ongoing long-term therapy and should perpetuate remission particularly in those naïve to purine analogues. This is also due to the side effect profile of calcineurin inhibitors including deterioration of renal function, hypertension, and, in case of tacrolimus, diabetes mellitus. Overall, perioperative morbidity may be slightly increased, comparable to infliximab.

In conclusion, although off-label due to lacking industry interest, calcineurin inhibitors are a vital option in steroid-refractory ulcerative colitis. Starting with them may leave the option of switching to infliximab in case of failure, whereas the reverse sequence is difficult due to the anti-TNF’s long plasma half-life.
The recent acknowledgement that IBD is a progressive disease has changed the focus of therapeutic strategies. It is now widely accepted that treating effectively at earlier stages of disease, before bowel damage occurs, is likely to produce better outcomes, resulting in reduced rates of hospitalisation and surgery. Unfortunately, despite ongoing efforts to change therapeutic paradigms, combining early diagnosis with best available effective therapies, drug-free remission or absence of progression of bowel wall damage remains a challenge in many patients. Once the diagnosis of IBD is made, bowel damage has already occurred in a significant number of patients, and the immune dysregulation, dysbiosis and tissue injury associated with full-blown disease is set, and in many cases, irreversible. At present, all therapeutic interventions in IBD target well-established disease, and even the most potent agents are not able to prevent or reverse chronic damage often present at diagnosis. In order to truly change the natural history and long-term consequences of IBD, an effective intervention should ideally occur at an earlier phase, targeting the primary biological processes that drive disease from a preclinical to clinical stage. There is increasing evidence that in IBD, like in other immune-mediated diseases (IMIDs), there is a period characterised by immunological changes that precedes symptoms and perhaps even organ injury and that starts years before diagnosis. In this presentation, we will review the concept of preclinical disease, supported by preliminary studies in IBD and complementary evidence from other IMIDs, as well as discuss the challenges and opportunities in application of novel preventive strategies in IBD.
Session V

Biologics, the end of the story?
Anti-TNFs: Lessons from 18 years

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The advent of infliximab at the end of the last millennium rewrote the treatment paradigms in Crohn’s disease and changed the way we were treating refractory ulcerative colitis 5 years later. More specifically, anti-TNFs provided a safe and effective alternative to surgery in patients with refractory IBD and an inflammatory phenotype. They also offered the first effective medical option in perianal Crohn’s disease often in an adjuvant setting with surgery. Finally, the success of anti-TNFs in IBD and other inflammatory disorders incited considerable interest from the industry to direct resources towards clinical development of other monoclonal and small molecules. Even if a considerable number failed to reach the clinic, others have submerged and offer new medical options to patients with IBD.

In the last 2 decades we have also learned important lessons by using monoclonal antibodies in our daily practice. First, we have come to realize that ‘one size fits all’ doesn’t apply to immune mediated disorders. The field of rheumatoid arthritis has seen a multitude of biologics enter daily care, whereas many of the same molecules failed to show efficacy in IBD or in SpA. Anti-IL17 antibodies appear to be highly effective in psoriasis and in RA, but if anything may worsen Crohn’s disease. Doses of monoclonal antibodies may also differ between indications. Therefore, we will have to diligently test new molecules in patients with IBD and avoid extrapolation from other indications.

A second important lesson, is the fact that all therapeutic proteins are immunogenic and are able to raise anti-drug antibodies in patients with major implications for treatment algorithms. We have succeeded in mastering to some extent immunogenicity by giving uninterrupted maintenance treatment and by combining biologics with immunosuppressive agents. This came at a price of an increased safety burden, but has improved long term efficacy. The importance of pharmacokinetics, or studying drug concentrations, is closely linked to immunogenicity. Particularly in patients losing response to a biologic, most clinicians nowadays will test for drug levels and anti-drug antibodies, if these are available to them, prior to optimizing the dose of a biologic or switching to another molecule.

Primary non response to biologics has also puzzled the IBD community. Although partially explained by late intervention in patients with non-inflammatory disease, more research is needed to identify predictive markers of response.

Accountability of care is a final lesson we have learned. Anti-TNFs have always been expensive drugs and their introduction has increased the direct drug cost in IBD care. Other direct costs, such as those attributable to surgery and hospitalization, should therefore be monitored and indirect costs, resulting from disability or loss of productivity, should also be factored in. With the advent of biosimilars the anti-TNF drug cost is expected to decrease and this should pave the way for newer medical and surgical options for refractory patients.
Biosimilars: The clinical experience

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Biosimilars’ tale in inflammatory bowel disease is a metaphor of the modern world. Few gastroenterologists or patients had any idea about this topic in 2012. However, the change has been dramatic in the last four years. Our world changes quickly. Economics are the key point in the biosimilars’ tale. Today’s world works whirls around money. The information about biosimilars is abundant. In fact, it’s so abundant that there is an excess of information. Sadly, this may not be an advantage: quantity doesn’t necessarily mean quality. The modern world produce too much information, but often of bad quality. In just a few years, physicians caring for IBD patients have completely changed their views on biosimilars; general distrust became general acceptance. The ECCO published a position paper in 2013, asking for specific clinical trials in IBD patients, an evidence based medicine way of reasoning. This paper casted some doubts on the extrapolation concept developed by EMA regulators. As EMA concepts were explained and clinical experience has increased, extrapolation was generally accepted. The ECCO has released a new position paper in 2016, and acknowledged the use of biosimilars in the updated Crohn’s disease guidelines. A lot of observational data, as well as a few controlled data experiments do confirm indeed, that the first biosimilar is also clinically similar in IBD patients. Market forces have been more important than regulatory agencies in these changes. Biosimilars can completely change the treatment landscape of IBD. Surprisingly not through clinical innovation, but by market changes. And we are only just getting started. Infliximab monoclonal biosimilars came as the first monoclonal, but many more are expected soon. Infliximab was the first monoclonal that worked and generated benefits profit for pharmaceutical industry. Infliximab biosimilars are leading a change in the pharmaceutical market that can affect thousands of monoclonals – and many other drugs in the future. Many questions remain, however, and only time and new studies will bring responses.
New molecules

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The mechanisms underlying the chronic intestinal inflammation that is a hallmark of inflammatory bowel diseases (IBD) are complex. Components of the pathological response include the adaptive and innate immune systems, as well as the intestinal epithelium and endothelium. Advances in the understanding of the roles of each of these components have resulted in the development of multiple biological agents that all represent an alternative to the use of current therapies in patients with refractory Crohn’s disease or ulcerative colitis. This presentation systematically reviews the mechanisms of action, efficacy and safety of new and emerging therapies that are currently in clinical trials and discusses future directions in the treatment of IBD.
New small molecules

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The therapy of IBD is at a new crossroad as promising studies with new small molecules that specifically target pro-inflammatory pathways have been published and first small molecules are on the edge of being approved. This is somewhat a change of paradigms as since the introduction of the first biologic agent, infliximab, we mainly have seen the development of biologicals. Besides TNF inhibitors (i.e., infliximab and its biosimilars, adalimumab, golimumab, and certolizumab pegol) and anti-integrins (i.e., natalizumab and vedolizumab or etrolizumab), anti-IL-12/IL-23 agents (i.e., ustekinumab and others to come) have been developed in recent years.

However, these biologicals (in most cases engineered monoclonal antibodies) have specific limitations with respect to efficacy, side effects, duration of response and costs. Biologicals, in addition, require parenteral (i.e., intravenous or subcutaneous) administration, which has impact on the quality of life for many patients. Therefore, the development of more specific small molecules is important as it may avoid some of the above-mentioned limitations of biologicals. One of the main advantages of small molecules is the oral route of administration. Further, small molecules in contrast to large proteins such as biologicals usually have a short serum half-life.

Several groups of small molecules are currently under development for IBD therapy. One group are small molecule Janus kinase (JAK) inhibitors. The JAK protein family comprises four intracellular tyrosine kinases: JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2). These kinases are intracellular signal transducers for many pro-inflammatory cytokines. Subsequently, JAK inhibitors block several cytokine and inflammatory pathways simultaneously. The most advanced development in the area of JAK inhibitors is for Tofacitinib (Xeljanz, Pfizer). Tofacitinib inhibits JAK1, JAK3 and JAK2. The FDA approved Tofacitinib for the treatment of moderate-to-severe rheumatoid arthritis. In a phase III study on the efficacy and safety of induction and maintenance therapy with tofacitinib in ulcerative colitis (OCTAVE) the number of patients in clinical remission at week 8 was significantly higher in the tofacitinib group (18.5% vs 8.2%, p = 0.007, and 16.6% vs 3.6%, p = 0.0005 rsp). Further JAK inhibitors (i.e., filgotinib, peficitinib and ABT-494) are in phase II of clinical development. They have different specificities for the different JAK proteins.

A second group of small molecules developed are S1P receptor modulators. Sphingosine-1-phosphate (S1P) is a lipid that binds to specific G-protein-coupled receptors (S1PRs). Lymphocyte trafficking is regulated by these S1PRs. Ozanimod is a novel, orally administered small molecule that selectively modulates S1P1 and S1P5 receptors. Ozanimod is currently evaluated for the treatment of immune-mediated inflammatory diseases, such as multiple sclerosis and IBD. In a double-blind, phase II RCT (TOUCHSTONE), ozanimod showed a higher clinical remission rate at week 8 compared with placebo (16% vs 6%, p = 0.048). Two more S1PR modulators (etrasimod and amiselimod) are currently tested in IBD.
Laquinimod is an oral quinolone-3-carboxamide with anti-inflammatory properties. In a phase III study in multiple sclerosis a positive effect has been demonstrated. The exact mechanism of action is not completely understood. In a phase II RCT in CD patients laquinimod (0.5 mg/day) showed higher efficacy than with respect to clinical remission (48.3% vs 15.9%, respectively) and clinical response (55.2% vs 31.7%) and was well tolerated.

Mongersen is an anti-sense oligonucleotide inhibiting SMAD7 which itself is an inhibitor of TGFβ. TGFβ induces regulatory T-cells and thus has an anti-inflammatory effect. An inhibitor on an inhibitor of TGFβ would consecutively cause higher TGFβ activity and thus downregulate inflammation. As an oligonucleotide, Mongersen is not a "classical" small molecule. In two phase II trials in Crohn’s disease very promising preliminary data have been obtained. A phase III trial is under way. The safety profile appears to be excellent as there is none or only minimal systemic exposure. One concern, however, is the fact that TGFβ also is an important regulator of tissue fibrosis.

In addition to the mentioned small molecules, more orally administered new compounds are currently being investigated in clinical trials in both UC and CD. Besides monotherapy also combination therapies may be interesting and will be addressed in future trials. A combination therapy between the oral small molecules and biologicals may be a strategy in complicated disease courses. The current development of small molecules for the treatment in IBD patients is exciting but will also generate many open questions.
Session VI

From drugs to strategies:
The long term plan
How to deal with the patient – Focus on observational data

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Crohn’s disease (CD) is a chronic and progressive disease of unknown etiology, prone to relapses and disabling events. These new concepts on CD treatment are leaving behind the classical approach of controlling the disease symptoms, and studies focusing on the improvement of the quality of life and on the reduction of hospitalizations and surgeries are now emerging. The identification of clinical criteria that can predict CD outcomes at an early phase of the disease is therefore crucial, as it can guide the decision-making process on the therapeutic options. Age at diagnosis, perianal disease, disease aggressiveness and early therapeutic decisions were found to be significant factors, being used to create user-friendly matrices depicting the probability of each outcome given combinations of these factors, which exhibit good performance for the most important criteria. The disabling disease risk matrix shows that patients that were 40 years or less at diagnosis, have perianal disease, an aggressive disease phenotype, and that are treated with immunosuppressants (either before any surgery or after an initial one) have a higher risk of undergoing the disabling events. The need for a reoperation, on the other hand, is more likely to occur on patients diagnosed at 40 or less, that have perianal disease, an aggressive disease phenotype, and that underwent an early surgery upon diagnosis. Although neither early surgery nor immunosuppression seem to be able to prevent global disabling disease, an early start of immunosuppression by itself is associated with fewer surgeries and should be considered in daily practice as a preventive strategy. Therefore, the timing of therapeutic strategies affects the CD outcomes. Whereas an early surgery (within six months after diagnosis) can decrease the occurrence of disabling events, the introduction of immunomodulators more than one month after the initial surgery seems to increase the likelihood of needing further surgeries. The important clinical impact of these variables support their inclusion in the algorithms developed to back the decision-making aiding tools concerning the strategies followed for CD management and overemphasis the role of observational data in IBD.

References:


Preventing recurrence

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Despite advances in medical therapy, intestinal resection is still necessary in the majority of patients with luminal Crohn’s disease. Furthermore, recurrent disease remains the norm and further operations are eventually necessary in most of these patients. Strategies to prevent recurrent Crohn’s disease after surgery are, therefore, important but need to be individualized to the patient. An understanding of the risk of recurrence along with consideration of the disease history, severity and phenotype allows both medical interventions and strategies for monitoring to be adapted according to the situation. Fortunately, recent high quality studies have not only improved our understanding of the natural history of post-operative recurrence but also of the roles of specific drugs and monitoring tools. Perhaps most importantly, however, strategies for the management of post-operative Crohn’s disease have been tested in the randomized controlled setting.

Some interventions to prevent post-operative recurrence are easily applied and should be considered routinely; for all patients who smoke, discontinuation of tobacco use is associated with a decreased risk of recurrence and of further surgery. Other factors that influence the risk of recurrence should be considered when deciding on a therapeutic and monitoring strategy. Of these, prior resection and the presence of penetrating disease are the most important. Some practitioners use imidazole antibiotics in all patients post-operatively, tolerance being the main problem in terms of adherence. For patients at higher risk of recurrence, the use of thiopurines largely remains routine. This practice, along with the use of anti-TNF post-operatively, has recently been examined in a series of randomised controlled trials and, overall, supports a stratified, rapid step-up strategy. In this regard, the management of post-operative Crohn’s disease reflects that of all IBD; monitoring of disease activity, as well as assessment of therapeutic interventions and a change in therapeutic strategy when interventions are unsuccessful, are key to long term success. Indeed, in some ways, routine post-operative ileocolonoscopy 6–12 months after surgery and treatment of recurrent disease was the first treat-to-target approach used in IBD.

As our therapeutic options and available monitoring tools increase in number and decrease in price, so our post-operative strategies in Crohn’s disease will evolve; it is, therefore, to be hoped that the coming decades will see a greater impact on the natural history of post-surgical Crohn’s disease than the preceding ones.
Session VII

The clinical scenarios
When to stop therapy in IBD

Edouard Louis
University Hospital CHU Liège, Belgium

Stopping therapy in IBD has always been a preoccupation of both patients and physicians having in mind an optimal benefit/risk profile of the treatment strategy. It may also be important for payers when drugs are expensive like Biologics. Yet it may seem inappropriate in a chronic disease for which there is currently no cure. It is not absurd however because IBD are relapsing/remitting disease and that long phases of remission may interrupt phases of disease activity. The best example of the possibility to interrupt therapy in IBD is given by the natural history of Crohn’s disease after ileo-caecal full resection of affected intestine. Early pioneering study by Rutgeerts et al, showed that 30–40% may remain free of clinical relapse without treatment over 8 years.

The decision to stop a treatment in IBD is thus based on the benefit/risk ratio of the considered treatment. From this point of view, the situation may be different in Crohn’s disease and ulcerative colitis. In ulcerative colitis, a treatment with mesalazine should usually not be stopped. The toxicity of this drug is very low and, on the other hand, its cessation is associated with a relapse risk close to 50% over 1–2 years. The relapse rate after cessation of a purine treatment given as monotherapy or of an anti-TNF is also around 50% over 1–2 years. Importantly in this limited experience, the colectomy rate in the year following anti-TNF withdrawal was around 10%. Furthermore no clear predictive factor for the risk of relapse has been identified. For these reasons it is currently probably preferable to continue immunosuppressant and/or biologic treatment in ulcerative colitis. Future studies will have to explore the possibility of treatment deescalation and/or substitution to try and avoid severe relapse including the risk of colectomy.

Treatment withdrawal has been a bit more studied in Crohn’s disease, essentially immunosuppressant and/or anti-TNF. Here also the relapse rate has been consistently reported around 50% over 1–2 years. The risk of surgical resection in the years following immunosuppressant and/or biologic therapy interruption was low. Furthermore, predictors were suggested and even confirmed in several studies. Among the most important, there were mucosal healing of the intestine and normalisation of inflammatory markers. More recently, long term evolution has been reported after anti-TNF withdrawal in Crohn’s disease. Despite a high proportion of recurrent need for biologic therapy, there was still around 20% of the patients with biologics 7 years later and the ones who had resumed biologics did well with excellent response to re-treatment and only round 15% of surgery or new complex perianal lesions developing, which is close to what was observed in patients continuously treated with anti-TNF. Therefore, if good reasons exist to contemplate biologic treatment withdrawal in Crohn's disease (cost, patients’ preference, pregnancy, mild intolerance…), it could be discussed in a subgroup of low risk patients. The same can be concluded for the patients treated with a monotherapy with thiopurine in whom remission was achieved when resuming therapy in the vast majority of patients. Stopping concomitant immunosuppressant in patients treated with combo therapy is more frequently used. This seems justified in view of relatively good outcome in patients having reached sustained
and stable remission under combo therapy. The measurement of trough levels of the biologics may even strengthen this decision as high trough levels of infliximab have been associated with low risk of relapse after purine co-treatment discontinuation.

Beyond treatment withdrawal, the most important point is maybe what is next and how the patients should be followed up. Due to the relatively high rate of relapse after discontinuation, it seems logical to propose an intensified follow up regimen in those patients. Preliminary data suggest that biomarkers like blood CRP and even more fecal calprotectin increase several months before clinical relapse. This could allow to avoid disease progression and the development of disease complications by resuming the treatment before symptoms flare.
The simple Crohn’s disease patient

Dr. James O. Lindsay
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Evidence from clinical trials allows an estimation of the efficacy of specific drugs or therapeutic strategies in patients with Crohn’s disease. Real world data afford an insight into the effectiveness of these interventions in clinical practice. Consensus documents and guidelines intend to review these data in a systematic way and create practical statements that are graded as to their strength as a guide to therapeutic decision making in clinic. However, the patients that we see in clinic are not always the same that are included in this body of evidence. Crohn’s disease is heterogeneous and each patient will have a different disease pathway. There will be variability in disease phenotype, patient demographics, co-morbidity, and the translation of mucosal disease to symptom expression. The response to conventional and biological therapies varies between patients, as do the side effects that may occur. Moreover, the impact of the disease on all aspects of a patient’s quality of life will vary. Patients with poor prognosis disease can respond quickly to appropriate therapy, whereas on-going refractory symptoms in a patient with a limited disease burden may prove far more complex to resolve. To some extent there is no such thing as a ‘simple patient’! This talk will use clinical cases to develop a strategy for the assessment and management of patients with Crohn’s disease taking these factors into account. It will be based around patients with good prognosis Crohn’s disease.
Surgery: “Marker of failure”

Tom Øresland
Akershus, Universitetssykehus, Lorenskog, Norway

Surgery is still the best treatment for many IBD patients. In the era of symptomatic treatment with biologics many gastroenterologist seem to have lost this knowledge. Biologics are highly over rated. They perform about 20 percent better than placebo in most studies and these studies rarely have follow-up times more than a year. Quality of life for many patients on pharmacological treatment is rather miserable. The fact is that research on drugs that might prevent the disease i.e. therapy that address the cause of the diseases is scarce. Today pharmacological IBD treatments focus on the inflammatory pathways not on the causes of inflammation. The drugs are acting on processes below the mucosal cell lining but the disease start is probably a result of the breach of the mucosa. Treating the symptoms of inflammation is at best palliative – sometimes indeed it gives very good results at least for a while. Cessation of smoking is still probably the best non-surgical therapy for Crohn’s disease.

Surgery for inflammatory bowel disease is under constant development. Laparoscopic surgery has advantages, mainly in shortening the convalescence, minimizing the scars and creating less adhesions. We have new techniques in rectal excision, non-resection surgery for Crohn’s disease with non-conventional long strictureplasties. The options of restorative proctocolectomy for ulcerative colitis is more diversified with not only the ileal pouch-anal anastomosis but also the ileorectal anastomosis and the continent ileostomy still has a place. We often see that after an ileocolic resection for Crohn’s disease the patient gets well and stay well for the rest of her life without any additional treatment. Recent randomised studies show that patients with ileocolic Crohn’s disease not responding to initial pharmacological treatment will have an at least as good quality of life after surgery compared with continuous medical therapy. Furthermore surgery comes at a lower cost.

Then there is the notion of the diminished need for surgery in the era of biologicals. This need is too often in the chronically ill or intermittently ill patients defined by the gastroenterologist who together with the patient has a hope that the revolutionary drug is just around the corner. Actually the colectomy rates in ulcerative colitis started to sink before the introduction of biologicals. However quality of life after a restorative proctocolectomy might be better than that for the medically treated UC patients.

Until we have the drugs that not only modify the disease course but actually prevent the disease from developing in its early stages i.e. addresses the cause of the diseases surgery will be a very valuable treatment option. In many patients a fast track initial pharmacological treatment and an early recognition that surgery will be the optimal treatment is a true marker of success.
Value based care in inflammatory bowel diseases

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Value-based healthcare is a relatively new topic within healthcare delivery and refers to a model that centers on patient outcomes and how well healthcare providers can achieve this goal in a cost-effective manner. Within the newer value-based payment models, providers can be incentivized for their efforts through so called ‘shared savings’. This is potentially a new way for generating revenues for providers and hospitals moving forward. This also holds promise for participating patients who can be rewarded for their participation.

This shift from fragmented, departmentalized volume-based care to highly coordinated and integrated, patient-centric, value-based care will require significant change management in the face of traditional structures and customs of academic medicine in care design and delivery. Establishing transparency in performance documentation of improvements in care quality/outcomes at reduced costs, including reliable and valid metrics of clinical and economic efficacy, is central to this ongoing process.

At UCLA, a pilot of this type of value-based care delivery was performed for IBD patients between 2012 and 2017. This presentation will review the principles of value-based healthcare, the technology required for this type of care, and the performance in a cohort of IBD patients. The goal of this care transformation model was to produce a flexible and scalable model for IBD management that can readily diffuse and adapt not only across the clinical spectrum of UCLA Health but also across other health care systems that similarly seek to deliver high-quality, high-value care at performance-justifiable and -sustainable costs. IBD patients and providers have together experienced the impact of tightly controlled, coordinated team care and its health IT support infrastructure through improved clinical workflow, task differentiation, and care pathways, and facilitation and enhancement of patients’ active engagement in their own health and well-being, measurement of patient satisfaction, and mutual accountability of providers and patients in developing, understanding, and adhering to treatment plans.
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POSTER ABSTRACTS

Poster Numbers 1 – 118

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Inflammatory bowel disease in the UK: Is care improving?
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Introduction: The aim of this study is to examine the quality of care provided for patients with inflammatory bowel disease (IBD) in the UK.

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

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

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

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

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

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

Discussion/Conclusion: The knowledge about ionizing radiation doses among IBD specialists is poor. Training is needed to improve the awareness about the benefit versus the risk of ionizing radiation.
Influence of TGF-beta1 expression, -509C/T polymorphism and clinical correlations in gastric cancer patients

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Introduction: The aim of this study was to examine the expression of TGF-beta1 and TGF-betaRII and the impact of the -509C/T single nucleotide polymorphism (SNP) of the TGF-beta1 gene in relation to clinicopathological factors in gastric cancer (GC).

Methods: Using immunohistochemistry we investigated 43 patients with GC for expression of TGF-beta1 and TGF-betaRII. Consequently, RFLP-PCR was performed to analyze the presence of -509C/T polymorphism of the TGF-beta gene.

Results: We found that 72.1% of GCs had cytoplasmic TGF-beta1 expression and 27.9% were negative. The TGF-beta1 receptor- TGF-beta RII was expressed on tumor cell membranes in 58.1%. TGF-beta1 positivity in tumor cytoplasm correlated positively with TGF-beta RII expression in tumor cytoplasm in 67.4% of cases ($\chi^2 = 8.02; p = 0.005$). Also, the result showed that patients with low and moderate tumor differentiation had TGF-beta RII positivity in 53.3% and 81.8% resp. ($\chi^2 = 6.58; p = 0.037$). The analysis of -509C/T SNP in the TGF-beta1 gene and clinical stage distribution showed tendency. Among the 32 patients in III–IV clinical stage 53.1% were heterozygous (TC), 34.4% were homozygous for the C allele and 12.5% were homozygous for the variant T allele ($\chi^2 = 3.31; p = 0.069$).

Discussion/Conclusion: In conclusion the expression of TGF-beta1 was related to shorter survival time and rapid progression for the GC patients.
Fecal microbiome in patients with prolonged use of nonsteroidal anti-inflammatory drugs

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²Taras Shevchenko National University of Kyiv, Kyiv, Ukraine

Introduction: Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used drugs and their widespread use is associated with increased gastrointestinal injuries. Our objective was to analyse the composition of the fecal microbiome of the patients with prolonged use of NSAIDs compared to healthy controls, and to identify the role of probiotics in improvement of gastric healing.

Methods: We analysed the microbiome profiles of samples of 90 patients (H. pylori-negative) with the use of NSAIDs more than 3 months compared to the stool samples of healthy controls (mean age 64.1 ± 6.1). For all of them gastroscopy with further morphological examination was performed. The fecal microflora has been analyzed by bacteriological culture methods. Patients with erosive lesions were divided into 2 equal groups. The first group (control) was treated with pantoprazole (20 mg 2 times daily) for 28 days. The second group (main) received combined therapy: pantoprazole (20 mg 2 times daily) for 4 weeks and probiotic “Symbiter acidophilic” concentrated in dose 10 ml per day for 20 days. Over 4 weeks after the beginning of treatment we repeated all examinations which were done before.

Results: Changes in colonic microbiota were observed in all patients who used NSAIDs for more than 1 month. In 35% of them the level of Lactobacillus was less than 10⁶. After 20 days of probiotic therapy, patients had significantly increased numbers of both bifidobacteria and lactobacilli compared to the standard therapy where dysbiosis was even enhanced. Over 4 weeks during control gastroscopy erosions were absent in all patients in the main group compared to the control group where erosions were observed in 33% of patients.

Discussion/Conclusion: The long-term use of NSAIDs leads to quantitative and qualitative changes of colonic microbiota. The addition of probiotic in the general scheme of the treatment of NSAIDs-gastropathy leads to the total healing of gastric mucous over 4 weeks from the beginning of treatment.
The hematological anomalies in inflammatory bowel disease

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Introduction: The pathogenesis of the anemic syndrome in inflammatory bowel disease (IBD) can be generated by the chronic inflammation, repeated blood loss, malabsorption of the folic acid and B₁₂ vitamin and may preexist at the debut of the intestinal disease. The pathogenesis of thrombocytosis is complex and consists in mechanisms connected with the chronic inflammation, but also with the blood loss at the level of the digestive tract.

Methods: We evaluated 42 patients with IBD, 26 with ulcerative colitis (UC) and 16 with Crohn’s disease (CD). It was determined: Ht value, erythrocytes indices, number of reticulocytes, total capacity of iron binding (CTLF), latent capacity of iron binding (CLLF), transferrin saturation (TS), ferritin, CRP (C-reactive protein) and also the number of platelets.

Results: 12 of patients with UC and 6 with CD presented anemia. The medium Hb value was 8.3 ± 1.6g/dl and Ht value 28 ± 3.5%. In 11 of 18 anemic patients ($\chi^2 = 3.51$, $p < 0.055$) the intestinal disease was active. In 5 of 7 patients with anemia without active disease, the investigations and the epidemiologic study suggests an associated cause of the anemia (iron deficiency). In one case, the erythrocytes indices suggests macrocytosis and anemia is remitted after treatment with folic acid and B₁₂ vitamin. The thrombocytosis is present in 40.47%, correlated with the CRP value ($\chi^2 = 3.35$, $p < 0.05$), less with fibrinogen value ($\chi^2 = 3.20$, $p < 0.056$) and with the stage of the disease ($\chi^2 = 3.42$, $p < 0.05$).

Discussion/Conclusion: The anemia follows frequently IBD in 42.85% and it is correlated with the activity degree of the disease. The thrombocytosis is present in 40.47%, is much higher in CD and it is correlated with the stage of the disease. The thrombocytosis values can get to values that can raise problems of differentiated diagnosis, but the presence of the digestive disease and the evolution presents it.
Psychosocial impact of inflammatory bowel disease and its practice management as perceived by patients and physicians in Spain. The ENMENTE Project

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Introduction: IBD may cause psychological morbidity. We present here the perceptions from patients and physicians about the psychosocial impact of IBD and its approach by gastroenterologists

Methods: During April 2016 two surveys were available on-line, one for IBD patients, on the ACCU website (IBD Spanish Patients’ Association) and another one for physicians (n = 665) members of GETECCU (Spanish Group for IBD treatment). Both invited their members to participate by email and the patients’ survey was announced in social networks. Both were asked about a) how they perceive the impact of IBD on psychosocial aspects, b) how they think the initial management should be and c), physician behaviours during patients follow-up. A Mann-Whitney test was used to compare 165 valid physicians’ questionnaires with a random sample of 165 patients’ questionnaires.

Results: 912 patients (mean age 39 (± 10) years, 67% women) and 170 physicians (mean age 44 [± 10] years, 58% women) responded. Most physicians and patients agreed that IBD influenced patients’ psychosocial sphere, and that IBD activity can be influenced by patients’ emotional status (table, a). Similarly, both agreed that patients’ psychological evaluation should be routinely addressed in the IBD clinic, and that a clinical psychologist should be part of the IBD clinical team, however the role of the nurse as helping the patients to cope with their disease was less valued by patients than by doctors (table, b). Although > 50% of physicians declared to address psychosocial aspects always/nearly always during patients’ regular visits, this was only perceived by 15–20% of the patients (table, c).
Discussion/Conclusion: Patients and physicians agree on the impact of IBD on patients’ psychosocial sphere and on the importance of addressing it together with a psychologist. However, patients indicate that physicians address these aspects less frequently than doctors perceive. An optimal patient-physician communication would help to refocus on IBD-related morbidity.

Table. Proportion of physicians and patients who responded “agree/totally agree” (a,b) or “always/nearly always” (c).

<table>
<thead>
<tr>
<th></th>
<th>Physicians (n=165)</th>
<th>Patients (n=165)</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>a) Influence of IBD on different patient’s facets</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBD influences psychological status</td>
<td>90</td>
<td>77</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>IBD influences personal relationships</td>
<td>80</td>
<td>61</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>IBD influences every-day life</td>
<td>86</td>
<td>72</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Stress worsens IBD</td>
<td>79</td>
<td>84</td>
<td>ns</td>
</tr>
<tr>
<td>Sadness or depression worsen IBD</td>
<td>76</td>
<td>69</td>
<td>ns</td>
</tr>
<tr>
<td>b) Perception on how the initial management of psychosocial comorbidities should be addressed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician should inquire on patient’s psychological status</td>
<td>93</td>
<td>80</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Psychological treatment should be part of the therapy.</td>
<td>93</td>
<td>77</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>The psychologists should be part of the medical team</td>
<td>95</td>
<td>81</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>The psychologists would be helpful for patients to cope with their disease</td>
<td>77</td>
<td>71</td>
<td>ns</td>
</tr>
<tr>
<td>The nurse may help patients to cope with their disease</td>
<td>68</td>
<td>40</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>c) Percentage of physicians who address several aspects of psychosocial comorbidity of IBD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional status</td>
<td>60</td>
<td>21</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Working life</td>
<td>62</td>
<td>16</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Social life</td>
<td>47</td>
<td>16</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Family life</td>
<td>51</td>
<td>21</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Sexual life</td>
<td>12</td>
<td>4</td>
<td>ns</td>
</tr>
</tbody>
</table>
Intra-abdominal abscesses complicating Crohn’s disease. Clinical and therapeutic features

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Introduction: Intra-abdominal abscesses (IAA) complicating Crohn’s disease (CD) are still difficult to manage. This complication can be serious, especially when it occur in malnourished patients receiving immunosuppressive therapy. The purpose of our study was to describe in CD patients:

- the clinical features
- the management modalities of this complication.

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

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

Discussion/Conclusion: In our series IAA complicate 22.4% of CD patients. When feasible, the percutaneous radiological drainage and antibiotics should be the treatment of choice.
Extraintestinal manifestations in inflammatory bowel disease

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Introduction: Extraintestinal manifestations (EIM) of inflammatory bowel diseases (IBD) are frequent and may occur before or after IBD diagnosis. These manifestations may pose a diagnostic problem when they precede intestinal diseases or a therapeutic problem when they evolve on their own account. The aim of this study is to determine the prevalence and the types of these manifestations in chronic IBD.

Methods: This is a retrospective study including patients followed for a chronic IBD between January 2012 and June 2016. We have systematically researched dermatological manifestations (clinical examination), osteoarticular involvement (clinical examination, radiographs of the spine and sacro-iliac bones), ophthalmic involvement (ophthalmological examination) and hepatobiliary involvement (hepatic and abdominal ultrasound).

Results: There were 70 patients including 40 women and 30 men. The mean age was 54 years (22–65 years). The group of patients included 40 cases of ulcerative colitis and 30 cases of Crohn’s disease. Twenty-nine patients (41.4%) had extraintestinal manifestations, 70% of them had multiple ones. Extra-intestinal manifestations were an osteo-articular involvement in 15 cases (including 13 cases of arthropathy and 2 cases of osteoporosis), cutaneo-mucosal involvement in 10 patients (including 7 cases of oral aphthosis and 3 cases of erythema nodosum), ophthalmologic involvement in 7 patients (anterior uveitis in 3 patients and scleritis in 4 patients) and an hepatic involvement with primary sclerosing cholangitis in 2 cases.

Conclusion: The prevalence of EIM in our series was 41.4%. They were dominated by osteoarticular and cutaneo-mucosal involvements. Sometimes, these EIM can even be more debilitating than the intestinal disease. Careful screening for EIMs and early appropriate diagnosis may be imperative to prevent morbidity.
Inflammatory bowel disease and Sweet’s syndrome: An uncommon association

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Introduction: Sweet's syndrome (SS), also known as acute febrile neutrophilic dermatosis, can be associated with malignancy, autoimmune diseases and collagen vascular diseases. Its association with inflammatory bowel disease (IBD) is unusual. Fewer than 50 cases were published in the medical literature since its first description in 1964.

Methods: We present 4 cases patients with IBD and Sweet's syndrome diagnosed in our department.

Results: They are 4 patients: 3 women with Crohn’s disease and a man with ulcerative colitis. The mean age was 46.5 years. The diagnosis of SS was concomitant with the outbreak of IBD in all cases. Patients presented with a rash of infiltrated, non-pruriginous, erythematous maculopapular elements on the neck, the arms and dorsum of hands with an asymmetric distribution, associated with fever, diarrhea and abdominal pain. Laboratory results revealed inflammatory syndrome and leukocytosis. Blood and stool cultures were negative. Skin biopsy allowed to confirm the SS by showing the presence of a dense inflammatory infiltrate moderately rich in PNN of the superficial dermis and sometimes a leukocytoclastic vasculitis with an important papillary edema. A corticosteroid therapy 1 mg/kg/day was started allowing the disappearance of the digestive and cutaneous symptoms.

Conclusion: The association of SS with IBD is uncommon, appearing mostly in patients with Crohn’s disease with colonic involvement, and predominantly in females. IBD should be excluded in patients presenting with Sweet's syndrome and diarrhea. Alternatively, Sweet's syndrome should be considered as a diagnosis when a patient with IBD develops skin lesions.
Venous thromboembolism with inflammatory bowel disease

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Introduction: Venous thrombosis and thromboembolism appear to be increased in patients with inflammatory bowel disease (IBD). Although several acquired and genetic risk factors are known, about half that develop a thromboembolic event have no identifiable risk factor. Control of the inflammatory process is thought to be the key factor in risk reduction for thrombotic events. Prophylactic use of anticoagulants should be reviewed in an individual patient after evaluation of the risks, such as haemorrhage, compared with potential benefits.

Objective: To investigate the prevalence and risk factors for thromboembolism in IBD.

Methods: We conducted a retrospective study including all patients hospitalized for IBD in the Gastroenterology Department between January 1, 2000 and January 9, 2015. Characterization of the population consisted of the variables IBD (type, location, behavior, and therapy) and thromboembolic event (location and associated risk factors). Only thromboembolism confirmed on imaging were considered.

Results: In total, 295 patients were included. A venous thromboembolism occurred in 12 patients (4%), 7 men and 5 women. Moreover, 7 patients had Crohn’s disease and 5 had ulcerative colitis.

<table>
<thead>
<tr>
<th></th>
<th>Crohn’s disease (n=200)</th>
<th>Ulcerative colitis (n=95)</th>
</tr>
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<tbody>
<tr>
<td><strong>Mean age (years)</strong></td>
<td>38 [18; 72]</td>
<td>28 [17; 58]</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>Male/Female</td>
<td></td>
</tr>
<tr>
<td></td>
<td>87/113</td>
<td>52/43</td>
</tr>
<tr>
<td><strong>Location (n)</strong></td>
<td>L1: 68</td>
<td>E1: 19</td>
</tr>
<tr>
<td></td>
<td>L2: 66</td>
<td>E2: 41</td>
</tr>
<tr>
<td></td>
<td>L3: 46</td>
<td>E3: 35</td>
</tr>
<tr>
<td></td>
<td>L4: 8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p: 18</td>
<td></td>
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<tr>
<td><strong>Behaviour (n)</strong></td>
<td>B1: 92</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B2: 66</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B3: 42</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment (n)</strong></td>
<td>5-Aminosalicylates</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Steroids</td>
<td></td>
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<tr>
<td></td>
<td>Thalidomide</td>
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<td></td>
<td>Anti-TNFα</td>
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</tbody>
</table>

IBD was active in all patients at thromboembolic event. In addition, 5 patients had other concomitant risk factors (protein C deficiency [n = 2], protein S deficiency [n = 1], activated protein C resistance [n = 1], hyperhomocysteinemia [n = 1]).
**Conclusion:** In our study, the prevalence of venous thromboembolism was 4% amongst patients with IBD. Deep vein thrombosis was the most frequent thromboembolic event. All cases occurred during the active phase of IBD.
Factors associated with positive tuberculosis screening in patients with inflammatory bowel disease and efficacy of the screening strategy

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Introduction: Inflammatory bowel disease (IBD), by their own impact on the immunity of our patients, malnutrition and increased use of immunosuppressive treatments determine a group at risk of developing active tuberculosis (AT).

Aim: To report the outcome of the screening of latent tuberculosis and the effectiveness of the latter in the prevention of AT

Methods: We collected retrospectively patients’ records between January 2010 and December 2014 who underwent a tuberculosis screening including at least one Tuberculin Skin Test (TST), chest radiography (CR) (a CT scan was done when doubt on the CR) with or without a blood test: QuantiFERON-TB Gold In-Tube test (QTF). This has occurred as part of a pre-therapeutic assessment or systematically. We also studied the appearance of a possible subsequent AT.

Results: We have studied 123 cases. They were 70 men and 53 women. Smokers or weaned smokers were a total of 36. The average age was 33.24 years and average BMI 20.9 kg/m². Diabetics or hypertensives numbered 4 each. 7 patients had an ulcerative colitis (UC) which was a pancolitis in all cases. 116 patients had Crohn’s disease (CD). In the 6 months before screening tests: 25% of patients were under salicylates, 40.8% under corticosteroids, 44.16% azathioprine (AZA) and 10% under anti-TNF alpha. Patients were in flair-up at screening test in 67.5% of cases, it was a severe one in 36.6% of cases. Biology at the time of the tests: average CRP 71.82 mg/l, an average of 28.8 g/l albumin and hemoglobin average of 10.35 mg/dl. All patients had a TST and a CR, 99 of them (80.4%) had a QTF. 9 had a positive TST, 3 a positive CR and 7 a positive QTF. 4 patients had indeterminate QTF, they were all in severe flares of their disease, and were all under azathioprine, two under AZA and steroids. Chemoprophylaxis was prescribed in all 4 cases. No cases of AT were noted. As for the anti-tubercular chemoprophylaxis, 27 patients (22%) have benefited of it: 13 for a positive test (latent TB), 7 for an immunosuppression (drug-induced) and 7 for malnutrition (low BMI - biological findings).

AT cases under immunosuppressive therapy Number 5 (4.1%)
Received treatment before AT 3: ATF/2: ATF + AZA
Average time to AT 7 months
Localization 3 pulmonary – 1 ganglionic – 1 peritoneal
Positive screening all negative including QTF
Chemoprophylaxis prescribed in 3 cases for malnutrition

Discussion/Conclusion: Despite pretreatment comprehensive assessment including TST, CR and QTF, and despite a relative wide prescription of anti-tubercular chemoprophylaxis, 4.1% of our patients developed active tuberculosis undergoing immunosuppressant treatment. This pretherapeutic assessment is certainly necessary, especially in an endemic country like ours, but is still of limited effectiveness since all our patients who developed tuberculosis reactivation had a negative screening.
Impact of overweight on Crohn’s disease

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Introduction: Nowadays, overweight is becoming a worldwide issue. Its impact has been studied in some populations, however, it is still unknown in Crohn’s disease (CD). The aim of this study was to determine the prevalence of overweight in a Tunisian population of CD and to evaluate its impact on the course of the disease.

Methods: We investigated all the CD patients admitted in our department in the period between January 2014 and December 2015. We determined for each patient the body mass index (BMI). Overweight was defined by a BMI > 25 kg/m².

Results: A total of 55 patients were studied. The prevalence of overweight was 29% with a sex ratio of 1.28. The mean age of patients having an overweight was 42 years, and for those who hadn’t, it was around 31 years. There was no significant difference in age or smoking between overweighing patients and those having a normal weight. No statistically significant difference was noticed in the rate of surgery or the type of administrated medical treatment except for azathioprine which was statistically more prescribed in patients having an overweight (p = 0.034). We also compared the evolution of CD between patients having or not an overweight. There was no significant correlation between overweight and severe course of the disease.

Conclusion: According to this study, azathioprine seems to be more used in case of overweight. However, no impact on the course of the disease was noticed.
Quality of care and opportunities for improvement in the management of hospitalized for severe ulcerative colitis

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Service of Gastroenterology and Hepatology, Service of Emergency, Hospital San Jorge, Huesca, Spain

Introduction: The ECCO establishes quality indicators (QI) for the accreditation of inflammatory bowel diseases units. The aim of this study is to investigate the opportunities of improvement in the management of hospitalized for severe ulcerative colitis in our hospital in the last 10 years.

Methods: Retrospective evaluation of 80 patients for a total of 100 hospitalizations for a severe flare from January 2005 to December 2015 (Truelove-Witts index). A total of 97 items grouped in 14 dimensions allowed to gather information regarding the appropriateness of documentation, procedures, therapeutics (basic and advanced), ethics, communication and outcome. An 'improvement opportunity' was defined as any QI whose compliance was not achieved by 60% of the sample.

Results: We included a total of 80 patients (52% women) it represents 0.88/1000 of admissions in our hospital in 10 years. Mean age: 50.22 [CI: 47.04–53.40]. 26 of the 97 QIs analyzed (25%) presented values < 60%, including underestimation of the air luminogram, (9.7% [CI: 2.1–17.2]); Lack of information about antibiotic consumption, NSAIDs or pre-admission travels (29.73% [CI: 20.63–23.53]); (42.4% [CI: 32.5–52.3]), iron levels (32.9% [CI: 22.7–43.1]); (CI: 57.1% [46.3–67.9]), inadequate endovenous iron infusion rates (9.0% [CI: 3.3–14.7]), poor communication with the Surgery Service (CI: 0.0–13.8), difficulties in providing contact telephone numbers and e-mail addresses to a specialized post-discharge (6.3% [CI: 1.3–11.2], follow up in the first 2 weeks (CI: 18.5–36.6) or an information sheet on the nature of the disease (2.2% [CI: 0.0–5.2]) Average stay: 10.8 days [8.7–12.9], mortality: 0%, re-admission rate at 30 days: 2% and colectomy rate for long-term therapeutic failure: 2%.

Discussion/Conclusion: The management of the severe ulcerative colitis has been optimal in the 10 years of follow-up. However, there are opportunities for improvement especially in nutritional assessment, communication with the surgical service and the ethical dimension.
Characterization of human intestinal macrophage subsets in health and inflammatory bowel disease

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Introduction: Inflammatory bowel disease (IBD), including Crohn’s disease (CD) and ulcerative colitis (UC), is driven by an exacerbated immune response to the commensal microbiota. Intestinal macrophages (MΦ) are critical at shaping the type of immune elicited towards the microbiota. Here, we have characterized human intestinal MΦ in healthy controls and IBD patients.

Methods: Colonic biopsies were obtained from the inflamed and non-inflamed tissue from IBD patients (CD/UC), as well as from the non-inflamed tissue from quiescent patients and healthy controls. Biopsies were immediately processed and lamina propria mononuclear cells characterized by flow cytometry both in resting conditions and after overnight culture in the presence/absence of LPS.

Results: Human intestinal MΦ were identified within singlet viable cells as CD45+HLA-DR+CD14+CD64+ and further divided into CD11chigh, CD11cdim and CD11c- subsets. CD206 expression was higher compared with CD86 on total MΦ revealing a M2-biased MΦ profile in the healthy gut which however was not associated with any particular subset. However, the CD11c- subset had higher expression of HLA-DR, CD64 and PDL1 coupled with lower expression of SIRPα, CCR2 and CD40 compared with the CD11chigh/dim subsets. CD11c- MΦ had higher production of IL-10 and lower production of IL-6 and TNFα both in resting conditions and after LPS challenge compared with the CD11chigh/dim subsets. Finally, total MΦ numbers were increased in the inflamed tissue from IBD patients (both CD and UC), although not on the non-inflamed tissue or on quiescent patients, due to specifically higher numbers of the pro-inflammatory CD11chigh MΦ subset.

Discussion/Conclusion: MΦ subsets are likely to represent newly arrived monocytes (CD11chigh) differentiating into transient (CD11cdim) and resident (CD11c-) tolerogenic MΦ. The higher numbers of pro-inflammatory CD11chigh MΦ shown in the inflamed mucosa from IBD patients is probably reflecting the increased recruitment capacity of circulating monocytes elicited by the mucosa, hence exacerbating the immune response.
A viral FLIP homologue is able to disrupt intestinal immune homeostasis in vivo

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Introduction: We could recently show that the caspase-8 activity needs to be tightly controlled in the intestinal epithelium to regulate cell death pathways and to maintain barrier integrity. Interestingly certain poxviruses and herpesviruses express a viral FLIP (vFLIP) which is suggested to inhibit the caspase-8 activity. To elucidate the ability of vFLIP to influence the caspase-8 activity and the gut homeostasis, we analyzed mice, which express vFLIP in intestinal epithelial cells (IECs).

Methods: We generated mice which express KSHV-vFLIP in the intestinal epithelium (vFLIPIEC-tg). The gene expression pattern in IECs of vFLIPIEC-tg and control mice was analyzed by quantitative PCR. vFLIPIEC-tg and control mice were histologically analyzed by immunohistochemistry. Furthermore we analyzed the protein expression of IECs from vFLIPIEC-tg mice.

Results: Expression of KSHV-vFLIP in the intestinal epithelium leads to a spontaneous development of inflammatory lesions in the intestine. Immunohistochemical staining revealed a high amount of immune cell infiltration and quantitative PCR analysis showed increased levels of proinflammatory markers. Moreover vFLIPIEC-tg mice were characterized by a reduced number of Paneth cells due to a high amount of cell death in the small intestine. Furthermore we could discover a dysregulation of classical and alternative NFκB signaling by western blot and immunohistochemical staining.

Discussion/Conclusion: vFLIPIEC-tg mice develop a dramatic phenotype which is characterized by a spontaneous development of inflammatory lesions and a reduction of the Paneth cell number, indicating a dysregulation in the immune defence and the intestinal epithelial barrier. Interestingly these features resemble the phenotype observed in mice, which lack caspase-8 in intestinal epithelial cells, suggesting that KSHV-vFLIP in vivo might affect the caspase-8 activity and therefore disturb the cell death pathways leading to an imbalance of cell death and proliferation in the gut.
Study of fatigue, anxiety, depression, quality of life and work impairment in IBD

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Introduction: Inflammatory bowel diseases (IBD) is a chronic condition that presents with many different symptoms. Rectal bleeding, diarrhea and abdominal pain are the most common symptoms. These patients also seem to present fatigue, anxiety and depression more frequently than the general population. Our aim is to evaluate the frequency of these symptoms in our patients, work situation and productivity and the effect of different factors on work productivity and quality of life.

Methods: Descriptive cross-sectional study. Patients with IBD attended at our consultation, over 18 years old and previously informed and signed informed consent, were consecutively included. We used the following questionnaires to evaluate the symptoms: fatigue, “Fatigue Severity Scale”; anxiety and depression, “Hospital Anxiety and Depression Severity Scale”; work productivity, “Work Productivity and Activity Impairment questionnaire for general health”. The demographic and disease data, and the results of the questionnaires were introduced into a database and analyzed using the IBM Statistic SPSS v22 program. The frequency of patient’s fatigue, anxiety and depression and their impact on work productivity were analyzed through logistic regression analysis.

Results: A total of 90 patients between 22 and 81 years old were analyzed. Anxiety was detected in 60% of patients, depression 56.7% and fatigue in 35.7%. Work productivity was diminished in our patients. Fatigue was a key determinant of labor productivity, affected 4 times more in patients suffering from it (p < 0.001). The activity of IBD was another key factor (p < 0.034), although 32% of patients with IBD in remission had also affected their work productivity. Patients with active disease presented greater fatigue (p < 0.001).

Discussion/Conclusion: In our patients with IBD there is a high prevalence of fatigue depression and anxiety and impairness of work productivity. Fatigue and disease activity have a large impact on quality of life and labor productivity.
Azathioprine in the maintenance of steroid-free remission in inflammatory bowel disease patients: Efficacy and safety in five years of follow-up

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

Methods: We investigated its efficacy and safety in maintaining steroid-free remission in steroid dependent IBD patients five year after the institution of treatment. Data from consecutive IBD outpatients referred in our Institution between 1985–2014, were reviewed and all patients treated with AZA were included. AZA was administered at the recommended dose of 2–2.5 mg/kg.

Results: Out of 2684 consecutive IBD outpatients visited in the index period, AZA was prescribed to 398 patients, 216 (54.3\%) were affected by Crohn’s disease (CD) and 182 (45.7\%) by ulcerative colitis (UC). One hundred and thirty-eight patients with a follow-up < 60 months were excluded from the study. Two hundred and sixty patients were evaluated, 145 (55.8\%) with CD and 115 (44.2\%) with UC. One hundred and forty-six (56.2\%) were male and 114 (43.8\%) female (average age of 34.85 ± 14.92 SD years, range 14–74 years). Five year after the institution of treatment, 135 (51.9\%) patients still were in steroid-free remission (86 CD vs 49 UC, 59.3\% and 42.6\%, respectively, \(p = 0.0087\)), 71 (27.3\%) had a relapse requiring retreatment with steroids (29 CD vs 42 UC, 20\% and 36.5\%, respectively, \(p = 0.0033\)), 54 (20.8\%) discontinued the treatment due to side effects (30 CD vs 24 UC, 20.7\% and 20.9\%, respectively). Loss of response from 1\textsuperscript{st} to 5\textsuperscript{th} year of follow-up was low, about 18\%.

Discussion/Conclusion: Five year after the onset of treatment 52\% of patients did not require further steroid courses. After the first year loss of response was low in four subsequent years. In the present series the maintenance of steroid-free remission was significantly higher in CD than in UC patients. The occurrence of side effects leading to the withdrawal of AZA treatment has been low.
Association between anti-TNF serum levels and mucosal healing (MH) in inflammatory bowel disease (IBD)

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Objectives: a) To evaluate the diagnostic accuracy of anti-TNF through levels to predict MH in IBD; b) to determine the best cut-off point to predict MH in IBD patients treated with anti-TNFs.

Methods: Multicenter, prospective study. IBD patients under anti-TNF treatment for at least 6 months that had to undergo an endoscopy for medical indication were included. Patients with incomplete endoscopy, those with intestinal segments affected by the disease non-accessible to endoscopy, and those receiving anti-TNF to prevent postsurgical recurrence were excluded. MH was defined as: Simplified Endoscopic Score for Crohn’s disease (SES-CD) < 3, Rutgeerts score < i2 or Mayo endoscopic score < 2. Anti-TNF concentrations were measured using SMART ELISAs (Sanquin Reagents, Amsterdam, The Netherlands).

Results: 182 patients were included; 50% were male, 70% had Crohn’s disease and 49% had MH. 52% of patients were under adalimumab (ADA) and 48% under infliximab (IFX) treatment; 26% of patients had previously received another anti-TNF agent. 32% of patients were on concomitant treatment with thiopurines. IFX through levels (median) were significantly higher among patients that had MH than among those who did not (4.8 vs. 3 μg/mL, p = 0.04). Similarly, ADA through levels were significantly higher among patients with MH (9.8 vs. 6.6 μg/mL, p = 0.04). The accuracy of anti-TNF through levels to predict MH is shown in table 1. Concomitant treatment with immunomodulators had no impact on anti-TNF drug levels. In the multivariate analysis, to have anti-TNF drug levels above the threshold (3.4 μg/mL for IFX, and 7.2 μg/mL for ADA) and to have ulcerative colitis (instead of Crohn’s disease) were the
variables associated with a higher probability of having MH (OR = 3.1, 95% CI = 1.5–6.5 and OR = 4, 95% CI = 1.7–9.5, respectively). On the other hand, to have needed an escalated dosage (OR = 0.2, 95% CI = 0.08–0.45) and to be current smoker (vs. non-smoker) (OR = 0.2, 95% CI = 0.09–0.52) were associated with a lower probability of MH.

**Conclusions:** There was an association between anti-TNF through levels and MH in IBD patients; however, the accuracy of the determination of both IFX and ADA concentrations to predict MH was suboptimal. To have IFX through levels above 3.4 μg/mL had a positive predictive value for MH of > 70%.

*Table 1: Accuracy of anti-TNF through serum levels to predict mucosal healing in inflammatory bowel disease patients*

<table>
<thead>
<tr>
<th>Anti-TNF</th>
<th>AUC</th>
<th>Best cut-off point</th>
<th>S</th>
<th>E</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFX</td>
<td>0.63</td>
<td>3.4</td>
<td>60%</td>
<td>60%</td>
<td>73%</td>
<td>42%</td>
</tr>
<tr>
<td>ADA</td>
<td>0.60</td>
<td>7.2</td>
<td>65%</td>
<td>56%</td>
<td>46%</td>
<td>72%</td>
</tr>
</tbody>
</table>

IFX, infliximab; ADA, adalimumab; AUC, area under the ROC curve; S, sensitivity; E, specificity; PPV, positive predictive value; NPV, negative predictive value.
**Malnutrition in Tunisian Crohn’s disease patients**

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

**Methods:** We conducted a retrospective monocentric study including hospitalized patients with CD between January 2011 and January 2016. The patients were divided into 2 groups:
- Group 1: patients with normal body mass index (BMI) and
- Group 2: Malnourished patients.

Undernutrition was defined as a BMI < 18.5 kg/m² and classified according to the WHO classification in deep (BMI < 15), severe (15 < BMI < 17) and moderate (17 < BMI < 18.5).

**Results:**

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 37)</th>
<th>Group 2 (n = 7)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>37</td>
<td>34.43</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>22/15</td>
<td>3/4</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
<td>54%</td>
<td>42.8%</td>
<td>NS</td>
</tr>
<tr>
<td>CD operated</td>
<td>18.9%</td>
<td>28.5%</td>
<td>NS</td>
</tr>
<tr>
<td>Seat of the disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ileal</td>
<td>35.2%</td>
<td>28.5%</td>
<td>NS</td>
</tr>
<tr>
<td>Ileo-colic</td>
<td>37.8%</td>
<td>71.5%</td>
<td>0.06 NS</td>
</tr>
<tr>
<td>Colic</td>
<td>27%</td>
<td>0%</td>
<td>NS</td>
</tr>
<tr>
<td>Ano-perineal manifestations</td>
<td>21.1%</td>
<td>14.2%</td>
<td>NS</td>
</tr>
<tr>
<td>Extra-intestinal</td>
<td>40.5%</td>
<td>42.8%</td>
<td>NS</td>
</tr>
<tr>
<td>complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuminemia &lt; 30 g/l</td>
<td>43.2%</td>
<td>42.8%</td>
<td>NS</td>
</tr>
<tr>
<td>Complications:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stenosis</td>
<td>62.1%</td>
<td>85.6%</td>
<td>NS</td>
</tr>
<tr>
<td>Abscess</td>
<td>16.2%</td>
<td>42.8%</td>
<td>NS</td>
</tr>
<tr>
<td>Fistula</td>
<td>16.2%</td>
<td>42.8%</td>
<td>NS</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>70.2%</td>
<td>42.8%</td>
<td>NS</td>
</tr>
<tr>
<td>Immunosuppressive therapy</td>
<td>62.1%</td>
<td>85.7%</td>
<td>NS</td>
</tr>
<tr>
<td>Surgery</td>
<td>24.3%</td>
<td>57.1%</td>
<td>NS</td>
</tr>
</tbody>
</table>
Discussion/Conclusion: In our series, malnutrition was observed in 16% of CD patients. No characteristics related to the patients nor to the disease are significantly associated with undernutrition.
Significant disabling anxiety as a side effect with anti-TNFs necessitating cessation of treatment. More common than we thought

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Methods: We have prospectively kept a database since 2008 of all patients on anti-TNFs (infliximab or adalimumab) used at our hospital to treat inflammatory bowel disease. As part of their follow up, side effects have been logged. These side effects have been obtained either in clinic consultations or telephone consultations with the patients.

Results: Since 2008 we have treated 178 patients with adalimumab and 167 with Infliximab. In patients on adalimumab, 21 (11.8%) patients have complained spontaneously of becoming very anxious, 5 (2.8%) of whom it was significant enough to necessitate stopping adalimumab. 15 carried on as their IBD was significantly better but still with a new onset of marked anxiety. 4 patients carried on with a new prescription of anxiolytics. Of the 167 patients on Infliximab, 14 patients (8.3%) patients have complained spontaneously of becoming very anxious, 3 (1.8%) of whom it was significant enough to necessitate stopping infliximab. 11 carried on as their IBD was significantly better but still with a new onset of marked anxiety. 2 patients carried on with help of a new prescription of anxiolytics. None of the patients in the study had ever previously reported problems with anxiety and were not previously on medication for anxiety or depression. The patients who had to stop adalimumab and were previously TNF naive were switched to infliximab (n = 3). One managed to switch completely successfully, the others had anxiety on the infliximab but not as severe. The patients who had to stop infliximab and were previously TNF naive were switched to adalimumab (n = 2). One managed to switch successfully, the other had anxiety on the adalimumab but not as severe.

Discussion/Conclusion: Previous studies looking at side effects of anti-TNFs have recognised anxiety as a side effect but these have always been regarded as very uncommon eg approximately 0.05%. Our study would suggest that the rate of this as a side effect is much commoner and when looked for will certainly be over 5% with approximately 2% of patients having to stop treatment with the anti-TNF. Some of these patients can be managed by switching anti-TNFs of by using anxiolytics.
Magnetic enterography and Crohn’s disease activity index: The correlation between imaging technique and clinical index of disease activity

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Background: Magnetic enterography (MR) represents the gold standard in the evaluation of disease activity of the small intestine in patients with Crohn’s disease (CD). Contrary, Crohn’s disease activity index (CDAI) is a well validated clinical activity index of CD in clinical practice. The aim of this study was to evaluate the correlation between MR and CDAI in patients (pts) with CD with small intestine involvement.

Methods: We evaluated retrospectively 40 pts with CD hospitalized in the period 2013–2015. In all pts CDAI was calculated in the standard manner; < 150 points remission; 150–450 points mild and moderate disease, > 450 severe forms. MR analyses included evaluation of further variables: presence of hyperemia, ascites, lymphadenopathy and fibrosis. Pts were phenotypically classified according to Montreal classification. For the purpose of this study MR results were presented as the sum of points (1 point for each variable – positive result, 2 points – negative results).

Results: We analyzed 40 pts (23 female, 17 male), average age 40 yrs (min 19, max 77 yrs). The average CDAI was 351. Isolated involvement of small intestine had 40%, ileocolitis 45%, and more severe forms of the disease (upper GI tract, perianal disease) 15% of pts. According to CDAI remission had 10%, mild-moderate disease 70%, severe disease 20% of pts. Hyperemia in MR had 57.5%, ascites 42.5% and fibrosis 45% of pts. The correlation among the variables were examined with Pearson coefficient for numerical, and Spearman coefficient for categorical variables. Correlation of MR and CDAI score was statistically significant (Spearman coefficient – 0.552, p < 0.05). Correlation of CDAI with single MR variables showed that lymph node involvement positively correlated with CDAI (Pearson 0.245), hyperemia negatively correlated with CDAI (Spearman – 0.260), ascites positively correlated with CDAI (Spearman – 0.158). There was a positive correlation between the presence of fibrosis and CDAI (Spearman – 0.169) and fibrosis and MR score (Spearman – 0.272).

Conclusion: MR enterography score in patients with CD positively correlated with CDAI, especially for variable lymphadenopathy and ascites. Interestingly, fibrosis as a separate indicator also showed the positive correlation with CDAI. We can conclude that CDAI, despite advanced imaging techniques, still represents good clinical indicator of disease activity, also in the most different phenotypes of inflammatory bowel disease.
Onset-time of acute severe colitis in the course of an inflammatory bowel disease: Is it a prognostic factor?

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Background: Acute severe colitis (ASC) is a potentially life-threatening condition that may occur at any time during the course of inflammatory bowel diseases (IBD).

In this study, we aimed to compare outcomes of patients with a known diagnosis of IBD who develop ASC and those who had an ASC as a first flare-up of their disease.

Methods: We studied retrospectively a cohort of IBD patients admitted to our unit for an ASC over a 10 year-period (2006 to 2015). Patients were divided in two groups based on the onset time of ASC (Group A: ASC inaugurating IBD; Group B: ASC occurring during the course of a known IBD). Demographics, clinical presentation, response to medical treatment and colectomy rate were compared between the two groups. Statistical analyses were performed using analysis of variance when comparing continuous variables between multiple groups and x2 test (and Fisher’s exact test when necessary) for categorical data.

Results: A total of 86 patients, divided into group A (n = 36) and group B (n = 46), were enrolled during the study period. There were no statistical difference between both groups in terms of sex ratio (A: 0.75 Vs B: 0.66; p = 0.806), median age (A: 36 years Vs B: 34 years; p = 0.7), laboratory findings including hemoglobin (A: 11.6 g/dl Vs B: 11.1 g/dl; p = 0.305) and C reactive protein (A: 86.9 mg/l Vs B: 105 mg/l; p = 0.204), response to steroid therapy (A: 52% Vs B: 44.6%; p = 0.102) and colectomy rate (A = 8.6%; Vs B: 11.1%; p = 0.561). Only endoscopic signs of severity were significantly more common in patients of group A compared to those of group B (68.7% Vs 44.2%; p = 0.002).

Conclusion: Acute severe colitis occurring as a first flare-up of IBD seemed to have more severe endoscopic lesions than those witch develop during the course of the disease. However, response to therapy and need for colectomy are similar in both groups.
Telemedicine enables a safe shift from examination room based care to personalized care for inflammatory bowel disease: A pragmatic randomized multicenter trial with myIBDcoach

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Introduction: Inflammatory bowel disease (IBD) is a group of chronic diseases with a heterogenic disease course and therapy response. Tight and personalized control of disease activity, with attention for all aspects influencing activity, is warranted to prevent long-term complications and improve quality of life (QoL). This is challenging given the increasing economic pressure on health systems, moreover since the incidence of IBD is rising. We developed myIBDcoach: the first telemedicine system for IBD patients, regardless of phenotype, severity or treatment. We aimed to evaluate the effect of myIBDcoach on number of outpatient visits, patient-reported quality of care (PRQoC) and health outcomes in a pragmatic, randomized trial.

Methods: From September 2014 to May 2015, all consecutive IBD outpatients in 2 academic and 2 non-academic hospitals in The Netherlands, aged 18 to 75 years, with internet-access and Dutch proficiency, were eligible for inclusion. Patients were randomized (1:1) to use of myIBDcoach (intervention group) or standard care (control group) and followed for 12 months. Patients using myIBDcoach were invited to visit the outpatient clinic at least once a year, or on demand. Data on outpatient visits, flares, corticosteroid use, hospitalizations, emergency visits and IBD-related surgery were collected from the hospital electronic patient record and analyzed using multivariate linear regression analysis. At baseline and 12 months, patients were requested to fill out a questionnaire including PRQoC, QoL (SIBDQ), adherence (MMAS-8) and self-efficacy (IBD-SES). Questionnaire data were analyzed using linear mixed models.

Results: In total, 465 patients used myIBDcoach and 444 continued standard care. The mean number of outpatient visits during follow up was lower in the intervention group compared to the control group (1.55 ± 1.50 and 2.34 ± 1.64; p < 0.001). After 12 months, both groups reported high scores on PRQoC on a VAS-scale, respectively 8.16 ± 1.37 and 8.27 ± 1.28 (p = 0.411). The mean number of hospitalizations was
lower in the intervention group compared to the control group (0.05 ± 0.28 and 0.10 ± 0.54; p < 0.001). No differences were observed in flares, corticosteroid use, emergency visits or surgeries. Patients using myIBDcoach reported higher medication adherence rates (p < 0.001), higher, but not significant, QoL (p = 0.057) and similar self-efficacy scores (p = 0.572).

Discussion/Conclusion: This pragmatic trial showed that telemedicine through myIBDcoach was safe, reduced outpatient visits and hospitalizations and improved medication adherence with equal PRQoC compared to standard care. MyIBDcoach monitors disease activity, patient reported outcomes and drug side-effects and may therefore be used to reorganize IBD-care enabling value based healthcare.
**Aeromonas infection in inflammatory bowel disease patients**

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**Introduction:** *Aeromonas* infection has been suggested both as a trigger of flares in inflammatory bowel disease (IBD) and as a cause of *de novo* colitis in patients with no history of IBD. The aim of this study is to determine the prevalence and clinical characteristics of *Aeromonas* gastrointestinal infection in patients with IBD.

**Methods:** Observational retrospective study in a Spanish tertiary referral center including all patients (with and without IBD) with a stool or a colon biopsy culture positive for *Aeromonas spp.* between January 2009 and December 2014.

**Results:** 75 *Aeromonas* isolates in stool or colon biopsy cultures were detected. The full analysis set included 75 *Aeromonas* isolates in 71 patients (69 in stools and 6 in colon biopsies). Six patients had diagnosis of IBD (IBD cohort of 1,190 patients): 3 Crohn’s disease (CD) and 3 ulcerative colitis (UC). One patient had *Aeromonas* infection during his first flare-up of UC. The severity of infection: 3 were mild, 2 moderate and 2 severe. More than half of the patients were hospitalized due to the severity of the infection without deaths. We found 3 strains of *A. veronii*, 3 of *A. hydrophila* and 1 of *A. caviae*. All the patients received ciprofloxacin. *Aeromonas* infection recurred in one patient after antibiotic. Changes in IBD treatment were performed: 1 patient shortening the interval of biological therapy, 2 patients initiated oral low systemic bioavailability steroids and 1 patient initiated systemic corticosteroids. During the follow-up period none of the other 64 patients developed IBD.

**Discussion/Conclusion:** *Aeromonas* infection affecting the gastrointestinal tract is infrequent in our center, both in IBD and non-IBD patients. The majority of IBD patients with *Aeromonas* infection had a moderate/severe presentation with high hospitalization rates. More prospective studies are needed to establish the role of *Aeromonas* infection both in patients with and without IBD.
Expression of pro-inflammatory and apoptotic genes is associated with therapy in Crohn’s disease patients – A pilot study

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Introduction: Patients with the active Crohn disease (CD) have increased levels of pro-inflammatory cytokines. Deregulation of T-cells apoptosis contributes to the disease development. Elimination of activated T-cells is regulated by Fas and Fas ligand (FasL) interaction. Apoptotic rate is also regulated by the level of anti-apoptotic Bcl-2 and pro-apoptotic Bax. Decrease in a number of T-cells and their cytokine production, is an expected result of the therapy. The aim of this study was to measure levels of inflammation and apoptosis in CD patients treated with different therapies.

Methods: For 23 CD patients with active disease transcriptional levels of pro-inflammatory TNF-α and IL-6 cytokine genes, as well as Bcl-2, Bax, Fas, FasL apoptotic genes were measured in three types of tissue: healthy intestine, inflammation affected mucosa and peripheral blood mononuclear cells by real-time PCR method. Patients were divided according to their therapy in three groups: de novo patients who received no therapy, group treated with ASA only, and ASA with other anti-inflammatory drug such as corticosteroids or AZA (ASA+). Differences in transcriptional levels of analyzed genes were compared by Kruskal-Wallis test.

Results: There was statistically significant difference in levels of TNF-α and IL-6 in inflamed mucosa between groups that received different therapies (p = 0.01; p = 0.002, respectively). The highest levels of gene expression of both cytokines was observed in de novo CD patients. Also, significant difference was found in levels of Bax gene in peripheral blood mononuclear cells (p = 0.026). Bcl-2 and Bax genes were more expressed in ASA+ group than in other groups.

Conclusion: Patients who received more intense therapy had higher levels of pro-inflammatory genes. Interestingly, these patients had higher expression of pro-apoptotic and anti-apoptotic genes. Interaction between disease severity and therapy could be important for understanding the course of the disease and lead to patient stratification and improvement of therapy protocol.
Screening for liver diseases in IBD patients with non-invasive fibrosis scores

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Introduction: The prevalence of chronic liver damages in patients with inflammatory bowel disease (IBD) could be underestimated. Considering that liver disease is often asymptomatic until end-stage complications occur, identification of risk factors and early diagnosis is critical to the beginning of the therapy. The levels of transaminases alone have poor predictive value to evaluate liver fibrosis. Moreover liver biopsy is an invasive, painful intervention, which has several complications. The aim of our retrospective study was to investigate liver fibrosis in IBD patients by using routine laboratory data, non-invasive scores, measurements of redox parameters and determining elements in them.

Methods: Sixteen inactive IBD patients (male = 7, female = 9), treated with ordinary therapy were examined. Routine laboratory parameters were measured and compared to healthy controls (N = 16). Erythrocyte and plasma total scavenger capacity (TSC) and hydrogen donating ability (HDON) measurements were carried out to assess the redox homeostasis of the patients. Zn, Cu, Fe were measured with ICP-OES. Se content was determined with a cathodic stripping voltametric method. AAR, APRI, GAPRI, Fibrosis index were calculated to determine liver fibrosis.

Results: Liver fibrosis scores were higher in the IBD group, especially in Crohn’s disease. MCV, MCH, MCHC, albumin, Zn, Cu, Fe and Se levels were lower, and thrombocyte count and transaminase levels were higher in all IBD patients compared to the healthy group. Redox parameters were not significantly higher compared to the healthy group.

Discussion/Conclusion: The early screening for liver diseases in IBD patients would be necessary, although, routine laboratory parameters are not always sensitive enough to predict liver damage. Non-invasive scores of liver fibrosis with simple biomarkers could be set in the management of IBD patients in clinics. Further large-scale, prospective studies would be necessary to investigate the effect of screening with simple biomarkers or with new medical imaging techniques (TE, SWE, MRE).
Liver biological abnormalities in inflammatory bowel diseases

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Introduction: The discovery of liver biological abnormalities (LBA) during diagnosis or during the follow-up of chronic inflammatory bowel disease (IBD) is a common occurrence in our practice. The aim of our study was to determine the prevalence of LBA in IBD patients, and to identify the different etiologies responsible for these abnormalities.

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

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

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

Discussion/Conclusion: In our series, 12% of patients had LBA. These abnormalities were transient in the quarter of patients. Acute hepatitis B, which is independent of IBD, was the most common etiology.
Re-phrasing the question: A simple tool for evaluation of adherence to therapy in patients with inflammatory bowel disease

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Introduction: Non-adherence to medication in patients with inflammatory bowel disease (IBD) is a challenging problem which is often underestimated.

Objectives: To examine if re-phrasing the wording of the question used by the physician could help in revealing more patients who are non-adherent.

Methods: A cross-sectional questionnaire-based study of IBD patients was conducted. Patients received a questionnaire detailing their treatments, disease course and perceptions about disease. Two forms of questions were placed in two separate parts of the questionnaire: ‘are you taking your medications regularly as prescribed?’ (Standard question), and ‘how often does it happen that you miss a drug dosing?’ (Re-phrased question). The rate of non-adherence disclosed by each of these questions was compared. Sensitivity, specificity and predicative values were computed for each question. Predictors of non-compliance and of denying non-compliance were also explored.

Results: Overall, 165 patients were included (49% female, 29.6% with UC, 62.4% with CD). Fifty (30.3%) of the patients admitted to non-adherence in the last month when asked by the re-phrased question, compared to only 10 patients (6%) when asked by the standard question (OR 7.4, 95% CI 3.6–15.2, p < 0.001). Thus, a standard question format disclosed only 20% of genuinely non-compliant patients and had 16% sensitivity and 98.2% specificity for revealing non-adherence (PPV 80%, NPV 72.9%). No single demographic or clinical factor correlated with non-adherence. The only factor which correlated with higher probability for non-adherence was biological and combination treatment.

Discussion/Conclusion: Asking patients how often does it happen that they miss a drug dosing is a simple practical tool which performs significantly better in disclosing non-adherence compared to asking patients if they take their medication as they should.
Results of medical treatment in symptomatic stenosing ileal disease during Crohn’s disease and predictive factors of surgical treatment

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Introduction: The place (square) of the medical treatment in the disease of symptomatic Crohn iléale sténosante is badly defined. The therapeutic indication depends in a narrow way on the clinico-biological expression as well as the data of the imaging. The purpose of this study was to bring back (to report) the results (profits) of the medical treatment on stenoses symptomatic iléales and the predictive factors (mailmen) of its failure and appeal (recourse) to the surgery

Patients and Methods: We brought together afterward the patients having a disease of Crohn with a stenosis symptomatic iléale between 2009 and 2014. The clinical data and paracliniques were collected (taken in) from the files (cases) of the sick and compiled with the software Excel 2013.

Results (Profits): 53 cases of MC sténosante were brought together. The sex ratio was of the sex ratio was 1.57 H/F. The average age at the time of the diagnosis was of 31.6 years, the average age in the inclusion was of 40.5 years. The duration of evolution average of the disease was of 50.49 months. 22/53 (41.5%) patients were smoking (4 weaned [deprived]). The seat (siege) of the stenosis was the terminal iléon at all the patients. The chronic pains of the straight (right) iliac pit 35/53 (66%) with one gene in the broadcast (emission,issue) of gases. Subocclusifs syndromes were noted in 21/53 (39.6%) and the picture (board) was inaugurated by a pseudo-surgical shape to type (chap) of painful and feverish syndrome of the straight (right) iliac pit to 6/53 (11.3%) cases. 19/53 (35.8%) patients were put under mésalazine and 35/53 (66%) under corticoids. A treatment (processing) by azathioprine was established in front of a first severe push to 8/53 (15%) patients and in front of a corticodépendance to 15/53 (28.3%). The appeal (recourse) to anti-TNF was necessary at 4/53 (7.5%) patients in front of an association for an evolutionary SPA (SOCIETY FOR THE PREVENTION OF CRUELTY TO ANIMALS) to 1 case and the secondary appearance of complex anal fistulas at 2 patients and the area (extent) of the infringement (achievement) iléale to 1 case.

21/53 (39.6%) cases were operated after an average deadline (extension) of 22 months (3–60 months) in front of the arisen of an OIA at 15 patients, a corticorésistance to 4et a deep collection to 2des case.

The predictive factors (mailmen) of surgery was the smoking (64% vs 23%, p = 0.02), the presence of subocclusifs syndromes at the time of the diagnosis (57% versus 28%, p = 0.035), the presence of sub-mucous oedema in the imaging (49% versus 8%, p = 0.011 and the number of pushes ≥ 3 before the surgery (80% versus 0.47%, p = 0.05), the rate of albumin (34,4 vs 30,5, p = 0.02), and CRP (TEACHERS’ CENTRE) little raised (little brought up) initial (25,4 vs 31,36, p = 0.012)

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**Conclusion:** The medical treatment can establish (constitute) an effective stage in the coverage (care) of the disease of Crohn iléale sténosante allowing to delay at the most a sometimes mutilating surgery otherwise to cross(spend) an acute (sharp) course (cape) allowing to intervene in better conditions.
Long term outcome of Crohn’s disease patients treated with methotrexate: A retrospective monocenter study

Service de Gastroentérologie A, La Rabta, Tunis, Tunisia

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

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

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

Conclusion: Methotrexate is trivial and efficient to maintain clinical remission in Crohn’s disease patients. This treatment should be considered in Crohn’s disease patients, namely after failure or intolerance to thiopurines.
Frequency of the metabolic syndrome during inflammatory bowel diseases

Service de Gastroentérologie A, La Rabta, Tunis, Tunisia

Introduction: The metabolic syndrome (MS) is more and more frequent in the general population. However, its prevalence was not enough studied during inflammatory bowel diseases (MICI). The purpose of this study was to determine frequency of the SM in a population of IBD patients

Materials and Methods: The study includes all IBD patients hospitalised in our department during one year. We precised for each patient the body mass index (BMI), the blood pressure (AP), the blood glucose (G), the blood rate of total cholesterol (TC), triglycerides (TG) and the HDL cholesterol (HC). The diagnosis of MS was defined by the presence of 2 criteria among the following ones: BMI > 25 kg/m², AP > 13.5/8.5 cm Hg, TC > 2 g/l, TG > 1.5 g/l, HC > 0.5 g/l in woman or 0.4 g/l in man, G > 1 g/l.

Results: 75 patients were included during the period of study, 60 had Crohn’s disease (CD) and 15 an ulcerative colitis (UC). Total frequency of the MS was 38.66%. It was of 32.14% in CD group and 57.86% in UC group. The difference was not statistically significant between the both groups (p = 0.6). In CD patients, MS was significantly correlated with the existence of a family history of hypertension, diabetes or dyslipidemia (p = 0.004). However there was no statistically significant difference according to the age, the sex, the smoking, the location of disease and medical treatment. In the UC group, we found a significant association between azathioprine taken and a MS (p = 0.048).

Conclusion: In our study, a MS was observed in 38.6% of IBD patients. It seems to be associated to the existence of family history of diabetes, arterial hypertension or dyslipidemia during CD and the azathioprine taken during UC.
Prevalence and risk factors of overweight and obesity in Crohn’s disease patients

Service de Gastroentérologie A, La Rabta, Tunis, Tunisia

Introduction: It has been suggested that despite nutritional deficiencies, prevalence of overweight and obesity in Crohn’s disease patients is high. The aim of our study was to determine the frequency and risk factors of overweight and obesity in Crohn’s disease patients

Patients and Methods: We conducted a retrospective study including Crohn’s disease patients who were admitted in our department during a flare-up of their disease over a 12-month period. Epidemiologic and clinical features (weight, height, body mass index, blood pressure and characteristics of the disease) and laboratory data were abstracted from medical records. Patients having overweight (group A, 25 < BMI < 30 kg/m²) were compared with those with obesity (group B, BMI > 30 kg/m²). Statistical analysis was performed with SPSS software version 21.0.

Results: We have colligated 44 patients. There were 24 males and 20 females. Mean age was 30.3 years (14 – 65 years). CD was ileal (n = 16), colonic (n = 9), and ileocolonic (n = 19). Phenotype of the disease was non stricturing non penetrating (n = 22), stricturing (n = 16) and penetrating (n = 6). There were 7 patients in group A and 37 patients in group B. Over a mean follow-up period of 13.4 months, severe acute colitis occurred in 3 patients. Treatment consisted in: salicylates (n = 18), steroids (n = 23), thiopurines (n = 17), infliximab (n = 6) and surgery (n = 10). Patients from group A were significantly older than those from group B (40 years vs 28 years respectively, p = 0.016). Severe acute colitis were significantly more frequent in patients from group A than in those from group B (40% vs 2.7% respectively, p = 0.013). Ileal involvement was less common in group A than in group B (28.6% vs 89.2% respectively, p = 0.001). Glycemia and systolic blood pressure were higher in group A than in group B (respectively p = 0.05, p < 0.0001). There was no difference between both groups with regard to type of treatment.

Conclusion: In Crohn’s disease patients, overweight and obesity seem to be associated with age, colonic location of the disease and severity of flares.
Lipid profile in inflammatory bowel disease under maintenance with anti-TNF: A prospective longitudinal cohort study

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Background and Aim: The role of tumor necrosis factor (TNF) inhibitor in patients with inflammatory bowel disease (IBD) in mediating cardiovascular risk and changing lipid profile is controversial. The aim of the study was to evaluate the effect of anti-TNF monoclonal antibodies on lipid profile in IBD patients.

Methods: A prospective, observational cohort study was designed. Inclusion criteria were consecutive IBD patients in clinical remission for at least six months under a continuous standard dose of 40 mg/eow adalimumab therapy or 5 mg/kg infliximab therapy every 8 weeks. Relapse was defined as a Harvey-Bradshaw score > 4 in Crohn's disease and a partial Mayo score > 3 in ulcerative colitis. Hypercholesterolemia was defined as a cholesterol count above 200 and hypertriglyceridemia was defined as a triglyceridemia count above 150. They were quantified at 4 month intervals for one year. All patients completed a basal demographic and clinical questionnaire. Differences between laboratory results were evaluated with paired samples T test in cholesterol (normal distribution) and with nonparametric test with in triglycerides (not normal distribution).

Results: 95 consecutive patients were included. The median age was 44 years (18–78), 51% female and 75% with CD. 10.6% of patients presented arterial hypertension, 3.3% mellitus diabetes and 3.1% a previous cardiovascular event. 65 (68.4%) patients remained in clinical remission and 30 (31.6%) suffered from a relapse during the follow-up period. We compared lipid profile between month 0 and month 12 (table 1 and table 2), almost statically significant differences were noted in triglycerides (P = 0.05) but not differences in cholesterol (P > 0.5). There was not a statistically significant difference in lipid profile during the follow-up, the subgroup with relapse showed a not significant increase in both cholesterol and triglycerides.

Conclusions: In IBD patients under maintenance therapy with anti-TNF, triglycerides increased almost significantly after one year of follow-up. Anti-TNF therapy can have a role in changes in the lipid profile, but without clinical relevance.

Table 1: Triglycerides profile modification according to relapse (median, range).

<table>
<thead>
<tr>
<th></th>
<th>Month 0</th>
<th>Month 4</th>
<th>Month 8</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>REMISSION</td>
<td>88 (33-407)</td>
<td>98 (38-483)</td>
<td>101 (32-801)</td>
<td>100 (29-442)</td>
</tr>
<tr>
<td>RELAPSE</td>
<td>103 (40-189)</td>
<td>71 (33-240)</td>
<td>110 (44-214)</td>
<td>121 (44-353)</td>
</tr>
</tbody>
</table>

Table 2: Cholesterol profile modification according to relapse (mean, standard deviation).

<table>
<thead>
<tr>
<th></th>
<th>Month 0</th>
<th>Month 4</th>
<th>Month 8</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>REMISSION</td>
<td>178 (31.8)</td>
<td>178 (35.5)</td>
<td>181 (35.5)</td>
<td>180 (38.6)</td>
</tr>
<tr>
<td>RELAPSE</td>
<td>172 (34.5)</td>
<td>176 (38.0)</td>
<td>172 (32.1)</td>
<td>176 (38.1)</td>
</tr>
</tbody>
</table>
Clinical outcomes following open label switching from Remicade® to Remsima® and an assessment of outcomes in infliximab naïve inflammatory bowel disease patients treated with Remsima® in a prospective United Kingdom observational cohort study

Hannah Freer (University of Bristol, UK), Vanessa Cambridge (Royal United Hospital, Bath, UK), Benjamin Colleypriest (Royal United Hospital, Bath, UK) and John Saunders (Royal United Hospital, Bath, UK)

Introduction: Biosimilar infliximab was recently approved by European regulatory authorities. Whilst it is an increasingly accepted treatment, published data on its use in inflammatory bowel disease, particularly with regard to patients switching from the originator compound are sparse. In this study we prospectively assessed safety and clinical outcomes in a real life cohort.

Methods: All Crohn’s disease (CD) and ulcerative colitis (UC) patients treated with Remicade® were switched to Remsima® and all new infliximab naïve patients were commenced on Remsima®. These cohorts were prospectively followed up in accordance with standard clinical practice.

Results: The maintenance cohort consisted of 91 patients (85 CD and 6 UC). The median duration of treatment with Remicade® prior to switching in CD was 22 months (interquartile range 4.5–50.75) and 1 month in UC (interquartile range 0–7). The median duration of follow-up in this study was 7 months (interquartile range 6–8). In both CD and UC patients there was no significant change in CRP, haemoglobin or platelets after switching. In patients receiving maintenance treatment, 2 patients had secondary loss of response and 3 patients developed new side effects resulting in discontinuation of treatment. As a result of the switching process 7 patients discontinued Remicade® treatment due to detection of anti-drug antibodies or following clinical review. 94% of patients switched to Remsima® continued on treatment. 41 Remsima® naïve patients (23 CD and 18 UC) commenced treatment, median duration of follow-up 5 months. 4 patients (10%) were primary non-responders, 2 patients had adverse events which resulted in treatment cessation and 2 patients with prior Remicade® exposure re-treated with Remsima® developed moderate anaphylactoid reactions. 80% responded to treatment and continued with Remsima®.

Discussion/Conclusion: This study demonstrates that switching patients to Remsima® did not result in changes to predicted rates of secondary non response or an increase in safety signals.
Do patients with Crohn’s disease in “deep” remission need the full body-weight based dose of azathioprine?

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Introduction: AZA-responders can maintain long-term remission of Crohn’s disease (CD) but > 60% of patients will relapse following drug withdrawal. In patients on IFX/AZA combo-therapy, lower 6TGN erythrocyte levels are needed to maintain remission indicating that a lower AZA dose is sufficient1. This study aimed at assessing whether the full weight-based AZA dose is necessary for remission maintenance for CD patients in prolonged ‘deep’ remission [clinical (Harvey-Bradshaw index < 4), serological (normal CRP) and endoscopic (mucosal healing)] on AZA monotherapy.

Methods: Retrospective, single-center study (2006–2015) based on prospectively acquired data in CD patients in ‘deep’ remission for ≥2 years. Data for a 4-year period were retrieved and patients were divided in 3 groups based on adherence to AZA (consumption > 80% of medications/month): group A (cessation of AZA), group B (poorly adherent), and group C (fully adherent). Patients were followed by clinical examination and lab tests every 3 months. The 1st ulcer-free colonoscopy was considered as ‘index’ colonoscopy and was repeated every 1–2 years to assess for mucosal healing.

Results: Overall, 35, 28 and 24 patients in deep remission for a median of 3.2, 3.0 and 3.1 years were included in groups A, B, and C, respectively, and were followed for a median 4.5 (4.1–5.2) years. No differences in patient and disease characteristics were seen. After a median time of 4 years follow up, 27/35 (77%), 8/28 (28.6%), and 4/24 (16.7%) in groups A, B and C, respectively, relapsed (p < 0.01 between group A and groups B and C; no significant difference between groups B and C). The mean daily dose of AZA in group B was 1.1 mg/kg/d and 2.2 mg/kg/d in group C. No other factor was related to disease flares. None of the patients developed serious adverse events or stopped therapy for adverse events.

Discussion/Conclusion: CD patients in deep remission on AZA for > 2 years are probably not in need of the full BW-based AZA dose to maintain remission.

References:

Effect of infliximab on the Crohn’s disease healing intestinal anastomosis in a rat model

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Introduction: Infliximab is effective in the induction and maintenance of remission in Crohn’s disease. Whether, the perioperative administration of anti-TNFα compromises intestinal healing leading to anastomotic failure and increased risk of postoperative complications, remains controversial. The aim of the study was to evaluate the effect of infliximab on intestinal anastomosis healing similar to Crohn’s disease anastomosis in a rat model.

Methods: Fifty-six wistar rats were divided into 4 groups: (a) 20 rats were subjected to excision of part of the terminal ileum followed by anastomosis which was evaluated on the 3rd or 7th postoperative day; (b) 20 rats received infliximab and thereafter, the same surgical protocol as group (a) was followed; (c) 8 rats received infliximab and served as relative control group; and (d) 8 served as absolute control group. Bursting pressure was used for testing intestinal healing. Additionally, the anastomoses were examined macroscopically, histologically and immunohistochemically for TGFβ1, MMP1, MMP2 and Collagen V. The results were confirmed by Western blot analysis.

Results: There were no significant differences in bursting pressures and septic intra-abdominal events among non-infliximab (a) and infliximab-treated (b) groups. infliximab-treated (b) group showed mild to moderate inflammation, whereas the non-infliximab (a) group exhibited severe inflammation. Expression of TGFβ1, MMP2 and collagen V was significantly higher in the infliximab-treated (b) group.

Conclusion: Infliximab seems to influence intestinal healing in terms of less inflammatory activity and higher tissue remodeling activity.
A presumptive relationship between the therapeutic strategy for ulcerative colitis and the risk of developing a colorectal carcinoma

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Introduction: The aim of our retrospective study was to identify and assess the presumptive risk factors of developing a colorectal cancer (CRC) in patients with UC. The diagnosis was based by clinical picture, laboratory exams, colonoscopy and was confirmed by histology.

Methods: We monitored 67 patients with moderate to severe UC (for a period of 12 years) which were structured in two groups: the A group contain 40 patients who treated with oral mesalazine (Salofalk®, 2–3 g/day and oral budesonide, 3 mg 3 x/day) in period of induction of remission and B group consist of 27 patients were treated with azathioprine (1–1.5 mg/kg/day).

Results: The incidence of CRC at 5 years after the UC diagnosis was reduced and similar in A and B groups. After 10 and 12 years the CRC incidences was significantly high in B group (18.52% comparative with 10.00% in A group at 10 years). The incidence of CRC after 12 years was 14.93% (10 cases): 22.23% (6 cases) in B group and 10.0% (4 cases) in the A group. The most of them had extensive severe colitis (5 patients) or a long duration of UC (7 cases). The localization of carcinoma was: left side (3 cases), transverse colon (one case), right colon (one case), sigmoid (2 cases), rectum (3 cases). The type of adenocarcinoma was: papillary (2 cases), tubular (4 cases), mucinous (one case), villous (one case) and undifferentiated (2 cases). Most of those patients had Duke’s B stage (5 cases) or C stage (4 cases). The risk of development of CRC was correlated with UC duration and this relationship was strongest in the patients which received azathioprine in the maintenance therapy. Also, we identified a lower correlation between risk of CRC and frequency of recurrences. Development of CRC was not correlated with values of C reactive protein, baseline hemoglobin rates and albumin levels.

Discussion/Conclusion: The risk of developing a CRC was associated with long duration and extensive forms of colitis. The incidence of CRC associated with UC can be higher in patients who received long term therapy with azathioprine for induce and maintain the remission.
Therapeutic changes and duration of usual treatments in ulcerative colitis in elderly patients

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Introduction: The aim of this study was examining of the differences in medical management of UC in the elderly: the clinical features, the response to usual therapies, the treatment duration and risk to develop complications.

Methods: This comparative analysis was performed on 37 patients, which were structured in two groups: the A group composed of 12 older patients (> 60 years) and B group consist of 25 patients with ages < 59 years (37.3 ± 9.55 years). In the A group 5 patients were treated with oral mesalazine (Salofalk®, 2–3 g/day) and oral budesonide (3 mg 3x/day), for 6–8 weeks and 7 patients were treated with azathioprine (1–1.5 mg/kg/day). In B group 15 patients were treated with oral mesalazine and budesonide and 10 patients were treated with azathioprine. We evaluated and monitored the Powell-Tuck index, faecal calprotectin values, CRP levels and endoscopic classification after 1, 3, 6 and 12 months. Also, we assessed comparatively the evolution of the main clinical symptoms: the resolution of rectal bleeding and normalization of bowel habit.

Results: Most of the older patients (58.33%) presented left-sided UC, 4 patients had proctitis and only one had extensive colitis. In B group the localization was: left-sided UC in 11 cases and proctitis in 14 cases. The distinctive features in elderly patients consist in the high incidences of: rectal bleeding (66.66%), diarrhea or paradoxical constipation (83.33%) and extraintestinal manifestation (58.33%). Also, they have a lower incidence of abdominal pain (33.33%) or weight loss (8.33%). Rapid response to associated treatment was observed in most young patients (60.0%) and only in one case (20.0%) in the A group. At 3 months, the rate of clinical and colonoscopically confirmed remission after mesalazine-budesonide therapy was: 40.0% in older patients and 73.33% in B group. Comparatively, the remission rate after azathioprine monotherapy was: 42.85% in older patients and 60.0% in B group. In whole group CRP was correlated significantly with clinical activity status. Faecal calprotectin was correlated with endoscopic and histologic activity only in the A group. The diminution of the mean Powell-Tuck score at 3 and 6 months suggest a more slowly response in elderly patients.

Discussion/Conclusion: The elderly patients with UC present particular manifestations and a distinctive response to usual therapies. In older patients is need therapeutic changes, in particular on modifying treatment duration. The frequency of outcome assessment should be tailored to the patient’s symptoms and the period of monitoring should be extended.
Impact of overweight in Crohn’s disease

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Introduction: Nowadays, overweight is becoming a worldwide issue. Its impact has been studied in some populations, however, it is still unknown in Crohn’s disease (CD). The aim of this study was to determine the prevalence of overweight in a Tunisian population of CD and to evaluate its impact on the course of the disease.

Methods: We investigated all the CD patients admitted in our department in the period between January 2014 and December 2015. We determined for each patient the body mass index (BMI). Overweight was defined by a BMI > 25 kg/m².

Results: A total of 55 patients were studied. The prevalence of overweight was 29% with a sex ratio of 1.28. The mean age of patients having an overweight was 42 years, and for those who hadn’t, it was around 31 years. There was no significant difference in age or smoking between overweighing patients and those having a normal weight. No statistically significant difference was noticed in the rate of surgery or the type of administrated medical treatment except for azathioprine which was statistically more prescribed in patients having an overweight (p = 0.034). We also compared the evolution of CD between patients having or not an overweight. There was no significant correlation between overweight and severe course of the disease.

Conclusion: According to this study, azathioprine seems to be more used in case of overweight. However, no impact on the course of the disease was noticed.
Abdominal tuberculosis of the gastrointestinal tract: Review of 25 cases

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Introduction: Abdominal tuberculosis is an increasingly common disease that poses diagnostic challenge, as the non-specific features of the disease which may lead to diagnostic delays and development of complications. The accurate diagnosis of abdominal tuberculosis requires a high index of suspicion and combination of diagnostic modalities in clinic practice and takes a long time.

Methods: The records of 25 patients (16 females/9 males), mean age 38.4 years, range 24–64 years) diagnosed with abdominal tuberculosis (tb) between January 2008 and December 2016 were analyzed retrospectively. Patients’ characteristics, laboratory investigations, radiological, endoscopic and surgical findings were evaluated.

Results: 25 patients were enrolled in the study. The most frequent symptoms were abdominal pain 17 (68%), fever 4 (16%), ascites 19 (76%), diarrhea 6 (24%) and weight loss 8 (32%). Intestinal perforation occurred in one patient. Duration of symptoms before diagnosis was 3.14 months (range 0.3–8 months). There was not a past history of treatment for tb neither in our patients nor in their entourage.

Predominant site of involvement by abdominal tb was intestinal in 7 (28%) and peritoneal in 18 (72%) cases. Basis of diagnosis of abdominal tb were histopathology obtained by colonoscopic biopsies 7 (28%), laparoscopic/surgical interventions 14 (77.7%) and ascites examinations 4 (12%). Microbiological tests (tuberculin test) were positive only in 9 (36%) patients. Abdominal tb diagnosis was made by invasive procedures in 84%.

All the patients received at least 6 months of antituberculous therapy with good response. And the case of tuberculous bowel perforation was treated surgically.

Discussion: Intestinal tuberculosis is a complex disease with non-specific symptoms. The combination of high index of clinical suspicion and using multiple adjuvant diagnostic tools is required to make correct diagnosis.
Efficacy and safety of endoscopic balloon dilatation in Crohn’s disease

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Introduction: Endoscopic balloon dilatation (ED) of Crohn’s disease (CD) related strictures is an alternative to surgical resection in selected patients. The present study assesses clinical success rate, long term outcome and safety of endoscopic dilatation.

Methods: We identified all the patients undergoing EBD over a 19-year period (j1997-dec16). Technical success was defined when the endoscope got pass through the stricture after the procedure and therapeutic success when it was not necessary another endoscopic or surgical treatment after 1 year or until the end of the follow-up.

Results: 59 patients (31 male/28 female) were identified. The mean age was 40 years (22–69 years). Disease duration was 102.6 months (1–233 months). A total of 78 dilatations were performed in 59 patients with a mean of 1.3 dilatation per patient. The 65 strictures (three patients had two strictures) included 38 anastomotic strictures and 27 de novo strictures. During the follow-up, 33 (56%) patients underwent an intervention including 13 (22%) with repeat dilatation and 20 (33.9%) with surgical resection. Median time from first dilatation to surgery was 52 months (1–96 months) and to repeat dilatation was 42 months (10–96 months). The therapeutic and technical success was achieved in 78% and 88% of the EBD respectively with a median follow-up of 25 months (0.5–96). There was neither major complication nor procedure-related mortality.

At univariate analysis, treatment with biological or thiopurines (p = 0.03) and de novo stenosis (p = 0.05) were associated with therapeutic success. There was no influence of the following variables: age, gender, disease duration, active CD, stricture localization, length and number of strictures.

Conclusion: Our data confirms that endoscopic dilatation can be offered as a safe and effective first line therapy in CD associated strictures.
Comparison of clinical characteristics of Crohn’s disease patients according to the age of diagnosis

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Introduction: Age at diagnosis is known to influence the clinical course of patients with Crohn’s disease (CD), and the late-onset CD may have distinctive characteristics. The aim of our study was to describe the clinical characteristics and treatment of CD patients according to age at diagnosis.

Methods: This retrospective monocentric study included 40 patients diagnosed as CD between 2008 and 2015. Patients were divided into 2 groups by age of diagnosis (group 1 (A1): age ≥ 40 years (yr); group 2 (A2): age < 40 yr). Clinical presentation, disease location and behaviour at diagnosis, as well as natural history and drug exposure, were reviewed.

Results: CD prevalence in older group was 32.5% compared to 67.5% in younger one. The proportion of males was significantly lower in younger patients (38% versus 54%; p = 0.05). Duration of symptoms before diagnosis was shorter in ≥ 40 years’ patients (3 versus 8 months, p = 0.004). Clinical presentation at diagnosis was similar in both groups, except bloody stools being more frequent among A1 (72% versus 8%; p = 0.004). Ileocolonic location was more common in old group (62.5% versus 30.7%; p = 0.003). Stricture pattern was more common in A1 (62.5% versus 44%; p = 0.03). Regarding treatment, immunosuppressant use rates were significantly higher in A2 (38% versus 21%; p = 0.02). As regards extra intestinal manifestations, A1 showed a higher frequency of osteopenia and osteoporosis (36% versus 24%; p = 0.002).

Conclusion: The clinical characteristics of older CD patients were different from those of younger patients in the disease location, behaviour, and the use of therapeutic agents. These results indicated the distinctive characteristics in older CD patients that need to be taken into account when establishing therapeutic strategies.
Correlation between the imaging data and intraoperative findings during Crohn’s disease

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**Introduction:** The sectional imaging (SI) has a great contribution in Crohn’s disease (CD). It allows to realize lesional mapping and to look for complications. The purpose of our study is to compare SI data and intraoperative findings in patients following surgery for CD.

**Methods:** In this retrospective study, 94 patients who underwent SI and then surgery for CD were enrolled from 2006 to 2016.

**Results:** We included 94 patients, 45 men and 49 women, middle-aged of 32.1 years [12–64]. The location of CD was ileal in 41 patients (43.6%), ileocolic in 49 (52.1%) and colic in 4 (4.2%). SI identified bowel stenosis in 36 patients (38.3%), fistulae in 32 (34%) and associated stricture and fistulae in 26 (27.6%). Abscesses were identified in 30.8% of the cases. The preoperative SI was the Computed tomography (n = 47), computed tomographic enterography (n = 53), and magnetic resonance enterography (n = 23). The average period between the imaging and the surgery was 35.2 days. The comparison of the radiological and surgical data is summarized in the following table:

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<th>Compatible methods</th>
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<td>Extent of lesions</td>
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<td>56.3</td>
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<td>Stricture</td>
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<td>73.4</td>
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<td>Fistulae</td>
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<td>Abscess</td>
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N = number

**Conclusion:** Our study confirmed that SI findings correlate significantly with intraoperative findings. Once decided that the patient should undergo surgical treatment, SI can provide the surgeon useful and adequate information about abscess, stenosis and fistulae.
Iron deficiency anemia in Serbian IBD referral center

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Introduction: Anemia is one of most frequent complication in inflammatory bowel diseases (IBD). Most patients have iron deficiency (ID) as a consequence of intestinal bleeding, inflammation and malabsorption. Types of anemia are: iron deficiency anemia (IDA), anemia of chronic disease (ACD) and anemia of mixed origin (AMO). Anemia have significant impact on the quality of life (QoL) of this patients and correction is very important.
Aim was to evaluate the prevalence of ID and types of anemia among hospitalized IBD patients.

Methods: 175 patients with IBD from tertiary IBD Center were enrolled during Oct/2015–Oct/2016. IDA was defined as decreased serum iron (< 10 ng/mL), transferrin saturation and ferritin level (< 30 ng/mL) and normal CRP; ACD was defined as decreased serum iron and transferrin saturation also, but increased ferritin level (> 100 ng/mL) and CRP. AMO was defined as decreased serum iron and serum transferrin, normal ferritin level and increased CRP. The Fischer test performed for statistical analyses.

Results: Among 175 hospitalized IBD patients (115/68% CD and 60/32% UC) female/male ratio was 2:1. Median age at diagnosis was 25 ± 1 in CD, and 42 ± 2 in UC. Median duration of disease was 10 ± 4 in CD group and 12 ± 3 in UC. Overall prevalence of anemia in IBD patients was 68.3%. In CD group IDA was found in 29%, ACD in 8% and AMO in 9%. In UC patients 35% had IDA, ACE was found in 7% and AMO in 9%. In spite of significantly more frequent rectal bleeding in UC group (p < 0.001), there was no significant difference in IDA occurrence between UC and CD patients (p = 0.5).

Discussion/Conclusion: Two-thirds of IBD patients with long disease duration had anemia. IDA is the most common type of anemia diagnosed in one third of CD and UC patients.
The introduction of biosimilar infliximab (CT-P13) through a managed switching programme generates significant cost savings with high levels of patient satisfaction


Introduction: Biosimilar infliximab (CT-P5013) has been licensed in the UK for over a year with the potential for significant cost savings, though uptake to-date has been surprisingly slow. We report the introduction of biosimilar infliximab through a closely managed switching programme.

Methods: Following the licensing of biosimilar infliximab we made a decision to instigate a closely managed switching programme encompassing all patients on maintenance treatment with Remicade® and all new starters. A working party was set up with strong managerial support to deliver the project. We initially estimated savings of £400,000/year to the local health economy. Following meetings with the 3 local CCGs agreement was confirmed for a 50:50 gain share agreement between the CCGs and the Trust. To facilitate and monitor the switching programme a new Band 7 IBD Biological nurse, a Band 7 IBD Biological pharmacist, and an IBD administrator were recruited. All patients were informed by letter of the planned switch and the rationale for it. A variety of clinical and biological markers were also recorded at each visit along with PROM data.

Results: To date since the start of the project on 16th September 2015 88 patients have been treated with biosimilar infliximab. 78 (63 CD/15 UC) patients on maintenance treatment with Remicade were switched to CT-P13 with unchanged efficacy and safety (the detailed results are the basis of a separate abstract); a further 10 patients received induction therapy (7CD/3UC). 3/88 patients requested further clarification from the IBD team with all patients subsequently agreeing to the switch. All patients were seen by either the IBD pharmacist or IBD specialist nurse and stated they felt well informed. Over the first six months the programme has generated total cost savings of £232,576.52 with projected year savings of £540,000. Staff costs totalled £90,000. PROM data from the cohort revealed very high satisfaction with treatment with a mean score of 7.3 (range 3–10) for overall disease control. Patient feedback was universally positive.

Conclusion: The introduction of biosimilar infliximab can be achieved through a closely managed programme with very significant cost savings to the local health economy. Engaged conversations between primary and secondary care facilitate realising these savings allowing investment in the local IBD service with direct impact on patient care. Patients were overwhelmingly supportive of the project. Wider uptake in the UK would result in considerable cost savings to the NHS.
Paneth cell dysfunction and death is directly linked to IFN signalling

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Introduction: While lymphocyte-derived type II IFN (IFN-γ) has been implicated in the pathogenesis of inflammatory bowel disease (IBD), the impact of IFN-λ on intestinal inflammation remains unknown.

Methods: Overexpression of IFNs in different mouse strains.

Results: Recently, we have uncovered a previously unrecognized form of hepatocellular death that is strongly dependent on IFNs (Günther et al., JCI 2016). Importantly, we identified that hepatocellular death is driven by the MLKL-dependent pathway that occurs independently of RIPK3. Our preliminary data revealed that IBD patients and in particular Crohn’s disease patients have elevated levels of serum IFN-λ. Moreover, we observed strong IFN-λ immunostaining in biopsies from Crohn’s disease patients. IFN-λ immunostaining in these samples was particularly enhanced in IECs in areas of severe inflammation accompanied by reduced numbers of Paneth cells. These data strongly implicate that IFN-λ expression is linked to disease activity in CD. In line with our hypothesis, we found that overexpression of IFN-λ in mice resulted in a nearly complete depletion of Paneth cells, suggesting that type III IFN signalling in the intestinal epithelium affects Paneth cell homeostasis and thus antimicrobial defense. Notably, this effect was independent of type I and type II IFN signalling and directly mediated by STAT1 activation in IECs. Accordingly, we observed highly increased intestinal epithelial Mlkl expression in mice that received IFN-λ, suggesting that intestinal epithelial cell may undergo Mlkl-mediated necrosis. Further analysis of organoids revealed that IFN-λ signalling in addition affected the expression of tight-junction molecules (ZO-1, MLCK) suggesting an impact of this cytokine on intestinal barrier function.

Discussion/Conclusion: Taken together, these data strongly implicate a pathophysiological role for type III IFNs during intestinal inflammation. Our data provide compelling evidence for an important function of IFN-mediated regulated necrosis and hence the rational for the investigation of this pathway in other inflammatory diseases.
The immunohistochemical assessment of metalloproteinases in IBD

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Introduction: The extracellular matrix is a special matrix which is involved in the migration, cell adhesion and differentiation. Remodeling of matrix is an important element in the development of the various lesions. The group of proteins involved in this process is metalloproteinases, including MMP-2, MMP-7, MMP-9. Therefore, the aim of our study was to evaluate the expression of MMP-2, MMP-7, MMP-9 in patients with ulcerative colitis (UC) and Crohn’s disease (CD).

Material and Methods: The study group consisted of 20 patients with UC and 10 patients with CD. The expressions of MMP-2, MMP-7, MMP-9 in tissue sections were analyzed by immunohistochemistry.

Results: The absence, weak and medium expression of MMP-7 (54.9%, 29%, 16.1%), absence and weak reaction of MMP-2 (73%, 16.7%) and strong expression of MMP-9 (38.7%) were reported. There was a weak, medium and strong reaction of MMP-7 in inflammatory cells (35.5%, 32.3%, 25.8%). However, the strong reactions of MMP-2 and MMP-9 in inflammatory cells were present in 55.9% and 38%. In patients with CD, the weak, medium and strong expression of MMP-2 (10%, 10%, 60%) were found in glandular epithelium. In the same disease, the weak, medium and strong reaction of MMP-7 (50%, 40%, 10%), and weak and medium MMP-9 expression (41.6%, 16.6%) were observed in glandular epithelial cells. There was strong expression of MMP-7 and MMP-2 and weak reaction of MMP-9 in inflammatory cells of most cases. The increased levels of MMP-7 and MMP-2 were found to correlate with the location of diseases. Moreover, MMP-2 and MMP-9 correlate with patient's age in the CD.

Conclusion: The increased expressions of MMP-9 appear to be more important than MMP-7 and MMP-2 in UC, but MMP-2 was more important in CD. In addition, both MMP-2 is extensively secreted by inflammatory cells in UC and CD.
Expression of Fas/FasL in inflammatory bowel disease and colorectal cancer

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Introduction: Colorectal cancer is one of the most common and relatively late detected malignancies. Tumor progression depends largely on proliferation and death of cancer cells. Therefore, the objective of the current study was to assess the expression of Fas ligand (FasL) and Fas receptor (FasR) as the proteins of postmitochondrial apoptotic pathway in ulcerative colitis, Crohn’s disease and colorectal carcinoma.

Material and Methods: Fas and fasL expression was assessed by immunohistochemistry in formalin-fixed, paraffin-embedded tissues from 15 patients with ulcerative colitis, 10 patients with Crohn’s disease and in 50 colorectal carcinoma patients.

Results: The moderate Fas receptor expression was observed in epithelial cells in ulcerative colitis and Crohn’s disease, weak in 75.5% of colorectal cancer patients, as compared to normal glandular epithelium where FasR expression was strong in 100% of cases. Whereas FasL expression was mostly expressed in ulcerative colitis, strong in 70% of colorectal cancers, but absent in Crohn’s disease and normal colorectal epithelium. Moreover, over 50% of the lymphocytes present in the inflammatory infiltration accompanying the tumor showed strong FasR expression.

Conclusion: These proteins could become good therapeutic targets for colorectal carcinoma since their expression differs distinctly between normal intestinal epithelium, ulcerative colitis, Crohn’s disease and cancer cells, and known is the mechanism by which cancer cells escape death via apoptosis-inducing Fas/FasL pathway disorders.
Impact of smoking on the clinical course and the therapeutic response of Crohn’s disease

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Introduction: Active smoking is identified for a long time ago as a major risk for the development of the Crohn’s disease (CD). Many studies have also demonstrated its role for the recurrence of the disease after a surgical treatment. The present study was aimed to determine the impact of smoking on the clinical features and the therapeutic response of Crohn’s disease.

Methods: We conducted a retrospective study including patients followed for CD between January 2007 and December 2015. For all these patients, we specified the main epidemiological and clinical features of the disease. Statistical analysis was performed using Spss v 20.

Results: Eighty-eight patients were included. The main age was 41 years [18–88 years] with a sex-ratio of 0.5. Active smoking was reported in 43% of patients. The phenotype of CD was inflammatory in 38% cases, perforating in 33% cases and fibrostenosing in 42% cases. Fourteen percent of patients experienced severe symptoms of the disease. Anoperineal complications were present in 20% cases. Extra-intestinal manifestations were reported in 42% of cases. In multivariate and univariate analysis, active smoking was identified as a risk factor of severe disease (p < 0.01), of surgery (p = 0.004), of recurrence after surgical treatment (p = 0.035), of absence of clinical remission (p > 0.001) and of the need to biotherapy (p = 0.003). The prevalence of anoperineal lesions were substantially increased in smoking patients (p = 0.011). Extraintestinal manifestations, corticosteroids dependance and malignant degeneration were not significantly correlated to active smoking.

Discussion/Conclusion: A more severe clinical course of Crohn’s disease and a major risk of complications and absence of remission were described in smoking patients. Smoking cessation is a major part of the therapeutic management and a particular attention should be focused on patient education.
**Inflammatory bowel disease and thromboembolism**

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**Introduction:** Patients with inflammatory bowel disease (IBD) are thought to be associated with an increased risk of developing venous thromboembolic (VTE) disease and arterial thrombi (AT). In clinical studies, the prevalence of VTE disease and AT in IBD varying between 1.2% and 6.7%. Our aims were to evaluate the rate and risk factors of VTE and AT in a cohort of IBD patients.

**Methods:** We performed a retrospective review between 2005 and 2016 of all patients with IBD identified from the IBD database.

**Results:** There were a total of 175 patients with IBD, with 11 found to have VTE and AT, giving a prevalence rate of 6%. Of these 11 patients, one (0.09%) patient had recurrent disease having 2 incidents of VTE disease. The median age was 60.2 years old with a greater risk for males than females (54% versus 36.3%; p = 0.001) and with ulcerative colitis than Crohn's disease (9.3% versus 4%; p < 0.05). Hospitalization was related to a diagnosis of VTE/AT in half of cases; 36.3% patients were diagnosed with deep venous thrombosis (DVT) and one patient with pulmonary embolism (PE). The remaining six patients had portal vein thrombosis (n = 1), inferior member arterial thrombosis. The average duration from time of IBD diagnosis to VTE confirmation was 3.4 years. One patient was identified with VTE prior to IBD diagnosis. At the time of their diagnosis, one patient was treated for malignancy in the previous six months and 2 (18.2%) had undergone surgery in the previous four weeks. Two patients were being treated with 5-aminosalicylic acid (5ASA) drugs, 4 (36.3%) with azathioprine, 2 (18.2%) with oral steroids, 2 (18.2%) with intravenous (IV) steroids, 2 (18.2%) with infliximab. Blood tests at time of diagnosis showed a median CRP of 61.8 mg/L and platelet count of 304 x 10³/mm³. 81.8% of patients had elevated CRP. A thrombophilia assessment was performed in more than 50% of patients. A deficiency of protein S and factor V Leiden was noted in two patients. The mortality rate was 27.2%, of which one death directly related to VTE. 72.7% (n = 8) received anticoagulant therapy.

**Discussion/Conclusion:** Thromboembolism is an increasingly prevalent and preventable complication of IBD. Positive risk factors identified in our cohort were patients that were male and diagnosis of ulcerative colitis. Considering more than one third of those diagnosed were receiving oral or IV steroid therapy and the majority had an average raised CRP, this supports the view that a disease flare is an ongoing risk factor for developing VTE and AT.
Does overweight modifies the clinical profile and the course of inflammatory bowel disease?

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Introduction: Obesity has been linked to a pro-inflammatory state and development of inflammatory diseases. The data on the treatment and evolution of overweight patients with inflammatory bowel disease (IBD) are limited. The aim of this study was to describe the epidemiological, clinical, therapeutic and evolutive characteristics of patients with inflammatory bowel disease who are overweight.

Methods: This is a retrospective study, conducted between 2007 and 2015 on 175 patients followed for IBD. The diagnosis was retained on a range of clinical and biological, endoscopic and histological arguments. Body mass index (BMI) was used to classify patients. Overweight was defined for a BMI ≥ 25 kg/m².

Results: One hundred seventy-five patients followed for IBD were collected, of which 60 (33%) had a BMI ≥ 25 kg/m². Of these, 31 had Crohn’s disease (51.7%) and 29 had an ulcerative colitis (48.3%). They were 23 men and 37 women. The sex-ratio was 0.62. The median age was 41 years (18–88 years). Among these patients, 31.7% (19 cases) were smokers. In the group of Crohn’s disease patients, median disease duration was 59 months (5–180 month). The site of the disease was colic, ileocolic and ileal in respectively 22.64%, 42% and 22.64% of cases. Upper gastrointestinal lesions were observed in 4 patients (12.9%). Fourteen patients (23.3%) had an inflammatory phenotype (B0 according to the classification of Montreal), 4 patients a stenosing phenotype (6.7%), 8 patients a fistulizing phenotype (13.3%) and 5 (8.3%) patients had stenosing and fistulizing disease.

Regarding ulcerative colitis, it was distal in 16 cases (55.18%), pancolitis was seen in 13 patients (44.82%).

In addition, 30 patients (50%) among the overweight patients with IBD had extraintestinal symptoms. Ano-perineal manifestations were found in 10 patients (16.7%) which is the same for the prevalence of surgery (10 patients or 16.7%). Fifty percent of patients carrying IBD were under azathioprine and 20% were taking anti-TNF.

Overweight in patients with IBD was associated with female sex (p = 0.039), age > 40 years at diagnosis (p = 0.011), fatty liver (p = 0.042), high rates CRP (P = 0.008). We did not found an association between overweight on one hand and smoking, location of the disease, phenotype, surgery, ano-perineal lesions and the number of outbreaks on the other hand. However, a significant association was found between overweight and a lower rate of remission under immunosuppressive treatment (p = 0.034) and a lower response to anti-TNF (p = 0.042).

Discussion/Conclusion: In IBD, overweight seems quite common. In our study, it was associated with female sex, an advanced age at diagnosis as well as fatty liver. Regarding the evolutionary characteristics, a significant association was found with lower rates of remission under immunosuppressive and lower response to anti-TNF.
Calprotectin and C-reactive protein levels in patients can equally distinguish inflammatory and non-inflammatory diarrhea

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Introduction: All of us know that high level of calprotectin indicate the inflammatory reason of diarrhea. Our study shows that level of serum C-reactive protein (CRP) also can be used to differentiate between inflammatory diarrhea and non-inflammatory diarrhea.

Methods: This was a study include the medical records from a Gastrocentrum Olymed located in Kiev, Ukraine. The records of 587 patients, who presented with fever (≥ 37.6°C) and diarrhea between September, 2014 and October, 2016 were reviewed and 497 patients were selected. All of them had undergone colonoscopy within 5 days and blood and feces sampling also. Selected patients were divided into two groups based on their colonoscopy results: Group 1 (217) – inflammatory diarrhea group and group 2 (280) – non-inflammatory diarrhea group. Then we compared clinical and laboratory characteristics of these two groups.

Results: CRP, calprotectin and erythrocyte sedimentation rate (ESR) levels were significantly higher in group 1 patients than group 2 (6.92 ± 2.49 vs 1.79 ± 0.95 (p = 0.032), respectively; and 372.2 ± 5.86 vs 62.1 ± 4.22 (p = 0.012), respectively; and 16.47 ± 5.46 vs. 11.29 ± 5.72 p = 0.041), respectively). Multivariate analysis revealed that CRP and calprotectin level on admission were the most important predictor of inflammatory diarrhea (OR 7.39, p < 0.05 and OR 6.89, p < 0.05). CRP and calprotectin had a high sensitivity and specificity also (82–85% and 85–87% respectively). Compare these two predictors the study results show that both of them had the same meaning and importance of determine in inflammatory or non-inflammatory diarrhea. The conformity between these two predictors and inflammation activity index by endoscopy was practically the same and the difference between them was statistically not significant (p = 0.083).

Discussion/Conclusion: Calprotectin and CRP as an inflammatory diarrhea diagnostic markers appeared superior to the other inflammatory markers and clinical characteristics that were evaluated. A patient’s CRP level on admission may determine faster than calprotectin and may help in making a clinical decision – such as initiating empire antibiotics therapy.
Introduction of an inflammatory bowel disease nurse led flexible sigmoidoscopy clinic improves patient care by initiating earlier treatment and saves clinic slots

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Introduction: It is a marker of quality to be able to respond promptly and effectively to a patient with IBD at the time of a flare. Many patients who contact the IBD helpline with flare symptoms require a flexible sigmoidoscopy (FS) for accurate assessment. These are performed on generic lists where follow up is arranged resulting in delays in treatment and creating pressure on clinic slots. An experienced IBD nurse prescriber (IBDN) was trained in FS with the aim to endoscopically assess patients and potentially start new treatment the same day.

Methods: Records were reviewed of all patients attending the FS clinic.

Results: 410 patients underwent a FS with the IBDN
- 195 (47.6%) patients referred for rectal bleeding
- 215 (52.4%) had IBD, 152 (70.7%) ulcerative colitis and 63 (29.35%) Crohn’s disease. 130 (60.5%) female, mean age: 48 (range 16–88).
- Referral origin: 76 (35.3%) IBD Helpline. 58 (27%) IBD Consultant clinic. 39 (18.1%) IBDN Clinic. 27 (12.6%) Other clinic. 11 (5.1%) inpatient. 4 (1.9%) GP.
- FS outcome: 55 (25.6%) commenced azathioprine, 47 (21.9%) oral prednisolone, 38 (17.7%) 5 ASA therapy, and 19 (8.8%) no changes. 41 (19.1%) FS performed to assess need or response to biological therapy. The 11 (5%) in-patients returned to the ward, 4 (1.9%) diagnosed with ASUC.
- In total 137 clinic slots were saved. 76 direct from the helpline. Following FS, 51 (23.7%) patients were discussed at the IBD MDT. Endoscopy findings were reviewed at IBD MDT and discussed and appropriate treatment confirmed with the patient. 10 (4.7%) patients were referred direct to the day unit to commence biological therapy.

Discussion/Conclusion: The skilled prescribing IBD nurse endoscopist made changes in 91.2% at the time of the FS. The relatively small number of patients starting 5-ASA therapy suggests this had been optimised prior to FS suggesting patients attending the IBDN FS clinic had moderate to severe IBD.
Screening for enteric infection in inflammatory bowel disease patients contacting the IBD helpline and presenting with disease flares

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We participated in the UK National Audit of IBD service provision (Royal College of physicians, 2014). This recommends > 90% of IBD patients with diarrhoea, have a stool sample sent for culture and Clostridium difficile (CDT) on admission. ECCO guidelines recommend stool testing in both outpatient and inpatient disease flares. To date a national audit reviewing stool testing of patients contacting IBD Helplines for advice with diarrhoea has not been performed. We reviewed the results from our clinical practice of both inpatients and out-patients.

Methods: We searched the IBD telephone helpline electronic records from September 2011 to October 2014 identifying patients presenting with diarrhoea. Electronic records were reviewed to determine if stool samples for standard stool culture and CDT were requested, and the results of that testing. By searching hospital admission data we identified all patients admitted for > 24 hours with a diagnosis of Crohn’s disease or ulcerative colitis with symptoms of loose stool and increased frequency during the same time period and reviewed the same data.

Results: 357 patients contacted the IBD Helpline with diarrhoea. 357 (100%) were sent stool pots for standard stool culture and CDT by post. Results reviewed. 300 (84%) patients completed the tests. 15 (5%) were positive. 8 showed CDT, 6 Campylobacter and 1 Blastocystis hominis. 179 (99 male) IBD patients were admitted during the same 3 year period with a flare. 122 patients had diarrhoea on admission. 96 (79%) underwent stool testing. 2 (2%) were positive for infection: 1 for campylobacter, 1 for CDT.

Discussion/Conclusion: These results demonstrate that enteric infection is a relatively common cause of disease flares and underlines the importance of screening. Unfortunately frequency of stool testing in our inpatient population falls below recommended standards. In contrast testing undertaken by our nurse-led IBD helpline met the standard.
MicroRNA expression in colon of active and inactive ulcerative colitis

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Introduction: MicroRNAs (miRNAs) are small non-coding RNAs that post-transcriptionally regulate gene expression. These molecules are strongly implicated in the pathogenesis of various immune-related diseases, including ulcerative colitis (UC). Recent studies identified numerous altered miRNAs in UC, but there is a lack of information on miRNAs which are deregulated in different forms of the disease's severity. To get further insight into the pathogenesis of UC, the aim of this study was to examine miRNA profiles in active and inactive forms of UC.

Methods: The group of participants consisted of healthy controls (HC, n = 70) and patients with active (UCa, n = 61) and inactive UC (UCi, n = 57). In the discovery phase, small RNA transcriptomes of 76 individuals (HC = 32, UCa = 23, UCi = 21) were sequenced using Illumina NGS platform. Validation of the most deregulated miRNAs was determined in the independent cohort of 122 individuals (HC = 38, UCa = 38, UCi = 36) using TaqMan Low Density Array (TLDA). In order to identify the overall similarity structure of miRNA expression profiles, multidimensional scaling (MDS) analysis was performed.

Results: The comparative analyses of sRNA-seq data identified 108 differentially expressed miRNAs between UCa and HC and 31 miRNAs between UCi and HC. Comparison of miRNA profiles between UCa and UCi identified 74 differentially expressed miRNAs. To further validate the findings of sRNA-seq data, 22 highly deregulated miRNAs were selected for TLDA analysis. The expression levels of 11 miRNAs showed significant differential expression in the same direction as in the sequencing data. The MDS analysis either on sRNA-seq or TLDA data revealed two clusters corresponding to UCa and HC and one intermediate cluster corresponding to UCi.

Conclusion: The expression profiles of miRNAs differ among UCa, UCi and HC. Patients with the UCi have an intermediate miRNA expression profile that has similarities of both healthy and active UC-affected individuals.
Intestinal bacteria composition and translocation of bacteria at the inflammatory bowel disease

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Background: The gut microbiota is believed to play a central role in the development of the inflammatory bowel diseases (IBD); Crohn’s disease (CD) and ulcerative colitis (UC). Recently, it has been suggested that live commensal intestinal bacteria are present in the adipose tissue and the peripheral blood where they can induce inflammation. Since this process can trigger inflammation the aim of the present study was to evaluate the intestinal bacteria composition and translocation of bacteria in IBD.

Methods: Both blood and tissue biopsy samples were collected from adult patients with active CD (n = 6), inactive CD (n = 6), active UC (n = 14), and inactive UC (n = 6) as well as from healthy individuals (n = 20) that underwent screening colonoscopy. none of the patients received recently antibiotics. The majority of patients were on 5-ASA and/or Azathioprine. Using a sensitive reverse transcription-quantitative real-time PCR (RT-qPCR) method, we determined the composition of microbiota. NOD2/CARD15 genotyping, was also studied.

Results: Total bacterial DNA concentration was increased in tissue and blood samples of CD and UC patients compared to healthy controls (p < 0.05). Furthermore, the active IBD cases had higher total bacterial DNA concentration levels compared to the inactive cases (p < 0.05). Three species characterized dysbiosis in IBD, namely an increase of Bacteroides spp (p < 0.05) in active CD, in inactive CD and UC samples, and a decrease in C. leptum group (IV) (p < 0.05) and Faecalibacterium prausnitzii (p < 0.05) in both active and inactive IBD patients. Concerning the NOD2/CARD15 mutations, no significant association between bacterial translocation and NOD2/CARD15 was found.

Conclusions: The composition of the microbiota in IBD patients differs from that of healthy controls. The high rate of bacterial DNA in the blood samples indicates translocation of bacteria from the gut to the circulation in inflammatory bowel disease.
Increased paracellular permeability induced by adherent invasive E. coli LF82 in human ileum is inhibited by blocking the CEACAM6 receptor

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Introduction: The first signs of Crohn’s disease (CD) are erosions in the follicle-associated epithelium (FAE) overlying the ileal Peyer’s patches. We previously found an increased bacterial passage through FAE of CD compared to controls. Our aim was to study the effects of the adherent-invasive E. coli LF82 and its receptor CEACAM6 on paracellular passage in FAE and in regular villus epithelium (VE).

Methods: Ileal specimens were taken at surgery for CD (n = 9) and colonic cancer (n = 10), and mucosal segments of FAE and VE were mounted on Ussing chambers. The paracellular probe ⁵¹Cr-EDTA and live E. coli LF82 were added to the mucosal sides of 6 chambers with FAE and 6 with VE. Two of the chambers each were pre-incubated with anti-CEACAM6 to the mucosal sides. Serosal samples were collected and measured by gamma-reading.

Results: There was no significant difference in baseline ⁵¹Cr-EDTA passage between VE and FAE, neither in CD (VE: 0.97 ± 0.11, FAE: 1.38 ± 0.35 cm/s x 10⁻⁶) nor in controls (VE: 1.04 ± 0.15, FAE: 1.26 ± 0.19). Nor were there any significant differences in VE or FAE when comparing baseline ⁵¹Cr-EDTA passage between CD and controls. Interestingly, when adding E. coli LF82 to the chambers, ⁵¹Cr-EDTA permeability significantly increased (p < 0.05) in FAE compared to baseline in CD (3.89 ± 0.28) while there was no significant change in VE (2.58 ± 0.59) or in controls (VE: 2.11 ± 0.21, FAE: 1.77 ± 0.19). The LF82-induced increase in ⁵¹Cr-EDTA passage in FAE of CD was significantly blocked (p < 0.05) in chambers pre-incubated with anti-CEACAM6 (1.33 ± 0.19).

Discussion/Conclusion: Our results indicate that E. coli LF82 affects paracellular permeability in FAE of ileal CD via its receptor CEACAM6. This suggests a role of adherent-invasive E. coli in mucosal barrier dysfunction and identifies CEACAM6 as a potential treatment target in ileal CD.
Fecal calprotectin as suitable biomarker in assessment of histological and endoscopic disease activity

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Introduction: Colonoscopy is still standard procedure in assessment of ulcerative colitis activity (UC). However, histologic activity can persist even in patients with mucosal healing. Considering colonoscopy an invasive and expensive procedure, fecal calprotectin (FCP) seems to be suitable surrogate. Sparse data exist about prediction of histological activity by FCP.
The aim of this study was to explore the association of FCP with histological activity.

Methods: 82 patients with UC from a single tertiary IBD Centre were enrolled in this prospective observational study. Endoscopic activity was evaluated by Mayo endoscopic sub-scores. For the assessment of histologic activity, Geboes score was used in evaluating active and chronic inflammation. Buhlmann rapid test was used to determine FCP. Statistical analysis was carried out using SPSS 20.0 (Chicago, IL).

Results: 38% (31/82) of patients were in endoscopic remission while 33% (27/82) achieved histological remission. Positive correlation was found between endoscopic activity and Geboes score (Z = -4.746, p < 0.001), as well as between FCP and endoscopic activity (p < 0.001 and Rho = 0.726 - Spearman correlation). Also strong correlation was found between level of FCP and Geboes score (p < 0.001 and Rho = 0.521 - Spearman correlation), but relation with chronic inflammation was not observed (p = 0.002, CI ± 9.37).

Discussion/Conclusion: It seems that FCP may be a useful marker not only for the monitoring of endoscopic but also as an indicator of active histological inflammation.
Irritable bowel syndrome correction during pregnancy

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Irritable bowel syndrome (IBS) during pregnancy is accompanied by the growing threat of pregnancy termination (48–50%) and the threat of premature delivery (42–45%). Research necessary is aimed at treatment tactics development of pregnant women suffering IBS. The aim of the study is to reduce the incidence of obstetric complications in pregnant women with IBS.

Materials and Methods: 50 pregnant women with complaints on periodical aching lower abdominal pain and varying degrees of dysbiosis, which lasted from 3–6 months. Results and discussion. All pregnant women with IBS experienced abuse dysbiosis of the colon. We revealed hemolytic flora, E. coli with moderate enzymatic properties, enteropathogenic E. coli, prevalence of opportunistic microflora and their associations (Staphylococci, Proteus, Yeasts, or lactosenegative and hemolytic Escherichia, etc.). Therapeutic measures consisted of diet, probiotic (a mixture of multidrug-resistant strain spores of Bacillus clausii 2 x 10⁹) taking 1 capsule three times a day, anti-spasmodics (40 mg drotaverine hydrochloride) taking 1 tablet twice a day and Magne B6 (magnesium lactate dihydrate 470 mg and pyridoxine hydrochloride 5 mg) taking 6 tablets per day. The course of treatment was 14 days. It was noted a significant subjective complaints reduction (reduction of pain, flatulence, dyspeptic phenomena, constipation elimination) in 92% of pregnant women after treatment, proving the high efficiency of the recommended treatment complex.

Conclusions: Treatment of pregnant women with IBS is symptomatic and includes intestinal microbiota correction, pain elimination and psycho-emotional sphere stabilizing. Implementation of the developed complex of medical measures has reduced the incidence of obstetric complications (threatened abortion and premature birth) by 52%.
A possible impact of Helicobacter pylori-related metabolic syndrome in patients with inflammatory bowel disease

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Introduction: Some experimental and observational human studies suggested a possible association of Helicobacter species and Helicobacter pylori (Hp) with inflammatory bowel disease (IBD); it is conceivable that Hp infection may influence the clinical course of IBD by triggering both specific and nonspecific immune responses in the human intestine. Moreover, Hp-related metabolic syndrome (MetS) might contribute to pathogenesis of IBD. We aimed to investigate mainly the possible presence of Hp infection with or without MetS parameters, in upper and lower gastrointestinal tract of patients with Crohn’s disease (CD) and ulcerative colitis (UC), by using histology.

Methods: We introduced histology, the practical diagnostic gold standard for current Hp infection, in IBD patients underwent upper and lower gastrointestinal endoscopy with concomitant biopsy specimens received for detection Hp bacteria, by using fast Alcian Blue stain. Moreover, parameters of MetS such as central obesity, type 2 diabetes mellitus, dyslipidemia, hypertension, nonalcoholic fatty liver disease and/or cardiovascular disease were also evaluated in our patients.

Results: 20 adult IBD patients, 12 with CD and 8 with UC, were included in this pilot study (9 men and 11 women); mean ages of CD and UC were 33 and 47 years, respectively. The activity of the disease was categorized in moderate activity with the use of the Mayo score and CDAI for UC and CD, respectively. Presence of current Hp infection was observed in both gastric and colonic mucosa in 6 out of the 8 patients with UC (75%). Comparable features were observed in 8 out of the 12 patients with CD (66%). Both Hp infection and parameters of MetS were observed in: a) 4 out of 6 Hp-positive patients with UC (66%) and b) in 7 out of 8 Hp positive patients with CD (88%).

Discussion/Conclusion: This pilot study shows a possible impact of active Hp infection on UC (mainly) and CD pathophysiology. Moreover, both Hp infection and MetS might also contribute, at least partly, to IBD pathobiology. However, further large-scale relative studies are needed to elucidate these fields.
Efficacy and safety of azathioprine in inflammatory bowel disease patients: Results of a Tunisian survey

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Introduction: Azathioprine (AZA) is widely used in the treatment of inflammatory bowel disease (IBD). The aim of our study was to assess efficacy and safety of AZA in IBD patients.

Methods: Retrospective study including patients with IBD treated with AZA referred in our department between January 2006 and June 2016. AZA was administrated at the recommended dose of 2–2.5 mg/kg/d. Epidemiological, clinical and therapeutic characteristics were collected from medical records.

Results: Eighty two patients were evaluated, 58 patients (70.7%) with Crohn’s disease and 24 patients (29.3%) with ulcerative colitis. They were 38 male and 44 female with a mean age of 37.6 years, range from 19 to 58 years. The indication of AZA was maintenance therapy after severe acute colitis in 24 patients (29.2%), prevention of postoperative recurrence in 22 patients (26.8%), corticosteroid dependence in 20 patients (24.3%) and extensive ileal involvement in 16 patients (19.5%). During a mean follow up of 22.7 months, adverse reactions to the treatment occurred in 26 patients (31.7%): digestive tolerance leading to switch to 6-MP in 8 cases, hematologic toxicity in 18 patients (8 had leucopenia, 4 had neutropenia, 6 had lymphopenia) and hepatic cytolysis in 6 cases. A response to the maintenance therapy with AZA was observed in 56 patients (68.2%).

Discussion/Conclusion: In the present series, the use of AZA in IBD patients seems to be safe. The maintenance of remission with this treatment is achieved in two third of cases.
Impact of endoscopic remission in patients with ulcerative colitis

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Background/Aim: It has been recommended that the treatment of active ulcerative colitis (UC) should be maintained until complete healing of endoscopic lesions. However, there is no strong evidence supporting this recommendation. The aim of our study was to assess the impact of endoscopic remission after the first course of treatment on the outcome of patients with UC.

Patients and Methods: We have conducted a retrospective study including patients who were hospitalised to treat a first flare UC and who underwent colonoscopy after clinical remission. Endoscopic remission was defined as restitutio ad integrum of the colonic mucosa. During retrospective follow up, we assessed clinical relapse rate, lesion extent and incidence of acute severe colitis.

Results: We colliged 46 patients. Endoscopic remission was obtained in 33 patients (71%). After a mean follow up of 41 months, clinical relapse and severe acute colitis rate was similar in patients who achieved endoscopic remission and those who did not (respectively 51% vs 46%, p = 1 and 0% vs 16%, p = 0.2). Lesion extent occurred more often in patients who did not achieve endoscopic remission than those who did with trend toward statistical significance (11% vs 50%, p = 0.08).

Conclusion: Endoscopic remission should be considered as therapeutic target in UC patients. Further studies are needed to assess the prognostic significance of endoscopic remission in our UC patients over a longer follow up period using specific endoscopic indices.
Impact of dietary fibers intake on disease outcome in inflammatory bowel disease patients

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Introduction: It has been suggested that in addition to mutant genes and a hazardous environment, epigenetic factors may have a great impact on the outcome of Crohn’s disease (CD) and ulcerative colitis (UC). The aim of our study was to assess the impact of dietary fibers intake on the outcome of CD and UC.

Patients and Methods: Patients with CD or UC diagnosed at least 2 years ago were evaluated. prospective registration of alimentary habits was conducted through a recall questionnaire to provide information on the type and the daily intake of dietary fibers during a 1-week period. Retrospective analysis of clinical data on the disease outcome was carried out. We investigated correlations between dietary fibers intake and the need for surgery, immunosuppressors or immunomodulators, the occurrence of an acute severe flare, and serum albumin level. Statistical analysis was performed with SPSS software version 21.0.

Results: Ninety-eight consecutive patients were colligated: 59 patients having CD (60%), and 39 patients having UC (40%). Male to female ratio was 0.71. Severe CD was noted in 68% of patients: there were 16 patients who had severe acute colitis, 27 patients had underwent surgery and 61 patients have been put on immunosuppressors or immunomodulators. Soluble fibers intake from legumes was associated with a higher risk of colonic resection surgery (75% vs 25%, p = 0.03). Patients who had more insoluble fibers consumption from lens, chickpea and rice had been significantly more commonly put on immunomodulators or immunosuppressors (respectively p = 0.03, p = 0.019 and p = 0.02). However, insoluble fibers derived from whole grain were significantly associated with less occurrence of severe flares (p = 0.04) and less need for immunosuppressors or immunomodulators (p = 0.05). Moreover, insoluble fibers intake from cumin was positively correlated with serum albumin levels in CD and UC patients (spearman rho: 0.394, p = 0.0009).

Conclusion: Epigenetics is a rapidly expanding and hugely promising area of research. From the above data, some insoluble fibers, particularly from whole grain, seem to improve outcome of IBD patients. Further studies are needed to determine the mechanisms that mediate this impact.
Peripheral organs’ autoimmunity is highly connected to the intestinal ecosystem’s events

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Introduction: The human gut possess all the components necessary to start the autoimmune cascade. The aim was to characterize the multiple gut-remote organ autoimmune axes.

Methods: A systematic review was performed to identify Studies referred to gut multiple organs axes, using Medline, Google, and Cochrane Library databases.

Results: The specific dysbiota and tight junction dysfunction are primary defects in autoimmune diseases. The end result of the passage of none-self-proteins, from the luminal compartment to the subepithelial one, initiates the autoimmune cascade. The richness of the mucosal milieu in immune components, cells and systems, blood and lymphatic vessels, entero-neuronal and endocrine network and mural endo-mesoderm cohabitation, constitute an ideal place to initiate, maintain and propagate the autoimmune process. Mucosal committed immune cells, modified proteins, proinflammatory cytokines and lymphokines circulate via the local vessels, distributing autoimmune messages to remote organs, thus creating a gut-extraintestinal axes. Brain, joint, bone, endocrine, kidney, lung, liver, heart and skin, are directionally relayed to the intestinal events taking place in the genetically susceptible individuals.

Discussion/Conclusion: The intestine is a major site of changing tolerance to autoimmunity. Disease specific dysbiota, its post translational capacity to modify proteins, the plethora of substrates, the leaky gut, the local immune, neuroendocrine, vascular and lymphatic systems make the intestine a prime candidate to drive systemic autoimmunity.
Gluten immunological side effects are detrimental to human health: The joint aspects

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Objectives and Study: Evolution is accompanied by enrichment of gluten content in the wheat and today 80% of the proteins are gluten. In parallel, some unwanted effects induced by gluten consumption in non-celiac affected populations are recently described.

Aims: To summarize the literature for gluten consumption and withdrawal effects on autoimmune diseases in general and rheumatoid arthritis (RA) in particular.

Methods: A systematic review was performed, using Medline, Google, and Cochrane Library databases.

Results: Multiple autoimmune conditions respond to gluten free diet (GFD), including RA. Several pathophysiological avenues were described for the detrimental effects of gluten: breach of intestinal tight junction integrity, decrease in viability and apoptosis induction in human cell lines, induction of neutrophil migration, decrease in NKG2D and ligand expression, increase of Th17 cell population, effect on regulatory T-cell subsets, change of innate immunity, change of dendritic cell functions and change of microbiome diversity. The articular tissue transglutaminase and its inflammatory effects, the intestinal peptidylarginine deiminase, the enterocyte’s origin of citrulline, the beached tight junction integrity, the arthritis in celiac disease, the enteritis in early RA and the partial response to GFD, are several potential pathophysiological pathways, connecting gluten consumption to RA.

Conclusions: Multiple non-celiac autoimmune diseases and conditions respond, to a variable degree to GFD. The protective mechanisms of GFD are constantly unraveled and involve multiple immunoregulatory pathways. Several pathophysiological pathways can explain the detrimental health effects of gluten consumption in RA.
Soluble syndecan-1: A novel biomarker of intestinal damage in children with celiac disease

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Syndecan-1 (SDC1) is essential for maintaining normal epithelial barrier. Shedding of SDC1 ectodomain, reflected by serum soluble syndecan-1 (SSDC1) levels. The association between SSDC1 level and mucosal damage in celiac disease (CD) has not been evaluated.

Aim: To determine serum levels of SSDC1 in children with CD and to evaluate its relationship with histological damage.

Material and Method: Cross-sectional, pilot study. Serum concentrations of SSDC1 were analyzed by ELISA in 49 untreated children with CD and 15 controls. CD was diagnosed based on positive celiac serology (anti-neo-epitope tissue transglutaminase and/or anti-endomysial antibodies) and small intestinal biopsy. SSDC1 levels were compared with Marsh grading. Controls were defined as none-specific abdominal pain having normal small intestinal biopsies.

Result: No baseline demographic differences were depicted. Soluble syndecan-1 levels in CD were significantly higher than the controls ones (116.2, 41.3 ng/ml, p < 0.01, respectively). SSDC1 concentrations displayed significant correlation with mucosal damage defined by Marsh (r = 0.39, p < 0.05). Anti-neo-epitope tissue transglutaminase antibodies concentrations correlated with mucosal damage defined by Marsh (r = 0.3, p < 0.05).

Conclusion: This is the first study demonstrating elevated levels of serum soluble syndecan-1 in children with CD compare to controls. Our results suggest that SSDC1 is a potential novel biomarker of intestinal mucosal damage in patients with CD. Its applicability as a diagnostic and a surrogate biomarker in CD remains to be determined.
Anti-enterocyte autoantibodies in celiac disease

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Introduction: Endoscopic and histological changes of autoimmune enteropathy (AIE) are similar to celiac disease before treatment, but these are not altered by any form of dietary restriction, including a gluten-free diet. Even antibodies to tissue transglutaminase have been described in over 30% AIE patients, but no anti enterocyte antibodies (AEA) were studied in pediatric CD.

Methods: CD (No = 33) was diagnosed based on positive celiac serology (anti-neo-epitope tissue transglutaminase (Aesku*) and/or anti endomysial antibodies) and small intestinal biopsy. Age and sex matched controls (No=48) were defined by abdominal pain, negative celiac serology, normal upper endoscopy and normal small intestinal biopsies. AEA test was performed using Western blot. Homogenates from normal human intestinal mucosa were electrophoreses on 7.5% SDS-PAGE and transferred on nitrocellulose membranes. Blots were treated with serum from celiac patients and controls and immunodeveloped using ELISA kit.

Results: 3/33 (9%) and 6/48 (12.5%) were positive for AEA in the pediatric celiac compared to the control group, respectively. The frequency of AEA positivity in abdominal pain control group was higher than in the celiac group (P < 0.0001).

Conclusions: Despite the clinical, endoscopic and histological overlap between AIE and CD, AEA are more frequent in non CD, non-specific abdominal pain children with normal intestinal histology. Most probably the AEA in CD represent an epiphenomenon. The presence of AEA in the non-CD abdominal pain children remains to be investigated.
Joint’s autoimmunity is highly connected to the intestinal ecosystem’s events

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Objectives and Study: The human gut possesses the components necessary to start the autoimmune cascade. The aim was to characterize the multiple gut-remote organ autoimmune axes, zooming on the gut-joint axis.

Methods: A systematic review was performed to identify studies referred to gut multiple organs axes, using Medline, Google, and Cochrane Library databases.

Results: The specific dysbiota and tight junction dysfunction are primary defects in autoimmune diseases. The end result of the passage of none-self-proteins, from the luminal compartment to the subepithelial one, initiates the autoimmune cascade. The richness of the mucosal milieu in immune components, cells and systems, blood and lymphatic vessels, entero-neuronal and endocrine network and mural endo-mesoderm cohabitation, constitute an ideal place to initiate, maintain and propagate the autoimmune process. Mucosal committed immune cells, modified proteins, proinflammatory cytokines and lymphokines circulate via the local vessels, distributing autoimmune messages to remote organs, thus creating a gut-extraintestinal axes. Rheumatologic conditions are directionally relayed to the intestinal events taking place in the genetically susceptible individuals. Rheumatoid arthritis (RA) shares multiple aspects with celiac disease: genes, post translational modification by PAD/cytrullination and TTG/deamidation, respectively, tTg induces arthritis and bone erosion, enteritis is described in 60% of early RA and some patients are responding to gluten withdrawal.

Conclusions: The disease specific dysbiota, its post translational capacity to modify proteins, the plethora of substrates, the leaky gut, the local immune, neuroendocrine, vascular and lymphatic systems make the intestine a prime candidate to drive systemic autoimmunity and RA.
Comparison of the reliability of 17 celiac disease associated biomarkers to reflect intestinal damage

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In view of the increasing importance of serological biomarkers for screening and diagnosing celiac disease (CD), lack of back-to-back comparison, and reliability of isolated or combined antibody test systems to reflect intestinal damage in children with CD, their differential performances were evaluated.

95 pediatric CD patients (mean age 8.3), 45 non-specific abdominal pain children (AP) (mean age 7.3), 99 normal children (NC) (mean age 8.5) were tested with the following ELISAs (detecting IgA, IgG or both, IgA and IgG [check]):

Aeskulisa® Gliadin (AGA), Aeskulisa® DGP (DGP), Aeskulisa® tTg “New Generation” (Neo-epitope tTg complexed to gliadin = tTg-neo), tTg (for in house research purpose only), Aeskulisa® mTg neo-epitope and mTg (RUO). Anti-endo-mysial antibodies (EMA) were checked by immunofluorescence (Aeskuslides® EMA). The results were compared to the degree of intestinal injury, using the revised Marsh criteria.

Most assays were able to discriminate between patients with low and high degree of intestinal damage. Comparing the different correlations between CD associated IgA and IgG antibodies’ isotypes, the tTg-neo IgA (r = 0.6165, p < 0.0001) and tTg-neo check (r = 0.6492, p < 0.0001) stood out, significantly, as the best indicators of the intestinal damage in CD. EMA-IgA, tTg and DGP check and mTg-neo IgG correlated nicely to the mucosal injury.

It is suggested that tTg-neo IgA/IgG antibodies should be used preferably to reflect intestinal damage during screening and diagnosing childhood CD. EMA-IgA, tTg, DGP checks and mTg-neo IgG titers followed the tTg-neo check performance. mTg-neo IgG presents a new serological biomarker for CD.
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.
The prevalence of *Helicobacter pylori*-positive gastritis in children with inflammatory bowel disease: Preliminary study

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**Background:** The incidence of pediatric inflammatory bowel disease (IBD), including ulcerative colitis (UC), Crohn’s disease (CD) and IBD unclassified (IBDU), has rapidly increased in highly developed countries. Recent reports have shown that patients with IBD are less likely to be infected with *Helicobacter pylori* (*H. pylori*) compared with non-IBD patients.

**The aim** of this retrospective study was to estimate the prevalence of *H. pylori*-positive gastritis in children coexisting with IBD in biopsy material in the Department of Medical Pathomorphology, Medical University of Bialystok, between January 2014 and December 2015.

**Methods:** Histopathological reports involved 89 children with active IBD. Biopsies obtained via colonoscopy and esophagogastroduodenal endoscopy underwent routine staining with Mayer’s hematoxylin and eosin (H&E). Gastric histopathology was defined and graded according to the Update Sydney System. To determine *H. pylori* infection, Alcian Yellow staining and in some cases Giemsa staining were used. Patients with *H. pylori* gastritis and IBD were selected from the study group.

**Results:** In the study period in the group of 89 children with active IBD we found 60 cases with UC; 17 with CD and 12 with IBDU. We detected *H. pylori* positive-gastritis with IBD in 19 patients (21.3%) – in 13 with CU, in 3 with CD and in 3 with IBDU. In 12 cases, the infection was minor, in 7 – moderate and no major infection was diagnosed.

**Conclusion:** Our results may be an interesting comparative material for other research centers. However, further observations of the protective role of *H. pylori* in IBD, suggested in literature, should involve more substantial biopsy material.
Risk factors for recurrence of postoperative Crohn’s disease – Single-center experience

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Introduction: Post-operative recurrence of Crohn’s disease is an important, recently recognized therapeutic challenge with 2-year clinical and endoscopic recurrence rates of up to 77% and 64% respectively. The primary endpoint of our study was to assess risk factors for clinical and endoscopic relapse after ileo-coecal resection in patients with CD.

Methods: This retrospective study enrolled 50 CD patients, with at least one resection examined and treated at single tertiary IBD Center. Clinical (by Clinical disease activity index [CDAI]) and endoscopic (by Rutgers’s score) assessments were made after median of 36 month after the operation. Age at diagnosis, gender, smoking status, duration of CD before the resection, presence of perianal disease, colonic involvement, length of resected segment, type of anastomosis, concomitant IMD and biologics (anti-TNF) were considered as potential risk factors for clinical and endoscopic recurrence. Data were analysed by univariate and multivariate logistic regression analyses. SPSS were used for the statistical analysis.

Results: 74% (37/50) of patients were in clinical remission, compared to 40% (20/50) patients in endoscopic remission after median of 3 years after the surgery. The group of patients in clinical remission were significantly younger (40.87 ± 1.82 years) than those with clinical relapse (49.33 ± 2.84 years) (p = 0.024). 66% of patients with T-L anastomosis were in clinical remission compared to 25% in relapse (p = 0.03; OR 3.84; CI 1.39 to 10.58). Anti-TNF therapy was significantly associated with the maintenance of clinical remission (p = 0.007; CI 3.58; 1.22 to 10.42). Multivariate logistic regression analysis revealed older age at diagnosis (p = 0.025; CI 5.03; 1 to 12.45) and extensive small bowel resection (p = 0.050; CI 2.89; 0.65 to 12.87) as risk factors for endoscopic recurrence.

Discussion/Conclusion: According to our results, it seems that older patients at the time of diagnosis, lack of biologics in postoperative course, latero-lateral or termino-terminal anastomosis and extensive resection may be associated with higher risk of relapse in previously resected CD patients.
The mechanisms of microbiota disorders’ influence on intestinal motor function in patients with diabetes mellitus type 2 with enteropathy

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In recent decades a clear upward trend in the incidence of diabetes mellitus (DM) type 2 is observed, a long course of the disease leads to early development of macro- and microangiopathy and autonomic polyneuropathy with the secondary target organ damage. The disorders of the motor-evacuation gastrointestinal (GI) tract function and intestinal microbiota are pathogenic substrate for diabetic enteropathy (DE) development.

**Aim:** To determine the microbiota disorders’ influence on intestinal motor function on the enteropathy background in patients with type 2 diabetes.

**Materials and Methods:** The study involved 126 patients with diabetes type 2 and diabetic enteropathy, of which 55 (43.6%) men and 71 (56.4%) – women, mean age 57.4 ± 8.5 years. The duration of the diabetes course was 7–10 years. Diabetes type 2 was in subcompensation stage: HbA1c level ≤ 7.5%, without ketoacidosis. Carbohydrate metabolism was corrected using the combined hypoglycemic therapy. In 72 (57.1%) patients the DE with the constipation syndrome was diagnosed, and in 54 (42.9%) – DE with diarrhea syndrome. The hydrogen breath test with lactulose was performed, the concentration of hydrogen in the exhaled air was measured before admission and at 15, 30, 60, 90 and 120 minutes after dosing. Simultaneously the feces analysis of dysbiosis was conducted.

On the DE background with the prevalence of constipation a gradual increase in the hydrogen concentration was noted with maximum values at 90 and 120 minutes – 38.09 ± 3.5 ppm and 40.71 ± 4.09 ppm respectively. Violation of the intestinal microbiota on the constipation background was characterized with the growth of Klebsiella, Cyanobacter, Proteus, Staphylococcus content in the feces of 57 (79.2%) patients and reduction of Bifidobacteria in 15 (20.8%) patients.

Under condition of enteropathy with diarrhea syndrome the presence of two peaks were revealed at 15 and 30 minutes with the hydrogen concentration 44.26 ± 4.08 ppm and 48.92 ± 3.94 ppm respectively. At 60 minutes the reduction of hydrogen 16.47 ± 2.9 ppm was noted with its increase at 90 and 120 minutes up to 41.05 ± 4.12 ppm and 40.86 ± 3.1 ppm respectively. Microbiota disorders on the background of diarrhea were characterized by Bifidobacteria decrease in feces of 38 (70.4%) patients and increased content of Klebsiella and Staphylococcus in 16 (29.6%) patients.

Thus, in the presence of DE with constipation the increased concentration of pathogenic microflora is observed, that leads to intestinal transit time prolongation. When the diarrhea syndrome is prevailed a significant reduction of normal anaerobic microflora is observed, accompanied by intensified propulsive intestinal activity.
New markers for celiac disease: Anti-neo-epitope human and microbial transglutaminases

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Objectives: Microbial transglutaminase (mTg) and human tissue Tg (tTg) complexed to gliadin peptides present neo-epitopes. Antibodies against these complexes are called tTg neo-epitope and mTg neo-epitope. Reliability of antibodies against the non-complexed and complexed forms of both transglutaminases to reflect intestinal damage and to diagnose the pediatric celiac disease (PCD) was compared.

Methods: 95 PCD patients, 99 normal children (NC) and 79 normal adults (NA) were tested using the following ELISAs detecting IgA, IgG or both IgA + IgG combined: tTg (for in house research use only), AESKULISA® tTg New Generation (tTg neo-epitope [tTg-neo]), AESKULISA® mTg (RUO) and AESKULISA® mTg neo-epitope (mTg-neo, RUO). Marsh criteria were used for the degree of intestinal injury.

Results: All anti-mTg-neo and anti-tTg-neo levels were higher (p < 0.001) compared to the single antigens. tTg-neo IgA and IgG + IgA were higher than mTg-neo IgA and IgA + IgG (p < 0.0001). The antibody activities reflecting best the increased intestinal damage were: mTg-neo IgA > mTg-neo IgA + IgG > tTg-neo IgG ≥ mTg-neo IgG > tTg-neo IgA > tTg-neo IgA + IgG. Taken together, mTg-neo IgG and tTg-neo IgA and IgA + IgG correlated best with intestinal pathology (r = 0.5633, r = 0.6165 and r = 0.6492; p < 0.0001, p < 0.0001 and p < 0.0001 respectively).

Conclusion: The complexed forms of both transglutaminases exhibited a higher OD activity and better reflected intestinal damage in PCD, compared to the non-complexed forms. mTg is immunogenic in children with CD and by complexing to gliadin its immunogenicity and pathology reflection is enhanced.
Antibodies against neo-epitope tTg complexed to gliadin outperform the uncomplexed anti-tTg to follow rheumatic arthritis patients

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Rheumatoid arthritis (RA) is a high risk disease for celiac disease (CD), sharing multiple aspects. IgA-tTg autoantibody is a classical marker for CD, however, it has many false positives. Anti neo-epitope tTg complexed to gliadin is a reliable biomarker for CD, has never been compared to the IgA-tTg performance and false positivity in naïve and treated RA population.

**Methods:** 135 RA adult patients, mean age 55 ± 12.7 years, F/M 1:0.2, respectively, from the ADAPThERA study cohort, where studied in naïve patients and longitudinally at 3 follow-up visits. ADAPThERA is a network to improve patient care and to find new bio-markers for RA. Patients were tested using the following ELISAs detecting either IgA, IgG or both (IgA + IgG): tTg (for in house research purpose only) and Aeskulisa® tTg New Generation (tTg neo-epitope).

In the naïve patients, on the first visit after diagnosis and along the follow up under pharmaceutical therapy, for 3 consecutive visits, the % positivity of the IgA-tTg (Visit 1, 2, 3, 4, 6.7%, 3.1%, 4.6%, 7.0%, respectively) was significantly higher than in the tTg-neo antibodies (Visit 1, 2, 3, 4, 2.2%, 0.8%, 1.1%, 2.8%, respectively, p < 0.05).

Determinations of CD associated autoantibodies in naïve and treated RA groups reveal that IgA-tTg is less specific for CD (mirrored by its higher false positivity) in relation to the lower false positivity of its competitor (anti-neo-tTg) in RA patients’ sera.
Autoantibodies against CD74 – A new diagnostic marker for spondyloarthritis (SpA)

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Background: Spondyloarthritis (SpA) is a common debilitating inflammatory disorder. The pathogenesis of axial spondyloarthritis (axSpA) including ankylosing spondylitis (AS) is still largely unclear. Establishing the diagnosis is difficult, since abnormalities in X-ray develop with a latency of several years and only HLA-B27 or radiographic sacroiliitis is used as a laboratory marker yet. Hence, to prevent destructive effects early diagnosis in SpA patients is indispensable. Therefore, we evaluated antibodies to the HLA class II- antigen associated invariant chain (CD74) as a diagnostic marker of SpA.

Methods: 118 sera of axSpA patients and 200 control sera (120 blood donors, 80 non-SpA patients) were analyzed for IgA antibodies against CD74 by ELISA. All donors provided informed consent for the study, which was approved by the local ethics committee (project number 4928).

Results: SpA patients were more often male and younger. HLA-B27 status was available in 109 patients. CD74-antibodies were detected in 91% of SpA but in only 4% and 8% of healthy controls and other autoimmune disease patients, respectively (p ≤ 0.0001). Remarkably, IgA autoantibodies against CD74 had a sensitivity of 91% and a specificity of 94%, (likelihood ratio: LR+: 15.6, LR-: 0.09) and were even more frequent in SpA patients with short disease duration. Furthermore, IgA anti-CD74 antibodies significantly correlate with more advanced radiological sacroiliitis and reduced spinal mobility.

Conclusion: CD74 IgA antibodies were strongly associated with SpA and can be used as a new marker. Moreover, they were found to be strongly associated with the grade of sacroiliitis.
Anti-neo-epitope tTg complexed to gliadin vs. tTg for celiac disease diagnosis

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Introduction: The guidelines of ESPGHAN for the diagnosis of pediatric celiac disease (PCD) rely on anti-human tissue transglutaminase (tTg) as the prime and unique antibody for screening PCD population. None of the CD-associated antibodies has challenged tTg premiership. tTg complexed to gliadin presents neo-epitopes and antibodies against the complex are called tTg neo-epitope. Reliability of anti-tTg and tTg-neo antibodies in diagnosis of PCD was compared.

Methods: 95 pediatric CD patients (mean 8.3 y), 99 normal children (NC) (8.5 y) and 79 normal adults (NA) (28 y) were tested using the following ELISAs detecting IgA, IgG or both IgA + IgG: tTg (internal research use only) and AESKULISA® tTg New Generation (tTg neo-epitope). The results were compared to the degree of intestinal injury, using revised Marsh criteria.

Results: A significantly higher OD activity was detected for tTg neo-epitope IgA, IgG and IgA + IgG than for tTg (p < 0.0001, p < 0.0001, p < 0.001, respectively). tTg neo-epitope IgA, IgG correlated better with intestinal damage than tTg (r = 0.6165, 0.5334 compared to 0.4692, 0.2601 [p < 0.001], respectively).

Conclusion: The tTg neo-epitope IgA, IgG and IgA + IgG isotypes exhibited a higher OD activity and better reflected intestinal damage in PCD, compared to tTg isotypes. The tTg neo-epitope IgA + IgG ELISA kit had higher sensitivity and a comparable specificity for the diagnosis of childhood CD. tTg neo-epitope should be included in the ESPGHAN diagnostic flow chart.
Pediatric celiac disease, cryptogenic hypertransaminasemia, and Helicobacter pylori infection among children with dysmotility-like dyspepsia

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Introduction: Hypertransaminasemia (HT) is present at diagnosis in a significant proportion of children with celiac disease (CD). Our aim was to investigate the prevalence of HT in pediatric CD patients and the relationship between CD, HT and Helicobacter pylori (HP) infection.

Methods: We conducted a case-control study including CD children older than 2 years of age hospitalized at the "Sfanta Maria” Children’s Hospital between January, 2012-June, 2014 admitted with symptoms of upper abdominal disturbances. CD patients with positive results for HP infection were identified (n = 15) and matched with negative HP-CD patients (n = 27). Alanine transaminase (ALT) and aspartate transaminase (AST) values were assessed upon admission.

Results: Of the 42 patients diagnosed with CD included in the study, HP was detected in 15 patients, 10 (66.6%) male, mean age 6.20 ± 4.57 yrs. Upper endoscopy and biopsy were performed in 17 subjects with 8 (47%) having mucosal inflammation (HP in 4 patients). Viral, metabolic, autoimmune, and drug induced hepatitis were evaluated by appropriate tests. HT was found in 11 (26.2%) patients. Only 2 CD HP-negative patients were positive for viral C hepatitis. When comparing the study groups, we found that the means of serum anti-tissue transglutaminase antibody IgA levels in children with HP and control were 7.87 ± 10.31 u/mL vs 119.56 ± 54.23 u/mL (P < 0.0001) and iron levels 56.93 ± 10.38 vs 63.69 ± 8.77 (P = 0.045). Mean AST levels were 123.73 ± 91.48 in the HP-positive group vs 41.67 ± 4.83 in the non-HP group, and mean ALT levels were 66.20 ± 46.05, respectively 23.48 ± 3.35 (P < 0.0001). Pediatric CD patients with HT were younger than those with normal levels (5.42 ± 3.21 vs 12.01 ± 2.34 yrs, P < 0.0001). Sex and symptoms at diagnosis were not predictive of elevated liver enzymes.

Discussion/Conclusion: Young CD patients are more likely to have an elevation in transaminases. Clinical presentation may range from typical malabsorption syndrome to apparently unrelated extra-intestinal symptoms.
Association between MDR1 gene polymorphisms and the risk of ulcerative colitis in Serbian patients with inflammatory bowel disease

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Introduction: Inflammatory bowel disease (IBD) is a chronic disease of unknown etiology in which genetic factors contribute to development of disease. Single nucleotide polymorphisms (SNPs) in the multidrug resistance 1 (MDR1) gene coding transporter P-glycoprotein have been associated with IBD, but their role in disease susceptibility remains unclear due to contradictory results. Therefore, the aim of this study was to investigate the association of three MDR1 polymorphisms, C3435T (rs1045642), C1236T (rs1128503) and G2677T/A (rs2032582), with Serbian IBD patients.

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

Results: Significantly lower frequencies of C allele (OR: 0.63; p = 0.006) and CC genotype (OR: 0.4; p = 0.004) of C3435T SNP were observed in UC patients compared to controls, implying protective role of C allele. Conversely, T allele of C1236T SNP could be recognized as a potential predisposing factor, since both T allele and TT genotype were more frequent in UC group (OR: 1.83; p = 0.0003 and OR: 1.9; p = 0.013, respectively). Likewise, T allele and TT genotype of G2677T/A SNP were found more frequently in UC patients (OR: 1.74; p = 0.001 and OR: 1.74; p = 0.037, respectively). In contrast to UC, none of the analyzed markers was associated with CD.

Discussion/Conclusion: All three MDR1 gene variants were associated with Serbian UC patients further supporting their potential role as biomarkers of UC.
A single-center experience in inflammatory bowel disease after liver transplantation for primary sclerosing cholangitis

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Introduction: Primary sclerosing cholangitis (PSC), a chronic immune mediated cholestatic disease of the liver, is often associated with extrahepatic manifestations in the form of inflammatory bowel disease (IBD). End stage parenchymal disease due to progressive inflammation and fibrosis of the biliary tract is an accepted indication for liver transplantation (LT). Exacerbation of pre-existing IBD as well as development of de novo disease following LT occurs despite life-long immunosuppressive therapy. The aim of this report was to examine characteristics of patients transplanted for PSC, with reference to IBD burden and outcomes.

Methods: Data was gathered retrospectively on 29 patients (71.4% male, mean age at LT 38.03 ± 9.58 years) in the period from 2004–2016. The diagnosis of PSC was made by magnetic resonance cholangiopancreatography (MRCP) and/or liver biopsy, and confirmed in all patients by histopathologic examination of the hepatectomy specimen. The diagnosis of IBD was confirmed in 19 patients by histopathologic examination of tissue samples. One patient was excluded from analysis due to insufficient records.

Results: The diagnosis of IBD was made in 19 (67.9%) patients prior to LT- 14 (74%) with ulcerative colitis, 4 (21%) with Crohn’s disease and one (5%) “indeterminate colitis”. Recurrent IBD constituted the most significant adverse event, affecting 10/19 patients, while de novo IBD occurred in a single patient. PSC recurrence, verified by graft biopsy or MRCP, was recorded in 4 (14.3%) cases. Four patients transplanted due to cholangiocarcinoma did not experience malignancy relapse. The mainstay of immunosuppressive therapy included calcineurin inhibitors, with 75% receiving tacrolimus and 25% cyclosporine, and the majority also receiving mycophenolate mofetil (79%).

Overall survival following LT for PSC was excellent, with only one patient death due to post-transplant lymphoproliferative disease. Graft loss occurred in 3 patients, one re-transplantation was performed due to PSC recurrence, and the rest due to vascular damage.

Discussion/Conclusion: Primary sclerosing cholangitis is a rare indication for LT, with excellent long-term graft and patient survival. Despite life-long immunosuppressive therapy IBD remains a significant cause of morbidity in this population, however with little influence on overall graft and patient survival.
Inflammatory bowel disease and kidney – Is there a connection?

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Background/Aim: The aim of the present study was to investigate whether patients with inflammatory bowel disease (IBD) have some degree of renal involvement. Furthermore, we were investigated whether this connection is related to active bowel disease.

Methods: In this cross-sectional study 50 patients mean age 47.1 ± 16.5 years with a diagnosis of IBD were recruited from September 2012 to September 2013. The diagnosis of IBD was based on clinical history, endoscopic, histological and radiological findings. Disease activity was assessed using the UC activity index (UCAI) for ulcerative colitis (UC), and CDAI for Crohn’s disease (CD). There were 38% patients with UC and 62% patients with CD.

Results: The prevalence of abnormal albuminuria in UC and CD patients was 21.1% and 29% respectively. There was a high negative correlation between duration of bowel disease and 24-h albuminuria in UC patients, as well as a high correlation among albumin creatinine ratio (ACR) and UCAI score in UC patients, but those correlations weren’t statistically significant, probably due to small number of UC patients. On the other hand, eGFR showed negative correlation with disease activity in CD patients (r = -0.569; p = 0.05), while there was no statistically significant correlation between active UC and eGFR (r = 0.343; p = NS).

Conclusion: Abnormal albuminuria is quite frequent in patients with IBD. It seems that patients with IBD have some degree of glomerular damage, mainly those with CD. Collaborative, prospective studies of gastroenterologists and nephrologists that will investigated this association are needed.

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Hepatic toxicity to azathioprine: A report of 4 cases

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Introduction: The hepatotoxicity of azathioprine (AZA) is clearly demonstrated and is associated to a very large spectrum of liver diseases. It is a rare complication, reported in 1–3% of patients with inflammatory bowel disease (IBD) and is mostly asymptomatic.

Methods: We report 4 cases of patients with IBD who developed hepatic toxicity to AZA.

Results: The study included 4 patients (2 women and 2 men) with a median age of 49 years (24–67 years). AZA was prescribed for corticodependent Crohn’s disease in 2 cases and for severe acute colitis in the other 2 cases. The time between the initiation of AZA and the occurrence of hepatic toxicity varied between 7 and 15 days. The circumstances of the discovery were abdominal pain in 3 patients and cutaneous-mucosal jaundice in a patient. Biological examinations showed cholestasis (3–5 times ULN) in the 4 patients and cytolysis (5–7 times ULN) in 2 patients. The evolution was favorable in all cases with normalization of the hepatic tests following cessation of treatment after an average duration of 10 days (9–15 days).

Discussion/Conclusion: The causality of AZA in hepatic toxicity remains difficult to establish, especially because there are other pathologies associated with taking other hepatotoxic drugs or comorbidities affecting the liver.
Health-related quality of life in inflammatory bowel disease in a Tunisian population

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Introduction: The management of the health-related quality of life (HRQoL) is increasingly considered as an important treatment goal in chronic diseases including inflammatory bowel diseases (IBD). The aim of our study was to determine the impact of IBD on HRQoL of patients and identify the factors involved in the deterioration of HRQoL of these patients to optimize their medical care.

Methods: We conducted a case-control study including 108 patients; 66 had Crohn’s disease (CD) and 42 had ulcerative colitis (UC). In the measurement of HRQoL, we used a general questionnaire "Short Form 36: SF36" and a specific questionnaire "Tunisian Inflammatory Bowel Disease Questionnaire: T-IBDQ".

Results: In our study, HRQoL of patients was worse than controls with a statistically significant difference for six of the eight dimensions of the SF 36 “Physical Functionning PF”, “Role Physical RP”, “General health GH”, “Social Functionning SF”, “Mental Health MH” and “Role Emotional RE” and the Mental summary score (MCS) and the Physical summary score (PCS) (p < 0.05). The factors involved in the alteration of HRQoL were: age < 30 years (p = 0.045), poor socioeconomic conditions (p = 0.018), disease activity (p < 0.05), use of corticosteroids (p < 0.05), a number of surgeries ≥ 2 (p = 0.008) and anterior hospitalization history (s) (p = 0.05).

Discussion/Conclusion: In this study, IBD cause impaired HRQoL objectified by lower scores of SF-36 compared to controls and affecting almost all areas of the SF 36 questionnaire. Incriminated factors may be related to the patient, disease and even treatment. In addition to gastroenterologists and surgeons, the management of these patients should include psychologists, psychiatrists and sociologists.
Inflammatory bowel diseases in children: A multicentric Tunisian study

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Introduction: Inflammatory bowel disease (IBD) is rare in children. However, their frequency is clearly increasing even in developing country. They have several specificities compared to those of adults. The aim of our study is to determine the epidemiological, clinical, therapeutic and evolutionary characteristics of IBD in Tunisian children.

Methods: It was a retrospective study including children with IBD followed in four Tunisian pediatric departments from January 2000 to December 2014.

Results: We collected 41 cases. There were 32 cases of Crohn’s disease (CD) and 9 cases of ulcerative colitis (UC) with an average age of 11.2 years. The sex ratio M/F was 1.9 for the CD and 2 for the UC. A family history of IBD was found in 10 patients. Abdominal pain was present in all cases while diarrhea was reported in only 80.4%. The most frequent localization was ileocolic in CD (53%) and pancolic in UC (55%). The initial outbreak was severe in 43.7% cases of CD and 44.4% cases of UC. Ano-perineal lesions were present in 31% of CD cases. The extra-digestive signs dominated by joint and skin involvement were noted in 14 children (34%). Weight retardation was found at the time of diagnosis in 34% of children. The statural growth retardation was found in 24.3% of the children. A delayed puberty development was noted in 15% of CD cases. While five children with CD required surgical treatment, only three have nutritional management. Maintenance therapy was initiated in 29 children (70%). The disease was quiescent in 33% of cases with a mean follow-up of 3 years 4 months.

Discussion/Conclusion: Little is known about inflammatory bowel disease in pediatric Tunisian population. Nutritional treatment is an attractive therapeutic option in children but seems to be difficult to apply in Tunisian environment.
Introduction: Chronic pancreatitis (CP) is of a rare occurrence in childhood. Pancreatic abnormalities are common in inflammatory bowel disease (IBD) patients. Some authors have proposed that CP may be an extraintestinal manifestation of IBD. The aim of this study was to investigate the prevalence of IBD in children with CP from well-defined homogenous single-center cohort.

Methods: 329 children with CP (aged: 0.6–18 years; mean 8.8) hospitalized between 1988 and 2016 were enrolled into the study. Clinical and epidemiological data were recorded and analyzed. All patients were screened for gene mutations predisposing to CP. All children had preceding imaging studies, including US, CT, MRCP and/or ERCP.

Results: IBD were found in 8 children with CP (2.4%) (aged: 6–18 years; mean 10.5; M-6; F-2). Colitis ulcerosa (CU) was diagnosed in 6 children. Crohn’s disease (CD) was diagnosed in 2 children. Gene mutations were found in 3 children with IBD (CTRC-G60G in 2 patients and SPINK1 – N34S in one child). Anatomic anomaly of pancreatic duct- pancreas divisum was diagnosed in 2 other patients with IBD. PSC was found in 2 patients with CU. Autoimmune pancreatitis (AIP) was diagnosed in 2 children with IBD. Autoantibodies (ANA, ASMA) were present in all CP with IBD cases. CP without other common etiologic factor was diagnosed in 2 children with IBD (25%) only.

Discussion/Conclusion:
1. Coexistence of CP and IBD is rare in pediatric population.
2. In patients with CP and IBD we should be aware of coexisting other etiological factors of CP, as gene mutations, anatomic anomalies, or AIP.
Unusual course of tuberculosis in a patient treated with infliximab for indeterminate colitis: A case report

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Introduction: Anti-Tumor Necrosis Factor (anti-TNF) agents are important medications in the treatment of inflammatory bowel disease, but they carry a burden of possible severe adverse effects such as severe infections. TNF-alpha has a central role in immune response to Mycobacterium tuberculosis and its suppression by anti-TNF agents could lead to tuberculosis infection or reactivation.

Methods: We analysed a case of a patient with indeterminate colitis (IC) who developed tuberculosis during treatment with an anti-TNF agent infliximab (IFX) and tuberculous meningitis 12 months afterwards.

Results: 54-year old male patient was admitted to the Department of Infectology of our tertiary centre for headache, fever and altered consciousness. Tuberculous meningitis was diagnosed based on M. tuberculosis isolation from cerebrospinal fluid. Patient was previously treated with IFX for IC, which was initiated 16 months before, and stopped after 4 months of therapy because development of pulmonary tuberculosis. Screening for tuberculosis was negative prior to initiation of anti-TNF therapy. Despite finishing anti-tuberculotic therapy and not receiving any of the immunosuppressive agents for IBD (as patient was in a clinical and endoscopic remission), patient developed tuberculous meningitis, which could possibly be associated with prolonged immunosuppression caused by infliximab. Patient was released after a three-month hospitalization with CNS sequelae in the form of dementia.

Discussion/Conclusion: Despite the negativity of screening tests for tuberculosis prior to initiation of anti-TNF therapy, there is a risk of developing tuberculosis infection during the anti-TNF treatment. As well, anti-TNF agents cause significant immunosuppression that could possibly change the normal course of tuberculosis.
Association of mir-146 rs2910164, miR-119a rs11614913 and miR-221 rs113054794 polymorphisms with anti-TNF treatment response in a Greek population with Crohn’s disease

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Background: MiRNAs are being studied as candidate biomarkers in many diseases, among which in Crohn’s disease (CD). The aim of this study is to investigate the correlation between rs2910164, rs11614913 and rs113054794 polymorphisms and response to anti-TNF treatment in Greek patients with CD.

Methods: One hundred seven patients with CD based on standard clinical, endoscopic, radiological, and pathological criteria were included in the study. They all received infliximab intravenously at a dose of 5 mg/kg at weeks 0, 2, 6 and every 8 weeks thereafter, as per international guidelines. Clinical and biochemical response was assessed using the Harvey-Bradshaw index and CRP levels respectively. Endoscopic response was evaluated by ileocolonoscopy at week 14–20 of therapy. The changes in endoscopic appearance compared to baseline were classified into four categories, and patients were classified as responders and non-responders. Whole peripheral blood was extracted and genotyping was performed by PCR.

Results: Seventy-two (67.3%) patients were classified as complete responders, 22 (20.5%) as partial while 13 (12.1%) were primary non-responders. No correlation was detected between response to infliximab and patients’ characteristics such as gender, age and disease duration while clinical and biochemical indexes used were associated with endoscopic response. Polymorphisms under investigation were not shown to correlate with response to infliximab in this group of Greek patients. Regarding rs113054794, normal genotype CC occurred in both patients and controls suggesting that this specific polymorphism does not exist or is very rare in our population.

Conclusion: No correlation was found between rs2910164 and rs11614913 polymorphisms and our study’s population response to anti-TNF treatment. Polymorphism rs113054794 was not detected in our population. Consequently, these polymorphisms cannot be used as biomarkers for predicting response to anti-TNF treatment of Greek patients with CD.
Vedolizumab and predictive factors of clinical response in Crohn’s and ulcerative colitis patients

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Introduction: The role of biologics in medical management of inflammatory bowel disease (IBD) is well established since anti-TNF agents invaded the market several years ago. Vedolizumab, an anti-integrin gut-selective molecule, is a fairly recent biologic which has been approved for the management of IBD. Its efficacy in inducing and maintaining remission was shown in GEMINI studies, although this was a selected group of patients, the majority of whom had previously failed anti-TNFs. The aim of this study was to describe outcomes in a real life cohort of IBD patients treated in a tertiary referral ventre, consisting both of anti-TNF naive and exposed patients, and to identify predictive factors of response to vedolizumab.

Methods: All patients with IBD who received at least 3 doses of vedolizumab in UCLH since the drug was licensed in the UK were included in the study. Demographics, clinical and endoscopic response rates were recorded and analysis was conducted in the whole cohort and in the subgroups of Crohn’s and ulcerative colitis (UC) patients separately. Univariate analysis and logistic regression were conducted in order to identify important associations with clinical response.

Results: 59 patients with IBD were treated with vedolizumab from May 2015 to October 2016. 28 (47%) had Crohn’s disease and the majority (n = 43, 73%) had mainly colonic inflammation (12 colonic Crohn’s, 29 UC, 2 IBDU). Median time from diagnosis to vedolizumab initiation was 8 years. 17 (29%) were anti-TNF naïve (all UC) and 28 (67%) had previously failed both infliximab and adalimumab. 36 (61%) were on a concomitant immunomodulator (IM).
41 (70%) had a clinical response to vedolizumab based on a reduction of HBI ≥ 3 or partial Mayo score ≥ 2 points. The rates of response were similar in Crohn’s and UC patients while there was no difference in response according to gender, previous anti-TNF exposure, disease duration or location of inflammation. Patients on no concomitant IM were less likely to respond to vedolizumab (OR 0.26, 95% CI 0.07–0.91, p = 0.036). 11 (18.6%) patients experienced adverse events while treated with vedolizumab, 5 of which were related to active IBD. There were two minor allergic reactions and two mild infections.

Discussion/Conclusion: Clinical response to vedolizumab was observed in two thirds of our IBD patients. Concomitant IM were the only factor which was importantly associated with response rate. Overall there were no serious adverse events.
Source of initial referral, rate of pre-investigation clinical diagnosis and first diagnostic test requested in a cohort of newly diagnosed colorectal cancer patients: The Poole Experience

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**Introduction:** To identify the initial route of referral-fast track route (GP referral), iron deficiency anaemia clinic route, non-fast track (GP referral), bowel cancer screening, the in-patient route and surveillance programme patients for a cohort of colorectal cancer (CRC) patients diagnosed at Poole Hospital. To further identify the percentage of referrals with a positive clinical examination at the time of referral and to determine the first line diagnostic investigation requested (colonoscopy/lower gastrointestinal endoscopy, CT colonoscopy (CTC), CT abdominal scanning) or the modality of diagnosis (laparotomy, PET, other) and any differences between referral groups.

**Methods:** Retrospective audit of all patients diagnosed with CRC during period 1st October 2015–30th September 2016 inclusive identified using the Somerset cancer database for Poole Hospital. The route of referral, positive clinical examination at time of referral and first line investigation confirming CRC diagnosis or other modalities of how the diagnosis was made identified by review of each individual electronic patient record.

**Results:** 202 patients were identified, 10 were excluded (7 non adenocarcinoma, one out of area, two patients with dementia where earlier decision best supportive care) leaving 192 patients for analysis. In only 14 patients (7.3%) was a rectal or abdominal mass palpable at the time of referral. 39.6% of patients diagnosed with CRC came through the fast track and IDA clinic. Similar numbers of patients diagnosed with CRC came through the screening service as well as via the late presentation of a surgical emergency (16.7%), 14% via the non-fast track route, 11.4% as medical referrals and 1.6% via the surveillance programme (Fig 1). Colonoscopy was the diagnostic test in all of the screening patients, 65% of fast track patients, 77% IDA clinic patients, 71% non-fast tracks and 6.3% surgical in-patients referrals. Abdominal CT was the initial test of choice in the surgical in-patient group (65.6%) and medical referrals (60%). CTC was the first line investigation in 14% of all patients diagnosed with CRC with the highest referral group being offered CTC as first test coming via the fast track route (26%) (Fig. 2).
**Discussion/Conclusion:** Only a small number of patients with bowel cancer had a palpable rectal or abdominal mass on first presentation. Nearly a fifth of all bowel cancers were diagnosed late via the emergency presentation route. With increasing uptake of screening and population education the hope is that this number will decrease in time. A quarter of all the fast track patients diagnosed with CRC were offered CTC over colonoscopy as first test. This audit offers further opportunities for greater understanding as to the decision making for choosing CTC over colonoscopy in this group. IDA clinic referral patients are seen urgently akin to fast track referrals but are seen in physician and nurse led IDA clinics, whereas GP referred fast tracks are seen in the colorectal clinics. Factors such as patient age, co-morbidity, symptoms and service capacity as well as clinician and patient preference are likely to influence the initial test decision.
Post investigation colorectal cancer rates (PI-CCR) including post colonoscopy colorectal cancer rates (PC-CRC): The Poole Experience

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Introduction: Post colonoscopy colorectal cancer (PC-CRC) rates are proposed as a quality indicator of a colonoscopy service. Extrapolating the data is challenging but important to assess local practice and to compare with recent published National Data. We aimed to calculate the PC-CRC and the post CT (Colonoscopy + abdomen) CRC rate at Poole Hospital using the number of colonoscopies or CT scans done within 3 years of a CRC diagnosis as the denominator for post-investigation (PI)-CRC calculations as outlined in a previous study1.

Methods: Retrospective audit of all patients diagnosed with CRC during period 1st October 2015–30th September 2016 inclusive identified via the Somerset Cancer registry database for Poole Hospital using Crystal software. Previous colonoscopy and CT Colonoscopy (CTC) or CT abdomen results in the 3 years preceding the diagnostic investigations were reviewed across two neighbouring hospitals sharing the same electronic patient records. If patients had multiple surveillance colonoscopies the latest was counted as false negative as in previous studies1.

Results: 202 patients were identified, 21 were excluded (7 non adenocarcinoma, one out of area, two patients with dementia where earlier decision was best supportive care, 6 patients diagnosed at laparotomy, 2 abnormal PET scans, 3 incomplete datasets). 181 patients were included for analysis. Colorectal cancer was diagnosed by colonoscopy in 110 patients and by CTC or CT abdomen in 71 cases. In the colonoscopy diagnosed group, 32 were via Bowel Cancer Screening Programme (BCSP), 75 via the symptomatic service and 3 from the surveillance programme. In the BCSP and symptomatic service groups there were no preceding colonoscopies within the previous 3 years (6–36 months)1. In the surveillance group there were 2 preceding (“false negative”) colonoscopies within the previous 3 years. The overall PC-CRC was 1.8%. In the CT diagnosed group, all from the symptomatic service, there were 4 preceding CT abdomen scans but no preceding CTC’s within 6–36 months. The post CT-CRC rate was 5.3%.

Discussion/Conclusion: Our findings offer the opportunity for further review of individual cases at local governance level and within the limitations of data collection (NHS hospital records reviewed) our estimated PC-CRC rate of 1.8% compares favourably to the published National PC-CRC rate of 8.6% between 2001–20071. We question the validity of a post CT-CRC rate as a true quality indicator as a CT abdomen scan is a non-colon dedicated study. The method of calculating PI-CRC rates needs ratification as well as more robust IT systems to capture and analyse the data if it is indeed a measure that is to become part of endoscopic quality assurance. Our numbers are small and methods suitable for retrospective observational population based studies may not transfer to assessing quality indicators at a local level.
Reference:

The influence of 5-aminosalicylic acid on thiopurine metabolism in inflammatory bowel disease patients

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Introduction: Many patients with inflammatory bowel disease (IBD) are on a concomitant therapy with thiopurine drugs and 5-aminosalicylic acid (5-ASA). Thiopurine methyltransferase enzyme activity (TPMT) is involved in thiopurine metabolism. Some literature data suggests that 5-ASA may lower TPMT enzyme activity, thus leading to increased bioavailability of the metabolites, with potential toxic effects and/or potential therapeutic gain.

Methods: The aims of this study were to investigate the potential influence of 5-ASA on TPMT activity in patients treated with azathioprine (AZA) and to assess TPMT activity in patients treated only with AZA. A total of 38 IBD patients were enrolled. 18 of the patients were treated with AZA and 20 of the patients were treated with AZA and 5-ASA, concomitantly. TPMT enzyme activity was assessed using ELISA. Regarding the TPMT enzyme activity patients were divided in 3 groups: low (< 5.0 U/ml Er), intermediate (5.0–13.7 U/ml Er) and high enzyme activity (> 13.8 U/ml Er).

Results: Based on the TPMT enzyme activity, the average value of patients treated with AZA and AZA + 5-ASA was 18.29 ± 7.02 U/ml Er and 16.64 ± 8.24 U/ml Er, respectively (p > 0.05). None of the patient treated only with AZA belonged to the group of low TPMT enzyme activity. 45.45% of the patients treated with AZA and 54.55% of the patients treated with AZA + 5-ASA belonged to the group of intermediate activity. 52% of the patients treated with AZA and 48% of the patients treated with AZA + 5-ASA belonged to the group of high TPMT enzyme activity.

Discussion/Conclusion: Our data suggests the absence of significant interaction between thiopurines and 5-ASA regarding the TPMT enzyme activity. More studies, with larger sample of patients are needed to evaluate this interaction precisely.
Usefulness of a multidisciplinary approach combining both rheumatology and gastroenterology for the assessment and treatment of inflammatory bowel disease patients

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Background: More than one third of inflammatory bowel disease patients (IBD) present extraintestinal manifestations, with articular manifestations being the more common, clearly the more incapacitating and which more alter the quality of life of IBD patients. These patients could benefit from a multidisciplinary approach for quicker diagnosis and for optimizing treatments. The aim of the study was to evaluate the impact of a multidisciplinary approach carried out by both a rheumatologist and a gastroenterologist in the management of these patients. Therapeutic changes after the combined assessment were also evaluated.

Methods: From April 2015 to October 2016, all IBD patients reporting articular pain to the IBD-dedicated gastroenterologist were referred to an experienced rheumatologist. The day of the consultation a multidisciplinary committee with a rheumatologist and a gastroenterologist evaluated and discussed in all patients their possible diagnosis and potential changes in their treatment. Assessment was made according to current guidelines and data recorded in a common database regarding the reasons why patients were remitted from IBD, their rheumatologic diagnosis and all changes implemented in their treatments. Results are shown in percentages.

Results: 82 consecutive IBD patients were remitted from the IBD Unit and analyzed by the committee. Mean age 38 years (ranging from 18 to 73). Most patients were women (73%), 19% were smokers and 23% former smokers. 49% of patients analyzed had Crohn’s disease and 51% ulcerative colitis. The main causes for derivation from IBD were a suspicion of inflammatory arthropathies in 43% and of arthromyalgias in 40%. The more frequent diagnosis after the rheumatology consultation and the committee meeting were inflammatory arthropathies associated with IBD in 41% (51.5% presented axial arthropathies and 48.5% presented peripheral arthropathies) and fibromyalgia in 15%. Regarding treatment changes, after the multidisciplinary committee with a rheumatologist and a gastroenterologist, changes were made in 18 patients (22%). In 7 patients methotrexate was added in patients with biologic treatment (in some of them patients were in monotherapy, but in others the drug was introduced for replacing thiopurines). In 6 patients sulfasalazine was introduced instead of mesalamine. In the other patients either other biologics like ustekinumab were introduced or the doses of anti-TNF were optimized in accordance with rheumatologic schedules.

Conclusions: A multidisciplinary consultation combining inflammatory bowel disease and rheumatology allows both an earlier detection of inflammatory arthropathies associated with IBD and earlier changes in treatment, thereby helping to optimize the hospitality resources. Fibromyalgia is common among IBD patients, though it is important that it is detected it should not be confused with inflammatory arthropathies.
Ulcerative colitis – Factors and ways of evolution

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Introduction: Ulcerative colitis has evolved in ways that are varied and different to associate with exogenous or endogenous factors. We have attempted to assess the impact of environmental factors on the activity episodes of the disease, as well as the relation between the activity of the inflammatory bowel disease, the biological markers and the extraintestinal clinical manifestations.

Methods: We have followed and assessed, over a period of 5 years (October 2011–October 2016), 45 patients who were diagnosed with ulcerative colitis and admitted to our clinic. We have taken into consideration the number of episodes per year, the impact of certain environmental factors (smoking and dietary habits), the occurrence of intestinal infections, and the potential relation between the evolution of the disease and some biomarkers and extraintestinal clinical manifestations.

Results: Out of the 45 patients (aged 21–67), 30 (66.6%) had a mild evolution of the disease (1–2 mild or medium activity episodes per year). 7 (15.5%) patients had 2 or more mild or medium periods of disease activity per year and in the case of 4 patients (8.8%) the disease was inactive. Only 4 (8.8%) patients had a severe evolution of the disease and 3 of them underwent surgery two/three years after the beginning of the follow-up.

All the patients in whom the evolution of the disease was severe had high levels of C-reactive protein (> 45 mg/l), an increased erythrocyte sedimentation rate and detected fecal lactoferrin.

15 patients gave up smoking during the follow-up period; however, this did not prove relevant in the ulterior clinical evolution of the disease. Neither could the patients’ dietary habits be associated with the emergence of activity episodes in any of the cases under study.

In the case of 2 patients, the emergence of arthralgia was correlated with an increase in the clinical manifestations of the inflammatory bowel disease, as well as with the emergence of more frequent activity periods.

Conclusions: The clinical evolution of ulcerative colitis in the group of patients under study was mild. We have not identified any relation between the environmental factors taken into consideration and the emergence of acute episodes of ulcerative colitis. On a clinical level, the only factors that impacted negatively on the disease activity were the modification of the biological markers and the presence of extraintestinal clinical manifestations (arthralgia).
Correlations between fecal calprotectin concentrations and clinical and endoscopic features in pediatric patients with inflammatory bowel disease

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Introduction: The aim of the study was to analyze the correlations between fecal calprotectin concentrations (FCC) and the extent of intestinal lesions, clinical features, and severity of endoscopic changes in pediatric patients with inflammatory bowel disease (IBD).

Methods: The study group consisted of 37 patients with IBD (F = 18, M = 19; mean age 14.4 years; SD ± 2.43 years), including 17 patients with ulcerative colitis (UC), 15 patients with Crohn’s disease (CD), and 5 patients with non-UC, non-CD colitis. Fecal calprotectin concentrations were measured using enzyme-linked immunosorbent assay (ELISA) (PhiCal test, Calpro AS, Oslo, Norway).

Results: In patients with UC median FCC was 1515.0 µg/g and 25–75 percentile range was 456.1–1724.0 µg/g. In patients with CD median FCC was 1442.0 µg/g and 25–75 percentile range was 1183.0–1667.2 µg/g. No statistically significant differences between these groups were found. No correlation between the extent of IBD lesions in the gut and FCC was found. In patients with UC no significant differences were found between patients with left-sided colitis and patients with the involvement of the entire colon. In patients with CD no significant differences were found between patients with L1, L2 and L3 locations according to Paris classification. Significant positive correlations between Mayo endoscopic score and FCC in patients with UC (Spearman test r = 0.47; p = 0.025) and between Simple Endoscopic Score (SES) and FCC in patients with CD (Spearman test r = 0.737; p = 0.002), were found. Patients with new-onset IBD tended to have higher FCCs than patients with flares of IBD (median: 1437 µg/g vs. 634 µg/g; p = 0.07).

Discussion/Conclusion: In pediatric patients with IBD (both UC and CD), FCC is more dependent on the severity of mucosal lesions found on endoscopy, than on their location, extent of intestinal lesions and clinical severity of the disease.
Predictive factors for osteoporosis in patients with inflammatory bowel disease – A study in a tertiary care center in Romania

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Introduction: Osteoporosis in patients with inflammatory bowel disease (IBD) is increasingly recognized as a source of pain and disability with a negative impact on health-related quality of life. The aim of this study was to identify the predictive factors related to the development of osteoporosis in patients with IBD.

Methods: We have conducted a single-center clinical retrospective study. 103 IBD patients with dual-energy X-ray absorptiometry (DEXA) confirmed osteoporosis (hip and/or spine T score < -2.5 SD) and 103 age and gender matched controls were included in this study. Demographic, clinical characteristics and laboratory findings were collected from medical records. The variables analyzed were: sex, current age, age at the disease onset, body mass index (BMI), family history of IBD, disease duration and extent, medical and surgical treatment, endoscopic and histological activity, clinical course, smoking status, vitamin D deficiency and concomitant comorbidities. Logistic regression analysis was performed to identify significant factors associated with the development of osteoporosis.

Results: Of 103 patients, 36 (37.08%) had Crohn’s disease and 67 (69.01%) had ulcerative colitis (male/female: 31/72; mean age: 35.6 years, SD: 13.5). Negative predictors for osteoporosis were: female (p < 0.001), age at the disease onset (young, p = 0.002), postmenopausal status (p = 0.04), smoking habit (p = 0.006), previous corticosteroid therapy for more than three months (p = 0.007), body mass index < 20 kg/m² (p < 0.001), vitamin D deficiency (p = 0.5). In addition, previous surgery, family history of IBD, presence of other extraintestinal manifestations or other comorbidities and disease location and extent had no impact on development of osteoporosis. Long term remission more than 6 years after an initial period of activity was found to be a protective factor for the development of osteoporosis.

Discussion/Conclusion: Our results suggest that middle aged women with young onset of disease activity and low BMI are at higher risk for developing osteoporosis.
Claudin-4 protein expression in ulcerative colitis

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Introduction: Claudins are a group of proteins essential for the formation of epithelial cells connections (tight junction) by maintaining the epithelial cell polarity and tightness determination of connections. They have been identified in many tissues. Claudin-4 play a role as a gate trough the formation of transepithelial barier and can be an anion channel. In colon Claudin-4 is localized in lateral membrane and in cytoplasm of epithelial cells in crypts and in surface enterocytes. Therefore the aim of our study was to evaluate the expression of Claudin-4 in ulcerative colitis tissue.

Materials and Method: The study consisted of 22 patients with ulcerative colitis (UC). Endoscopic materials were taken from archival paraffin-embedded tissue. Sections were stained with H & E and subjected to routine histological evaluation. According to Geboes classification, an analysis of the severity changes (architectural changes, the assessment of crypt destruction, erosions and ulcers, infiltration of inflammatory cells) was performed. The expression of Claudin-4 protein in tissue sections was assessed by immunohistochemical methods. The color reaction was observed in cytoplasmic membrane and cytoplasm of the surface epithelium in villi and of the glandular epithelium of glands. The staining reaction was assessed as % of positive cells with normal cytoplasmic membrane reaction.

Results: We observed a loss of cytoplasmic membrane expression of Claudin-4 in surface epithelium of villi in 40% of cases and in glandular epithelium of glands in 68% of cases of ulcerative colitis. Lower cytoplasmic membrane expression of this protein in surface epithelium in villi and of the glandular epithelium of glands was occurred in patients with more advanced architectural changes (as diffuse or multifocal abnormalities) (p = 0.027 and p = 0.020, respectively). Statistical analysis also showed that lower expression of Claudin-4 in glandular epithelium of glands correlated with lower chronic inflammatory infiltrate (p = 0.004) and with an increase of eosinophils in lamina propria (p = 0.030). It was also observed that a decrease in cytoplasmic reaction of Claudin-4 in surface epithelium in villi correlated with a decrease of this reaction in glandular epithelium of glands.

Conclusion: Loss of cytoplasmic membrane reaction of Claudin-4 in ulcerative colitis is associated with advanced architectural disorders. Influence on this protein expression may have an eosinophils infiltration.
In patients with IBD switching from originator infliximab (Remicade®) to biosimilar infliximab (CT-P13) is safe and effective

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Introduction: Biosimilar infliximab (CT-P13) has been licensed for the treatment of IBD in Europe for over a year with the potential for significant cost savings. However, uptake in the UK has been slow primarily due to concerns over the lack of safety and efficacy data particularly with regard to switching patients from the originator product. We present the preliminary data from a controlled switch programme in a cohort of adult IBD patients.

Methods: A prospective study was undertaken to assess the safety and efficacy of switching patients receiving originator infliximab (Remicade®) to its biosimilar (CT-P13). Patient demographic data was collected along with disease severity scores (HBI and SCCAI), biological markers of disease activity, drug and antibody levels and PROM data (IBD-Control questionnaire) prior to the switch and at each subsequent infusion visit. Evaluation of the efficacy of biosimilar infliximab at the time of the last infusion was compared with the originator at switch over. Means, medians, and ranges were calculated. Adverse events were prospectively collected.

Results: 78 IBD patients were included in the cohort (63 CD and 15 UC). The average age for the CD and UC patients was 43 and 42 years respectively. The average length of therapy on Remicade prior to the switch was 46 months for CD and 25 months for UC. 66/78 (85%) patients were receiving the standard dosage of 5 mg/kg 8 weekly with 12/78 (15%) either on a shortened interval or a 10 mg/kg dose. 42/63 (67%) of CD patients were in remission at switch over compared to 43/60 (72%) at the most recent infusion (4–6 months). The number of patients with mild, moderate and severe disease remained stable throughout the study period (Mild 10/63 (16%) vs 11/60 (18%): Moderate 10/63 (16%) vs 5/60 (8%): Severe 1/63 (2%) vs 1/60 (2%)). 9/15 (60%) of UC patients were in remission at switch over compared with 11/13 (85%) at the most recent infusion. There was no difference in the mean CRP before and after the switch in either CD patients (5.4 vs 5.6 p = 0.32) or UC patients (3.1 vs 3.0 p = 0.73). The mean patient questionnaire score data also remained unchanged before and after the switch (CD 4.4 vs 4.0 p = 0.56, UC 4.9 vs 3.1 p = 0.61). Five patients (3 CD, 2 UC) discontinued infliximab during the study period (3 switched biological class, 1 infusion reaction, 1 deep remission). There were no adverse safety signals with one infusion reaction (1/283 infusions) and the rate of mild adverse events unchanged from before and after the switch.

Conclusion: Switching patients with IBD from originator infliximab to biosimilar infliximab appears both safe and effective. Wider uptake in the UK would result in considerable cost savings to the NHS.
Comparison between procalcitonin and C-reactive protein as indicators of inflammatory bowel disease activity

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Qena University Hospital, Qena, Egypt

Background/Aims: Procalcitonin and C-reactive protein are two acute-phase reactant proteins, although procalcitonin is a more specific marker for bacterial infections. Procalcitonin level might also be helpful to predict the disease activity of inflammatory bowel disease. This study aimed to compare the diagnostic value of serum procalcitonin and C-reactive protein as indicators of disease activity in inflammatory bowel disease. Methods: Patients admitted to the gastro-intestinal disease inpatient clinic with suspected inflammatory bowel disease who had not yet been treated with immunosuppressive treatments were included. Disease activity, white blood cell count, sedimentation rate, serum procalcitonin and C-reactive protein levels were evaluated in 45 newly diagnosed inflammatory bowel disease patients (9 Crohn’s disease and 36 ulcerative colitis). Fifty healthy volunteers were analyzed as a control group. Results: Crohn’s disease patients had higher procalcitonin and C-reactive levels than healthy controls (procalcitonin: 0.143 ± 0.081 vs. 0.065 ± 0.008 ng/ml, P < 0.05, C-reactive protein: 29 ± 7.5 vs. 2.9 ± 0.5 mg/dl, p < 0.001, respectively). Ulcerative colitis patients also had slightly higher procalcitonin levels and significantly higher C-reactive protein levels than controls (procalcitonin: 0.107 ± 0.042 ng/ml; C-reactive protein: 23 ± 5.5 mg/dl). Two Crohn’s disease patients had procalcitonin value above 1 ng/ml. Receiver operating characteristic curve analysis demonstrated that C-reactive protein is the best marker of disease activity in inflammatory bowel disease while procalcitonin has low sensitivity and specificity. Serum procalcitonin levels were highly correlated with serum C-reactive protein but no other disease activity parameters. Conclusions: Although still within normal ranges, procalcitonin levels were slightly elevated in Crohn’s disease but not in ulcerative colitis patients compared to healthy controls. Serum C-reactive protein is a reliable marker for disease activity in inflammatory bowel disease. Procalcitonin has no diagnostic value in determining disease activity.

Keywords: Procalcitonin, C-reactive protein, Crohn’s disease, ulcerative colitis

Introduction: Crohn’s disease (CD) and ulcerative colitis (UC) are both idiopathic inflammatory bowel disease. (IBD) generally complicated with systemic or local infections (1). Although some clinical activity indexes are commonly used in IBD, specific and sensitive laboratory markers that correlate with disease activity and associated complication are still lacking (2).

Procalcitonin (PCT), a prohormone of calcitonin, is an acute-phase protein containing 116 amino acids (6). It has been shown to be a specific marker for bacterial infections, while its level remains low during viral infections (7). Furthermore, it has been related to disease
activity in autoimmune diseases (8, 9). PCT might be a helpful marker to predict the disease activity of IBD. This study aimed to compare the diagnostic value of serum PCT and CRP as indicators of disease activity in IBD.

**Materials and Methods:** Patients admitted in Qena university hospital and Sohag university hospital during 2012 were evaluated. The diagnosis of IBD was confirmed by a typical history, appropriate endoscopic and radiologic imaging studies as well as histopathological evaluations (10). All consecutive patients newly diagnosed with IBD (9 CD and 36 UC) were included in the study. Patients with concomitant diseases including diabetes, hematological disorders, any malignancies, obvious infection or sepsis, chronic liver disorder or any liver diseases were excluded. Previously diagnosed IBD patients were not included in the study since they were either under immunosuppressive treatment or in remission, which both might have unknown effects on serum PCT levels. Patients included in the study were culture-negative for stool and no parasitic infestations were diagnosed. Febrile patients were evaluated further by blood and urine culture and pulmonary X-rays, showing no sign of infection. Fifty aged- and sex-matched healthy volunteers were included as a control group.

Disease activity was assessed by the Crohn’s disease activity index (CDAI) for CD (11). Patients with an activity score < 150 were considered to be in remission, and those with an activity score > 150 were considered to have active disease. UC patients with a Truelove index of “mild” were considered to be in remission, and patients with an index of “moderate” or “severe” had active disease (12).

Blood samples were collected on the day of definitive diagnosis for biochemical analysis. White blood cell count and ESR were evaluated in all patients. Serum levels of PCT were measured by a commercially available Kryptor based PCT kit (Brahms, Germany). Normal PCT level was defined as < 0.5 ng/ml. Serum CRP was determined by nephelometric method. Serum PCT, CRP and ESR were compared between groups.

Written consent was taken from all patients. All analyses were performed using the SPSS 12.0 for Windows. Values are expressed as mean ± SD or median. Statistical analysis was performed by using the Mann-Whitney test and the Kruskal-Wallis one-way analysis of variance on ranks. A receiver operating characteristic (ROC) curve analysis was used to calculate specificity and sensitivity. A p value < 0.05 was considered statistically significant.

**Results:** Nine CD and 36 UC patients (mean age: 47.11 ± 15.08 years; 21 male, 24 female) were included in the study. The age and gender distribution was similar to the control group (46 ± 12.00 years; 24 male, 26 female) (Table 1). We found that serum PCT levels were within normal ranges in most of the IBD patients. CD patients had significantly higher PCT and CRP levels than healthy controls (PCT: 0.143 ± 0.081 vs. 0.065 ± 0.008 ng/ml, p < 0.05; CRP: 29 ± 7.5 vs. 2.9 ± 0.5, p < 0.001) (Table 2). Two CD patients with entero-enteric fistula had PCT level above 1 ng/ml. In CD, the serum CRP was significantly increased in patients with active disease (n: 5) (36.2 ± 20.08 vs. 17.3 ± 6.6), while PCT levels were similar between groups (table 2). Although within normal ranges, UC patients also had slightly higher PCT levels and significantly higher CRP levels than controls (PCT: 0.107 ± 0.042, p: ns; CRP: 23 ± 5.5, p < 0.001). PCT level was not affected by disease localization. The difference between PCT levels was insignificant between active and inactive UC patients (table 2). Serum PCT levels were highly correlated with serum CRP (r: 0.43, p < 0.01) but not with any other disease activity parameters in IBD. PCT was also not affected by age or gender. CRP was the best marker to predict the activity of IBD (AUC: 0.88, 95% CI: 0.80–0.95; p < 0.001).
PCT cut-off value of 0.05 resulted in 67% sensitivity and 42% specificity for diagnosis of active IBD (AUC: 0.57, 95% CI: 0.44–0.70, p: ns) (figure 1).

Table 1: General characteristics of IBD patients and controls

<table>
<thead>
<tr>
<th></th>
<th>CD (n: 9)</th>
<th>UC (n: 36)</th>
<th>Controls (n: 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>4/5</td>
<td>15/21</td>
<td>24/26</td>
</tr>
<tr>
<td>Age (years: mean ± SD)</td>
<td>48 ± 4.6</td>
<td>46.7 ± 4.7</td>
<td>46 ± 12.0</td>
</tr>
</tbody>
</table>

Table 2: Serum PCT and CRP levels in IBD and control groups

<table>
<thead>
<tr>
<th></th>
<th>PCT (ng/ml)</th>
<th>CRP (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD n (9)</td>
<td>0.14 ± 0.08**</td>
<td>29 ± 7.5*</td>
</tr>
<tr>
<td>Active CD n (5)</td>
<td>0.18 ± 0.121</td>
<td>36.2 ± 20.8*</td>
</tr>
<tr>
<td>Inactive CD n (4)</td>
<td>0.09 ± 0.058</td>
<td>17.3 ± 6.6</td>
</tr>
<tr>
<td>UC n (36)</td>
<td>0.10 ± 0.040</td>
<td>23 ± 5.5*</td>
</tr>
<tr>
<td>Active UC n (21)</td>
<td>0.07 ± 0.012</td>
<td>29.7 ± 10.1*</td>
</tr>
<tr>
<td>Inactive UC n (15)</td>
<td>0.13 ± 0.067</td>
<td>17.9 ± 6.7</td>
</tr>
<tr>
<td>Total (IBD) n (45)</td>
<td>0.11 ± 0.038</td>
<td>23.9 ± 4.6*</td>
</tr>
<tr>
<td>Controls n (50)</td>
<td>0.06 ± 0.008</td>
<td>2.9 ± 0.5</td>
</tr>
</tbody>
</table>

*p < 0.001, **p < 0.05 compared to controls. Serum PCT levels were within normal ranges in most of the IBD patients. CD patients had slightly higher PCT levels than UC patients and significantly higher levels than controls. Serum CRP levels were similar in both CD and UC patients and were significantly higher than in controls.

Discussion: Different inflammatory markers are used as disease activity indexes in IBD (13). Classic and widely used markers include ESR, white blood cell count, and CRP (2). PCT is a 116 amino acids protein mainly produced by C cells of the thyroid gland as a prohormone of calcitonin (6). The probable other sites of PCT production during inflammation and infections are the intestine, monocytes and some neuroendocrine cells. Plasma level of PCT increases during bacterial infections and sepsis (14). There are some data showing that serum PCT level is a useful marker in many inflammatory disorders. Ammori et al. (15) showed that plasma concentrations of PCT appear to reflect the derangement in gut barrier function in patients with acute pancreatitis. Similarly, Sarbinowski et al. (16) showed that serum PCT levels increase significantly after colorectal surgery. Those findings suggested that inflammatory and
infectious disease of the bowel might increase serum PCT levels. We found that serum PCT levels were within normal ranges in most of the IBD patients. Only two patients with fistulated CD had high PCT levels, probably due to local inflammation. Serum PCT level, while still remaining within the normal ranges, was higher in CD patients than controls. As with CRP, PCT response seems to dominate in CD disease while it is subtle in UC. Similar to Fagan et al. (17), we found that serum CRP was still the best marker of disease activity in IBD. Herrlinger et al. (18) was the first to show the diagnostic value of PCT in self-limited infectious colitis. They included IBD patients with no sign of infection as a control group (6). They found that PCT was useful to discriminate the infectious colitis from IBD. However, they did not exclude patients in remission or those receiving immunosuppressive treatments. The effects of local and systemic steroids on CRP synthesis is well demonstrated, though their effects on the synthesis of PCT are not known (19). We can speculate that steroids might affect PCT level by changing PCT synthesis or causing occult infections. Since we included only the recently diagnosed patients who were not using steroids, our results solely reflect the disease activity. Our study has some limitations, since we included only a small group of newly diagnosed patients admitted to hospital and they had high disease activity scores. It would be better to follow up newly diagnosed IBD patients with serum PCT and CRP levels to demonstrate the real changes in PCT levels with immunosuppressive treatments, remission or concomitant infections. After well-organized long-term follow-up studies, PCT measurements could be extended to outpatient IBD clinics.

In conclusion, although within normal ranges, PCT levels were slightly elevated in CD patients but not UC patients compared to controls. Serum CRP is a reliable marker for disease activity; however, PCT has no diagnostic value in determining disease activity in IBD. PCT should be evaluated in further studies as a marker to predict the IBD-associated infections and complications.

References:


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

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

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

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

Discussion/Conclusion: Although commonly used in multiple clinical trials, none of the clinical disease severity indices in IBD had all the required measurement properties. Further validation studies are required.
Can the inflammatory bowel disease biologics registry lead to improved quality of care?

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

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

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

Discussion/Conclusion: In summary, having a successful IBD registry will ensure efficient patients monitoring and follow up. It will also support data collection for audit and research purposes. However, any registry should be tailored for individual users’ needs to ensure their engagement and participation. A few difficulties associated with setting a wide IBD registry may include lack of clinicians’ participation or interest, costs related to setting and maintaining the registry, providing enough time to use the registry and data quality assurance.
Correlation of fecal calprotectin levels and pathohistological findings in patients with irritable bowel syndrome (IBS)

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Introduction: IBS is a common disorder of gastrointestinal system. Combination of presenting symptoms, exclusion of other gastrointestinal diseases and certain biomarkers is used for diagnosing of this syndrome. It is known that assessment of fecal calprotectin levels is essential in distinguishing inflammatory bowel disease (IBD) from IBS. However, no correlation between histopathological changes of the colonic mucosa and the levels of fecal calprotectin in IBS has been investigated. The aim of this study was to compare fecal calprotectin levels with pathohistological features of IBS.

Methods: There were 16 patients of the Department of Gastroenterology, University hospital Split, included in this study; all had been diagnosed with IBS according to Rome criteria. Biopsy was performed during colonoscopy, and samples histologically analyzed at the Department of Pathology, Forensic Medicine and Cytology. Stool samples had been collected and levels of fecal calprotectin were assessed in hospital biochemical laboratory by Elisa method (referal level < 30 μg/g.)

Results: Fecal calprotectin levels between 70 and 200 μg/g were present in 43.75% patients. There was no inflammatory infiltrate of colonic mucosa in 25% of patients, and the highest number of patients have medium density of inflammatory infiltrate (43.75%). In 6.25% of patients dense inflammatory infiltrate was found, and 6.25% had active inflammation.

Discussion/Conclusion: in spite of importance of fecal calprotectin levels assessment in early diagnosing of IBD, as well as in distinction between IBD and IBS, this study has found no significant correlation between histopathological changes of the colon mucosa and fecal calprotectin levels in patients with IBS.
**Tacrolimus therapy in moderate-to-subacute ulcerative proctocolitis: A large single centre case series**

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**Introduction:** The treatment of refractory moderate-to-subacute ulcerative proctocolitis (UPC) remains challenging. In 2015, infliximab, an anti-tumour necrosis factor-α monoclonal antibody, was approved for this indication in the United Kingdom. Before this, subtotal colectomy was normally performed. Tacrolimus is a calcineurin inhibitor that reduces T cell proinflammatory activity. Since 2006, two randomised placebo-controlled trials have demonstrated its clinical benefit in refractory ulcerative colitis. We began using it for selected individuals in 2010 and report our consecutive case series.

**Methods:** Prospective data was collected for all patients started on tacrolimus for moderate-to-subacute UPC from January 2010 until August 2016 in our single district hospital. The decision was made by AWH. Conventional therapy had failed and, on initiation of tacrolimus (Prograf®) at 0.05 mg/kg twice-daily, all other immunosuppression was stopped and corticosteroids were rapidly weaned. Blood tests were monitored to identify adverse effects and to target trough drug concentrations of 5–20 ng/ml. Subsequent advice was provided via telephone and regular clinical review.

**Results:** Thirty-six patients commenced tacrolimus during this period. Their ages ranged from 18 to 85 years, mean 37.9 years. Disease varied from proctitis to pancolitis, with the highest number suffering from proctosigmoiditis (n = 14, 39%). Seventeen patients (47%) tolerated the drug and 10 patients (28%) responded clinically. For some, however, adverse effects necessitated drug cessation, despite effectiveness. Therefore, five patients remain in remission on tacrolimus, 14% of the total cohort. The others progressed mainly to surgery (n = 19, 63%) or biological therapy (n = 8, 27%). The main reason for intolerance was renal failure (n = 10, 28%), which was fully reversible on drug cessation.

**Discussion/Conclusion:** Tacrolimus is a useful option for the treatment of moderate-to-subacute UPC. It requires close monitoring but can preclude the need for expensive and potentially dangerous biological treatments, or surgery. Further large controlled studies are needed to assess its usefulness within the landscape of UC treatment.
The prevalence of vitamin B\textsubscript{12} deficiency in patients with Crohn’s disease

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Introduction: Vitamin B\textsubscript{12} deficiency has been recognized as a major cause of anemia in Crohn’s disease (CD). Anemia has a significant impact on the quality of life of this patients and correction is very important. The aim of this study was to determine the frequency of vitamin B\textsubscript{12} deficiency in a group of patients with CD.

Methods: We performed a prospective study, conducted over a period of 24 months (July 2014–July 2016) in a tertiary center from Northeastern Romania. 50 patients with diagnosed CD were included. Serum B\textsubscript{12} levels were measured in all patients enrolled in the study. Deficiency of vitamin B\textsubscript{12} was defined as levels < 200 pg/ml. We excluded the patients with incomplete medical history or with other known cause of vitamin B\textsubscript{12} deficiency.

Results: We studied 50 hospitalized patients with CD (males/females: 33/17). Median age at diagnosis was 29 ± 1 years and median duration of disease was 10 ± 4 years. Regarding the disease location 18% had ileitis, 46% ileocolitis and 36% colitis. The overall prevalence of vitamin B\textsubscript{12} deficiency was 22%, with higher incidence in subjects with ileal and ileocolic CD (p < 0.001). In multiple logistic regression the only independent predictor of vitamin B\textsubscript{12} deficiency was ileal localisation. No association was found with sex, current age, age at disease onset, disease activity (CDAI score) and smoking status.

Discussion/Conclusion: Vitamin B\textsubscript{12} deficiency is common in patients with CD. Our study demonstrates that patients with ileal and ileocolic CD have higher risk of developing vitamin B\textsubscript{12} deficiency than those with colic CD.
Factors associated with voluntary childlessness in women with IBD

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Introduction: Inflammatory Bowel Disease (IBD) affects many women of child bearing age, but requires complex decision making around pregnancy. While infertility is slightly increased voluntary childlessness (VC) rates exceed those of the general population. The reasons for VC remain incompletely understood.

Methods: 4300 female members of Crohn’s and Colitis UK aged 18–45 years were asked by email to complete an online questionnaire. Childlessness status and patient views were assessed as in the previous study by Marri (2007). Disease related pregnancy knowledge was recorded with the validated CCPKnow score.

Results: 1324 women with mean age of 33 years completed the survey (response rate 31%). Of these 76% were in a long-term relationship and 87% were in employment or education. 776 (59%) suffered from Crohn’s disease (CD), 496 (38%) from ulcerative colitis (UC) and 4% from IBD-U. 40% had children [14% pre diagnosis (I); 26% post diagnosis (II)], 36% planned to have children at some stage (III), 7% reported fertility problems (IV) and 17% were classified as voluntarily childless (VC). 673 patients had sought medical advice about pregnancy and IBD.

VC was associated with poorer disease-related knowledge (CCPKnow 5.98 vs 7.47 in (II); p < 0.001), older age (35 y vs 28 y in (II); p < 0.001), unemployment (9.7% VC; p < 0.001), being single (34.5% VC; p < 0.001, not seeking medical advice (p < 0.001), and diagnosis of CD (19.3% vs 13.9% UC; p = 0.015). Women with VC had more hospital admissions (mean 2.85 vs 2.17 (III); p = 0.03) and surgical interventions (mean 1.27 vs 0.65 (III); p < 0.001).

Discussion/Conclusion: VC occurs frequently in women with IBD and appears to be multifactorial. Disease type and severity influence VC. VC is associated with poor pregnancy specific knowledge and many women may stay childless unnecessarily. Patient education programs may help to reduce the rate of VC by correcting misconceptions and alleviating patient concerns.
The peculiarities of ulcerative colitis systemic manifestations

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Clinical features of ulcerative colitis (UC) are combined intestinal and extraintestinal manifestations of the disease. Special importance is the determination of risk factors for systemic UC manifestations that will define the features of the disease and response to treatment.

Aim: to evaluate the nature and incidence of systemic UC manifestations depending on the grade of clinical and endoscopic activity.

Materials and Methods: The study involved 17 patients with UC, including 7 women, 10 men, aged 25-49 years. The clinical data and endoscopic activity index were assessed. We determined the presence and severity of anemia according to blood count.

Research results: According to fibrocolonoscopy the rectum injury was found in 4 (25.3%) patients, rectosigmoid injury was observed in 6 (35.1%), left-sided colitis – in 4 (25.3%), total colitis – in 3 (17.6%) patients. Endoscopic Mayo activity index for UC was I grade in 5 (29.4%) patients, II grade in 10 (62.5%), and III – 2 (12.5%).

For clinical assessment of UC activity by doctor mild activity was detected in 5 (29.4%) patients, moderate – in 8 (47.1%) and severe – in 4 (23.5%) patients. Severe activity was observed in all 3 patients with the total injury of the colon and in 1 patient with left-sided colitis. Mild activity was observed in all 4 patients with the rectum injury and 1 patient with the rectosigmoid injury. UC extraintestinal symptoms were present only in 4 patients with left-sided colitis and 3 patients with the total colon injury that were characterized by 3–8 kg weight loss, fever above 37.5°C, arthritis.

The presence of anemia according to haemogram was diagnosed in 9 patients: 5 (62.5%) patients with moderate activity and 4 (100%) patients with severe activity. Severe anemia was present in 2 patients with the total injury of the colon, moderate – in 3 patients: in 1 patient with the total colon injury and 2 patients with left-sided colitis. Severe and moderate severity anemia was observed on the background of endoscopic Mayo activity of II and III grade.

Thus, the risk of systemic UC manifestations is increasing with the prevalence of the mucous membrane inflammation above the sigmoid colon with simultaneous endoscopic high grade activity.
Pathogenetic mechanisms of liver injury in patients with non-specific inflammatory bowel disease

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Non-specific inflammatory bowel disease (NIBD), which includes ulcerative colitis (UC) and Crohn’s disease (CD), is an important medical and social problem that is associated with a clear tendency to increase in incidence and prevalence of worldwide untimely diagnosis, frequent development of complications of the various organs and systems, primarily defeat and disability among young and middle age people.

Liver injury is diagnosed in 32–33% of patients with NIBD. The most frequently steatosis and steatohepatitis are detected, much less – autoimmune hepatitis (AH), primary biliary cirrhosis, primary sclerosing cholangitis. The key role in the pathogenesis of hepatic steatosis development in patients with NIBD plays the fatty acids absorption disturbance in the intestine, leading to their loss and the development of imbalances in hepatocytes with impaired production of lipoproteins and therefore transport of triglycerides, the secondary lipolysis activation, inhibition of β-oxidation free fatty acids, which leads to accumulation of fat in the liver. The development of hepatocytes steatosis in patients with NIBD may be potentiated by glucocorticoids intake. In these patients there is a rapid transformation of hepatic steatosis to the stage of steatohepatitis due to lipid peroxidation processes activation induced by circulating proinflammatory cytokines.

Thus, the lack of adequate medical correction of NIBD is associated not only with intestinal complications, but also with the appearance and progression of liver disease as metabolic and autoimmune nature. Proof of this provision is a clinical case of a patient K., 54 years old, the ulcerative colitis total colon injury, active phase, the second degree activity was diagnosed in 2006 based on endoscopic and histopathological examination. The patient periodically received therapy with 5-aminosalicylates (mesalazine 2000–3000 mg/day), glucocorticoids (methylprednisolone 4–12 mg/day). The patient’s condition was subcompensated, functional liver disorders were absent. After 6 years on the aggravation NUC and sharp deterioration of patient’s health background the following changes in the biochemical blood analysis were recorded: ALT – 318 U/L, AST – 237 U/L, GGTP – 378 U/L, alkaline phosphatase 1434 U/L, lactate dehydrogenase 434 U/L, total bilirubin 47 umol/L, indirect – 30 mmol/L, cholesterol 8.02 mmol/L. These changes cannot be explained solely by impaired liver metabolism and steatohepatitis development. The screening of autoimmune liver diseases was conducted and antibodies to liver and kidney microsomes LKM1, LKM2 were revealed that allowed to expose the combination of NUC with hypertension type II. Assignment of 5-aminosalicylates (mesalazine at a dose of 3000–4000 mg/day) and corticosteroids (methylprednisolone 32 mg/day) allowed to decrease the activity and degree of UC in 12 weeks and to achieve the level of liver enzymes, which didn’t exceed 2 standards.

Thus, patients with NIBD are at risk for development of associated autoimmune diseases. An important aspect is the possibility of joining them to NIBD in a few years after diagnosis, which will certainly be taken into account in determining the tactics of these patients.
A very rare case of IgG4-related sclerosing cholangitis with associated IgG4-related pancreatitis in a pediatric patient with ulcerative pancolitis: A pathomorphological study

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Background: IgG4-related cholangitis (IgG4-SC) is an immuno-mediated process frequently associated with autoimmune pancreatitis that results in inflammation and fibrosis of the hepatobiliary tract. It is assumed that IgG4-related sclerosing cholangitis (IgG4-SC) and autoimmune pancreatitis (IgG4-related pancreatitis) are IgG4 related disease in the hepato-bilio-pancreatic system. Patients with IgG4-SC are typically men over 60; this pathology is extremely rare in children. The diagnosis of IgG4-SC is based on the combination of clinical, biochemical, radiological and characteristic pathology findings. The diagnosis of IgG4-SC may be difficult to differentiate from primary sclerosing cholangitis (PSC). The aim of this report was retrospective pathomorphological assessment of liver bioplates obtained from a 17-year old boy diagnosed with active inflammatory bowel disease (IBD) associated with elevated serum IG4, bile duct and intrapancreatic strictures on imaging. IBD showed features of active ulcerative pancolitis (UC).

Methods: Blind needle liver biopsy material was fixed in buffered formalin solution; at the same time, the biopsy material was also secured for ultrastructural analysis by fixing the samples with fixative solution of paraformaldehyde and glutaraldehyde in cacodylate buffer. Routine staining with Mayer’s hematoxylin and eosin (H&E) was used; fibrosis was determined by a panel of stainings for fibrous connective tissue (Sirius red, Masson’s trichrome, Masson’s-Goldner, Azan and reticulin stains). Fibrosis stage and inflammation grade were assessed by Batts and Ludwig numerical scoring system. One also used immunohistochemical examinations with monoclonal antibodies (Dako) against CK7 and CK19.

Results: The microscopic picture of the liver bioplates showed dense, diffuse lymphoplasmacellular infiltration and extensive fibrosis in bile duct walls. Fibroinflammatory involvement was observed mainly in the stroma of the bile duct wall. The picture showed concentric periductal fibrosis and massive infiltrations; in places portal and periportal fibrosis with features of bridging fibrosis, mainly the portal-portal type was noted. The diagnosis of active ulcerative pancolitis preceded the diagnosis of IgG4-SC and was based on the characteristic endoscopic appearance of continuous inflammation of the colon and histologic appearance of acute colon inflammation without granulomata.

Conclusion: Further microscopic studies, also extended with ultrastructural assessment, are necessary to clarify the morphogenesis of IgG4-SC associated with active UC.
The level of procalcitonin in patients with inflammatory bowel disease

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Introduction: It is considered that the synthesis of serum procalcitonin are induced by endotoxin bacterial and fungal flora on a background of inflammation. Increasing the concentration of procalcitonin is an important laboratory marker of infection necrotizing bacterial degradation. There is evidence that its level correlates with the activity of inflammation.

Aim: To study the level of serum procalcitonin in patients with inflammatory bowel disease and to evaluate its relationship with inflammation activity.

Methods: 86 patients with IBD (62 with ulcerative colitis (UC) and 24 with Crohn’s disease (CD) were observed, mean age (38.54 ± 3.28) years). Procalcitonin level in blood sera was assessed by enzyme immunoassay. The concentration of procalcitonin in serum below 0.1 ng/ml was considered normal.

Results: The analysis of the data showed that procalcitonin level was elevated in 27 (31.4%) patients to (0.21 ± 0.053) ng/ml. Depending on the nosology this rate was increased in 17 (27.4%) patients with UC to (0.18 ± 0.053) ng/ml, and in 10 (4.6%) patients with CD to (0.24 ± 0.049) ng/ml. 88.2% of patients with UC, and all CD patients with elevated levels of calcitonin had a severe course of the disease. The relationship between the level of procalcitonin, absolute lymphocyte counts (r = 0.36, p = 0.003), C-reactive protein (r = 0.52, p = 0.002) and level of fecal calprotectin (r = 0.41, p = 0.008) was installed. All patients with elevated level of procalcitonin had dysbiosis of 3 degree, 62.9% from them had a bacterial or/and fungal infection.

Discussion/Conclusion: The data obtained confirmed connection between the activity of the inflammatory process and the level of serum procalcitonin in patients with IBD.
Activation of the bile acid receptor, farnesoid X receptor, may reduce ileal inflammatory cytokine expression in an animal model of diet-induced obesity

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Introduction: A high fat/high sugar (HF/HS), western diet has been implicated in the pathogenesis of IBD1,2. The bile acid receptor, farnesoid X receptor (FXR), is central to the crosstalk between the host and its microbiota3. FXR has an immunomodulatory role in the GI tract4,5. We hypothesised that disruption to FXR signalling, induced by a HF/HS associated dysbiosis, is a mechanism linking diet to the development of IBD. The aim of this study was to investigate the effect of HF/HS feeding and FXR agonism on ileal inflammation in a mouse model of obesity.

Methods: C3H/He mice (n = 44) were fed standard chow or HF/HS chow (trans-fats, with fructose corn syrup). At 24 weeks, feed was supplemented with an FXR agonist (5 mg/kg and 1 mg/kg feed) or control. At 42 weeks, body weight and visceral adipose tissue (VAT) weight was recorded and the ileum was dissected. The expression of TNFα, IFNγ and IL-6 was measured by RT-PCR (ΔΔCt method). FXR and its downstream targets, SHP and IBABP, were measured to assay for FXR activity. Unpaired t-tests, regression analysis and Pearson correlation were calculated using Prism.

Results: Mice fed a HF/HS diet were significantly heavier, with more VAT than mice on the control diet (mean weight of 49.9 g versus mean weight of 41.6 g, p < 0.01). There was a positive correlation between the amount of VAT and the ileal expression of TNFα and IFNγ (y = 1.32*X, p = 0.05, y = 1.24*X, p = 0.02 respectively) (figure 1). The FXR agonist significantly increased the expression of IBABP (fold increase of 2.0, p = 0.01). In HF/HS fed mice, supplementation with 1 mg/kg FXR agonist attenuated the increase in ileal expression of all cytokines assayed, although the observed trend failed to reach significance (figure 2).

Discussion/Conclusion: Mice fed a western lifestyle diet express more ileal inflammatory cytokine. There is a trend to suggest that supplementation with an FXR agonist reduces diet-induced ileal cytokine expression. By mediating dietary risk, FXR may be a potential therapeutic target in IBD, particularly to reduce relapses in patients with known disease.

References:
**Figure 1:** Visceral adipose tissue weight is positively correlated with ileal inflammatory cytokine expression

**Figure 2:** Cytokine gene expression in the ileum was reduced with low dose FXR agonist in HF/HS (ALIOS) fed mice
The impact of an open access, non-face to face nurse led inflammatory bowel disease service on service transformation and patient outcomes

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Introduction: Inflammatory Bowel Disease (IBD) follows an unpredictable clinical course, adversely affecting quality of life for many patients. Access to specialist IBD services is necessary in addition to routine review in the outpatient setting, when patients are often stable. Accessing these services is a considerable source of frustration amongst IBD patients. Due to the complex nature of IBD management GPs now play a relatively minor role, however often become the first point of contact. It is widely acknowledged that patients value access to specialist services. IBD specialist nurses are invaluable in providing continuity of care and bridging the gap to multidisciplinary secondary care services. By providing an open access, non-face to face nurse led IBD service; we are able to use our dataset to inform and commission service transformation and improve patient outcomes.

Methods: Data was extracted from a comprehensive dataset of unrestricted non-face to face interactions. This was taken from consecutive patients over a 12-month period for immunosuppression monitoring and a consecutive 3-month sample for all other data.

Results: The total number of consecutive contacts with the service in 12 months in the year 2015 was 4358, rising from 3000 contacts in 2014. Monitoring of immunosuppressive treatment constituted the greatest workload with 1500 contacts in 12 months from 450 patients. In a 3-month period, provision of our service avoided 20 hospital admissions, 34 accident and emergency department attendances and 110 outpatient appointments. We supported patients by issuing 120 prescriptions, organising 24 procedures, 22 multidisciplinary discussions and 12 urgent surgical reviews. This was achieved via 1600 emails, 1400 telephone calls and 1000 contacts from 400 patients using the ‘Patient Knows Best’ software, in a 12-month period.

Conclusion: Our dataset has enabled analysis of the workflow of an open access non-face to face service. The volume of workload demonstrates that patients highly value this form of support. The flexibility of the service has diverted pressure of immunosuppressive monitoring away from busy consultant clinics. This data has helped to inform service transformation by allowing costing on new local tariffs for non-face to face appointments. Contacts are currently tariffed at £25, regardless of time invested, value added or outcome. In the past, this has been a disincentive to seeing IBD follow ups in comparison to the tariffs attracted for new patient workflow. We estimate the tariff for each contract with the non-face to face service to be £60.
Modifying properties of symbiotic microorganisms (Lactobacillus plantarum) for immune response modulation in the complex therapy of IBD

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Introduction: A number of studies have shown an important role of disorders in microbiota balance in IBD development. Lactobacillus plantarum has a certain variety of biological properties in mammalian organisms: abilities to anti-oncogenic action, immune response modulation, antioxidants' generation; finally, it helps to maintain the intestinal permeability. Aim of the study was to increase the metabolic activity of symbiotic microbiota and its sustainability for immune response modulation.

Methods: In this study we used L. plantarum in two conditions: using a common growth media MRS and media, modified with gallic acid, found in tannins. Research was carried out on unidentified human WBCs samples in vitro. During the study we obtained levels of endogenous intoxication, lipid peroxidation, protein and glucose concentrations; mitochondrial membrane potential changes using the standard method with Rhodamine123, and changes in DNA and cell concentrations.

Results: L. plantarum were seeded in concentrations of $5.02 \pm 0.41 \times 10^7$ CFU/ml in MRS and $9.29 \pm 0.03 \times 10^7$ CFU/ml in modified MRS, caused by slower proliferation L. plantarum in modified MRS ($15.70 \pm 5.58 \times 10^7$ CFU/ml after 48 h). We observed DNA dye concentration per cell signal in modified MRS reduction from 196.29 ± 2.00 c.u. at the initiation and 142.90 ± 8.64 c.u. after 48 h of incubation. Also, we observed a minimal WBCs apoptosis value reached by the action of combination lactobacilli culture media (CM) and gallic acid (GA) in concentration 0.7% (1.59 ± 0.27%). Thus, GA affects on lactobacilli metabolism and changes cultural products: this fact was proven by apoptosis level in normal and malignant immune cells.

Discussion/Conclusion: Gallic acid increases the metabolic activity of the L. plantarum. The study of immune cells modulation in various concentrations and combinations of lactobacilli CM found 0.7% (CM + GA) the most effective in all combinations. L. plantarum in modified media has a magnificent antiinflammatory effect and modulates the organism’s immune response. To conclude, modified L. plantarum showed promising results and we recommend using it in IBD treatment.
Azathioprine-induced severe gastritis in patients with inflammatory bowel disease


Introduction: Approximately 20–25% of patients with ulcerative colitis (UC) or Cohn’s disease (CD) cannot tolerate azathioprine (AZA). Upper gastrointestinal track (UGIT) symptoms, such as dyspepsia, epigastric pain, nausea, and vomiting are amongst the commonest symptoms in AZA-intolerant patients but it is unclear whether these are due to drug-induced tissue damage. We aimed to assess UGIT lesions in patients who developed severe epigastric symptoms after initiation of AZA.

Methods: Consecutive patients receiving AZA (starting dose 50 mg/d; target dose 2.5 mg/kg/d) for steroid depended IBD who developed UGIT symptoms underwent gastroduodenoscopy within 24 hours of symptoms onset. Endoscopic findings were graded in a climax of 0–4 (0 = normal endoscopy; 1 = focal or diffused erythema; 2 = diffuse erosive gastritis; 3 = superficial ulcerations; and 4 = severe ulcerations). The presence of esophagitis and/or duodenitis was also recorded. Patients with pre-existing symptoms, esophagitis, peptic ulcer(s), NSAID and/or anti-coagulant use were excluded. Gastric biopsies were taken to assess for gastritis and Helicobacter pylori.

Results: Overall, 9 patients [7 males, 5 CD and 4 UC median age (range) 24 (17–57) years] met the inclusion criteria and comprised 4% of AZA-treated patients (2011–2016). One patient with UC had also autoimmune hepatitis. Three patients were current smokers. Epigastric symptoms developed in the first month of AZA treatment were epigastric pain (9/9), nausea (7/9), vomiting (6/9), hematemesis (1/9); additional symptoms were headache (6/9), and fever with chills (1/9). Concomitant treatments were prednisolone (all patients, 15–30 mg/d), folate (6/9), 5–10 mg/week proton pump inhibitors (PPIs, 5/9) and ranitidine (1/9). Endoscopy revealed severe, diffuse hemorrhagic gastritis and/or ulcerations. Four patients had fresh blood in the lumen and 5 had steaks of blood. A wide variety of ulceration was seen (aphthous, superficial, deep, and excavated). The duodenum appeared normal. Gastric biopsies revealed acute inflammatory infiltrate (9/9 patients) superimposed on a background of chronic inflammation in 3 patients. No histological evidence of H. Pylori, CMV, HSV 1+2, HIV, was documented. Lesions subsided within 7 days of AZA discontinuation irrespective of treatment or no with PPIs. Interestingly, symptoms recurred in 2/9 patients upon treatment with mercaptopurine.

Discussion/Conclusion: AZA-intolerance manifested with severe UGIT symptoms in IBD patients may be associated with severe erosive gastritis and/or gastric ulcerations despite prophylaxis with PPI inhibitors.
The complex action of hyperactivated *Lactobacillus plantarum* in the therapy of IBD

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**Introduction:** Seeing IBD as a result of effects’ combination of genetic and environmental factors it’s worth to pay attention to usage of symbiotic microorganisms’ waste products. One of the great number promising bacteria are *Lactobacillus plantarum* – producer of tannase, which contributes an active antioxidants’ production.

The **aim** of the study was to identify the resulting effect of symbiotic strain *L. plantarum* lifecycle products in IBD therapy.

**Methods:** In this study, we used *L. plantarum* in a common growth media MRS and *L. plantarum* after hyperactivation by the final products of tannins degradation – Gallic Acid (Sigma-Aldrich) in 0.2% concentration. Research was carried out in vitro on unidentified human WBCs and in Namalwa cells. Determination of changes of mitochondrial membrane potential (MMP) using the standard method with Rhodamine 123 («Fluka») and intercalating fluorescent DNA specific dye propidium iodide were performed on flow cytometer PAS (Partec, Germany).

**Results:** Our study had shown the next results: 3.00 ± 1.5% and 6.52 ± 1.31% of apoptotic and necrotic WBCs retrospectively, 0.64 ± 0.20% and 0.65 ± 0.31% of apoptotic and necrotic Namalwa cells retrospectively after treatment by 0.1% of common *L. plantarum*; 4.69 ± 0.80% and 5.88 ± 0.68% of apoptotic and necrotic WBCs retrospectively 1.41 ± 0.76% and 0.70 ± 0.38% of apoptotic and necrotic Namalwa cells retrospectively after treatment by 0.1% of hyperactivated *L. plantarum* compared to control values 2.88 ± 0.92% and 6.28 ± 0.64% apoptotic and necrotic WBCs retrospectively and 0.98 ± 0.85% and 0.94 ± 0.20% of apoptotic and necrotic Namalwa cells retrospectively.

**Discussion/Conclusion:** Thus, effects found in symbiotic bacteria strains *L. plantarum* are extremely important in the complex therapy of IBD, not only as factors reducing overall inflammation, but also in preventing abnormal cell transformation. To summarize, using hyperactivation allows more efficient use of symbiotic microorganisms’ potential without increasing the burden on the patient.
Regulatory role of the transcription factor GATA-3 in ulcerative colitis and inhibition of experimental colitis by GATA-3 specific DNAzyme technique

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Introduction: GATA-3 has been identified as a major transcription factor of Th2-cell differentiation. By the activation of the production of pro-inflammatory cytokines like IL-6 and IL-13 GATA-3 is considered as the pacemaker of Th2-cell mediated ulcerative colitis, one. We analysed the function of GATA-3 in the ulcerative colitis and with DNAzyme oligo-antisense technique in a therapeutic approach.

Methods: First, we analysed samples of UC patients and normal tissue for GATA-3 expression by immunofluorescence staining. Additionally, T-cell conditional GATA-3 deficient mice were used in the oxazolone-mediated colitis model. Inflammation level was documented with miniendoscopic analysis. The colon was isolated for histological sections for immunofluorescent staining as well as LPMC’s and splenic cells were isolated for the analysis of inflammatory cytokines. The GATA-3 DNAzyme is catalytically active and act as DNA antisense molecule with cleaving facility specific for the GATA-3 mRNA. We tested the oligo-antisense DNAzyme (hgd40) as a therapeutic treatment for colitogenic mice.

Results: We found a higher GATA-3 expression in samples of UC patients compared to normal tissue. GATA-3-CD4 KO mice showed compared to the WT mice a protection of inflammation in the colitis model. These results were supported by miniendoscopy analysis and the histological sections. To investigate further the protective effect we analysed the production of inflammatory cytokines by cell supernatant analysis and immunofluorescent staining. We found a reduced production of inflammatory cytokines like IL-6, IL-9 and IL-13 in the GATA-3-CD4 KO mice. Furthermore, we observed a protective effect of the GATA-3 DNAzyme in the oxazolone-induced colitis model compared to mice that get a control DNAzyme.

Discussion/Conclusion: In summary, we have targeted expression and function of the transcription factor GATA-3 by genetic ablation strategies and local administration of a GATA-3 specific DNAzyme in experimental colitis. GATA-3 blockade ameliorated colitis activity and was associated with suppression of local production of multiple pro-inflammatory Th2/Th9 cytokines in experimental colitis. GATA-3 specific DNAzyme emerges as a novel approach for therapy in human UC. This concept can be further improved in therapy regarding the oral route of administration.
The introduction of infliximab therapeutic drug level monitoring is associated with cost savings in a cohort of patients in a large District General Hospital

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Introduction: Infliximab is a chimeric monoclonal antibody directed against TNF-α, with proven efficacy in IBD. Reported loss of response is 15–40% per year. There is evidence to suggest that the development of anti-infliximab antibodies plays a major part in this. Antibodies may develop and not be associated with failure, however in this setting it is thought that infliximab does not have ongoing efficacy for maintaining remission. Whilst therapeutic drug level monitoring could optimise anti-TNF use, it could also be associated with cost savings, but the long-term cost savings are unknown. Not only this, it is likely that it will optimise the use of anti-TNF therapy and guide on future therapies improving long-term patient outcomes. Our aim is to show that the use of therapeutic drug level and antibody monitoring is associated with cost savings by stopping unnecessary anti-TNF, or dose de-escalation of therapy.

Methods: By interrogating our local IBD database and searching patient records we identified all patients receiving anti-TNF therapy, the indication for performing therapeutic drug and antibody levels. We identified patients in which results of the drug levels and antibody status alone influenced the future treatment strategy, then calculated the costs and cost savings made when treatment was altered. Maintenance therapy with biosimilar Remsima costs £3510 per year, calculations were based on the assumption that all patients were receiving Remsima.

Results: 104 patients receiving infliximab between 2013 and 2016 had infliximab levels checked at a total cost of £7280. 26 (25%) patients were identified as having their treatment changed as a direct result of the drug levels and antibody status. 18 (69%) patients in remission with positive antibodies and undetectable trough levels had infliximab withdrawn with an annual cost saving of £63,180. 6 patients in remission had the Remsima dosing interval lengthened to 12 weeks due to high trough levels of infliximab with a cost saving of £7020 per annum. 2 patients had the Remsima interval reduced to 6 weeks based on low drug trough level at an increased cost of £3510 per annum. No patient had a change in biologic drug based on drug levels alone. The total annual cost saving from the introduction of therapeutic drug level and antibody monitoring was £59,410 based on using Remsima. This cost saving would be increased to £140,920 if originator infliximab had been used.

Discussion/Conclusion: The use of therapeutic drug monitoring at a district general hospital leads to significant cost savings in the use of infliximab therapy.
Post-oesophago-gastro-duodenoscopy (OGD) upper gastrointestinal (UGI) cancer rates: The Poole Experience

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**Introduction:** Post-endoscopy cancer rates have been proposed as a quality indicator for endoscopy services but can be misleading. Firstly, there is little robust data as to rates of post-OGD UGI cancers and thus what would represent an acceptable standard. Recent publications have demonstrated that rates of post-colonoscopy colorectal cancer vary very significantly depending on how they are calculated. In addition, the extrapolation of national data to assess quality in local endoscopy units is potentially problematic. Our study aimed to calculate the rate of post-OGD UGI cancers using the number of OGDs performed within 3 years as the denominator but also to assess for other evidence of previous diagnostic opportunity.

**Methods:** A retrospective audit of all patients diagnosed with UGI cancers between 1st October 2015 and 30th September 2016. Patients were identified from the Somerset Cancer Registry using Crystal software. The endoscopy records and electronic patient records at two neighbouring hospitals sharing records were assessed. The results were analysed using the method proposed.

**Results:** 64 patients were documented as having newly diagnosed upper GI cancers during the study period; 5 were excluded as their diagnosis had been made out of area (they had moved or come to our hospital for only part of their treatment pathway); 4 patients were diagnosed without OGD, none of these had undergone OGD over the preceding 3 years. The remaining 55 patients were diagnosed with a pathway that had included OGD. 3 patients had undergone a ‘false negative gastroscopy’ (a procedure performed between 6 and 36 months prior to diagnosis, where as a cancer diagnosed within 6 months of gastroscopy was classed as a detected cancer) making our post-OGD upper GI cancer rate 5.2%. However, one of these patients was diagnosed as having a distal duodenal adenocarcinoma with an enteroscope (listed as an OGD on our endoscopy database) having previous undergone a standard OGD which could not have diagnosed cancer at this site, indicating that analysis simply by procedure may be misleading. An additional patient had undergone a gastroscopy 3 months prior to their eventual diagnosis at which their early gastric cancer had been identified but misdiagnosed as a benign process. A further patient had had an abnormality identified on barium swallow 9 months prior to their diagnosis which had not been followed up. These cases would not have been included as post-investigation cancers using the published methodology.

**Discussion/Conclusion:** Within the limitations of the data collection (NHS hospital records reviewed only) our estimated post-OGD cancer rate of 5.2% compares favourably with the published data and was derived using the current proposed methodology. However, our data illustrates that methods suitable for retrospective observational population based studies may not transfer to assessing quality indicators at a local level. Whilst quality indicators are integral to improving standards, an agreed
methodology needs to be implemented, and data needs to be robust, to allow meaningful assessments of quality both nationally and for individual units where numbers diagnosed may be small.

References:

Systematic review and meta-analysis: Is bowel preparation necessary in small bowel capsule endoscopy?

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Introduction: The optimal bowel preparation for small bowel capsule endoscopy (SBCE) remains controversial. While laxatives may improve image quality and SB mucosal visualization, potentially increasing diagnostic yield (DY), clear liquid diet and pre-procedure fasting has superior patient acceptability. This meta-analysis aimed to investigate the effects of laxatives in SBCE.

Methods: A comprehensive literature search was conducted for studies investigating the use of laxatives in SBCE, published from 2000 to September 2016. The primary outcome was DY for overall SB findings and significant findings; secondary outcomes were SB visualization quality (SBVQ), measured by proportion of patients with adequate visualization, and completion rate (CR). Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated, comparing patients given laxatives to those undergoing SBCE without laxatives. Number needed to treat (NNT) was estimated as the inverse of pooled risk differences.

Results: Forty studies (4380 patients given laxatives for SBCE, 2185 not given laxatives) were included. Laxative use did not improve DY for all SBCE findings (OR 1.11 [95% CI 0.85–1.44]) or for significant SB findings (OR 1.10 [95% CI 0.76–1.60]). However, laxatives improved SBVQ (OR 1.60 [95% CI 1.08–2.06]) with NNT 14. The OR for completed SBCE was 1.30 (95% CI 0.95–1.78).

Patients given polyethylene glycol (PEG) had lower DY compared to those given sodium phosphate (NaP); OR 0.90 (95% CI 0.74–1.10) vs 1.40 (95% CI 0.88–2.22). SBVQ improved more with NaP, OR 2.10 (95% CI 1.03–4.29) and NNT 7, compared to PEG, OR 1.44 (95% CI 1.01–2.06), NNT 53. The OR for CR was 1.34 (95% CI 0.91–1.97) for PEG and 0.83 (95% CI 0.45–1.51) for NaP.

Results did not change significantly in only studies where laxatives were given pre-SBCE: OR for DY 1.12 (95% CI 0.85–1.48), SBVQ 1.83 (95% CI 1.07–3.12), CR 1.26 (95% CI 0.90–1.76). However, due to the scant number of studies giving laxatives after SBCE administration, outcomes from this method warrant further investigation.

Discussion/Conclusion: Laxatives do not significantly improve DY or CR in SBCE, but improve SBVQ. Laxatives may be beneficial in patients with subtle findings, therefore different indications for SBCE may affect the decision to administer laxatives. There are significant differences in methodology/definitions between studies, hence the need for standardized visualization scoring and recording of SBCE findings.
The expression of CEACAM1 protein in inflammatory bowel diseases

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Introduction: Carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) is a cell adhesion molecule, which belongs to the carcinoembryonic antigen family and is expressed on epithelial cells. CEACAM1 is known to be a tumor suppressor, which acts as a regulator of apoptosis. Overexpression of this protein has been observed in many cancers including in colorectal cancer. One of the risk factors of this cancer are inflammatory bowel diseases such as ulcerative colitis and Crohn’s disease. Therefore, the aim of our study was to evaluate CEACAM1 protein in patients with ulcerative colitis and Crohn’s disease.

Material and Methods: The study group included 13 patients with ulcerative colitis and 11 patients with Crohn’s disease. The expression of CEACAM1 in tissue sections was evaluated by immunohistochemical method. The reaction was observed on the surface of intraepithelial cells of villi. The reaction was assessed as a positive (+) or negative (-).

Results: Our study revealed lack of positive expression of CEACAM 1 in the group of patients with Crohn’s disease. Positive reaction of CEACAM1 was found in 69.2% patients with ulcerative colitis and was absent in 30.8% patients. The expression of CECAM1 was present in the group of patients without dysplasia and low grade of dysplasia whereas lack of positive expression of this protein was observed in patients with high grade dysplasia (p > 0.05).

Conclusions: Positive expression of CEACAM 1 in ulcerative colitis but not in Crohn’s disease may indicate that this disease has increased risk of cancer development. However, correlation with grade of dysplasia require more advanced research on larger group of patients.
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Abstracts
Poster Abstracts