Evolving Therapies in Clinical Practice in IBD

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Abstracts/Poster Abstracts

Symposium 202

FALK FOUNDATION e.V.
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Symposium 202

Evolving Therapies in Clinical Practice in IBD

Prague, Czech Republic
April 29 – 30, 2016

Scientific Organization:
M. Bortlik, Prague (Czech Republic)
W. Kruis, Cologne (Germany)
M. Lukas, Prague (Czech Republic)
E.F. Stange, Stuttgart (Germany)
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Session I

Novel therapeutic approaches in medical therapy
Anticytokine strategy beyond the anti-TNF-alpha therapy – Pathophysiology and clinical implication

G. Rogler
Klinik für Gastroenterologie und Hepatologie, Universitätsspital Zürich, Zürich, Switzerland

It is well established that antibodies directed against tumor necrosis factors (TNF) are effective in both inducing and maintaining remission in Crohn’s disease and ulcerative colitis. The fact that only about 50% of patients respond well and that a significant number of patients experiences a secondary loss of response to anti-TNF therapy has stimulated research for other cytokine directed antibodies beneficial for IBD patients. A cytokine target with promising results in clinical trials is IL-12/IL-23. Both, IL-12 and IL-23 consist of a dimer of the common p40 subunit and of a specific subunit: p35 for IL-12 and p19 for IL-23. Both cytokines are produced by dendritic cells and crucial for induction and maintenance of Th1 and Th17 responses. Several drugs inhibiting the IL-12/IL-23 axis are currently under investigation, namely ustekinumab, briakinumab, apilimod mesylate, AMG139 and SCH-900222. Ustekinumab has been shown to be effective in Crohn’s disease. It is a fully human IgG1 monoclonal antibody targeting the p40 subunit of IL-12/IL-23 and has been approved for the treatment of moderate to severe plaque psoriasis already. Anti-IL-23 targeted therapy may become an alternative in patients not responding to anti-TNF therapy.

Interleukin-6 (IL-6) also plays an important pivotal role in the pathogenesis of IBD. IL-6 is produced by many different cell types and secretion is induced during acute phase response. IL-6 serum levels were shown to correlate with disease activity of CD and UC. Several antibodies targeted at IL-6 have been investigated in IBD patients, namely sirukumab, olokizumab (CDP6038), C326, PF04236921 and BMS-945429, as well as tocilizumab targeting the IL-6 receptor. Preliminary data indicate that there is potential efficacy for anti-IL-6 strategy in IBD.

IL-13 is a cytokine mainly produced by T-cells and natural killer cells (NK-cells). It may play a critical role for the development of UC. Anrakinumab, a humanized monoclonal antibody targeting IL-13, as well as tralokinumab (CAT-354), a recombinant human monoclonal antibody directed against IL-13, have been tested in phase II studies in patients with moderate to severe UC. Both antibodies were not successful in demonstrating a significant benefit versus placebo.

May other anti-cytokine antibodies have failed in clinical trials in IBD patients. Anti-IL-1β and anti-IL-18 strategies have not been successful. Basiliximab directed against IL-2R did not increase efficacy of corticosteroids in patients with steroid-refractory UC in a recent trial after providing promising results in early studies. Daclizumab, a further anti-IL-2R antibody did not result in increased rates of clinical remission at week 8 compared to placebo in a phase 2 trials in patients with moderate to severe UC. Other targets are under current development.
References


Leukocytes anti-trafficking strategy: Current status and future directions

Bruce E. Sands, M.D.
Dr. Burrill B. Crohn Professor of Medicine, Chief of the Dr. Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai and Mount Sinai Hospital Mount Sinai Health System, New York, NY, USA

In inflammatory bowel diseases, a pivotal step in the initiation and perpetuation of mucosal inflammation entails the recruitment of inflammatory leukocytes to the gut. Understanding the carefully coordinated series of molecular events that culminate in the recruitment of leukocytes to the gut has led to novel interventions with new capabilities in treating both Crohn's disease and ulcerative colitis. Natalizumab, an anti-α4 integrin antibody, was the first agent to demonstrate the efficacy of this approach for induction and maintenance of response and remission in Crohn's disease. Widespread adoption was mitigated by the previously unknown risk of progressive multifocal leukoencephalopathy (PML) with this approach. Current approaches employ more selective inhibition of adhesion molecules targeting the gut to avoid broad suppression of surveillance for JC virus, the causal pathogen of PML. Subsequently, vedolizumab, a humanized anti-α4β7 integrin antibody, has demonstrated efficacy in patients with IBD and has an excellent safety profile. To date, there have been no cases of PML in patients treated with vedolizumab, suggesting that this more selective agent does not have the same risk for PML as natalizumab. Other agents target β7 integrin (etrolizumab) and mucosal addressin cellular adhesion molecule-1 (MAdCAM), the endothelial ligand of α4β7 integrin. Efforts to inhibit the chemokine receptor CCR9 using the agent CCX282-B in Crohn's disease were not successful. An orally administered anti-α4 integrin compound showed some promise in a phase 2 trial, but raises concern for PML. Finally, the S1P1 agonist ozanimod showed promise in early trials in ulcerative colitis. In summary, anti-trafficking agents have the potential to provide safe and effective therapy for IBD, and are a burgeoning class of novel agents.
Improvement of “leaky” intestinal barrier

Eduard F. Stange
Abteilung für Gastroenterologie, Hepatologie und Endokrinologie, Robert-Bosch-Krankenhaus, Stuttgart, Germany

The intestinal barrier essentially consists of the normally continuous epithelial layer, the cells stuck together by tight junctions and, as a complex secretory product, the mucus layer. The function of this double layer is to remain permeable to small absorptive molecules like sugars and amino acids while restraining access of bacteria and possibly bacterial compounds such as LPS. The mucus layer actually consists of two strata: a 100 µm layer immediately above and firmly attached to the epithelial cells that is virtually sterile and on top towards the lumen (and its massive bacterial contamination) another more liquid and therefore contaminated layer of around 700 µm. The minimal bacterial counts directly above the epithelium are not just a consequence of mucus’ physical structure but due to the epithelial secretion of positively charged antibacterial peptides (mostly defensins) binding to various negatively charged mucins (mostly MUC4). The defensins in the small intestine are mostly produced and secreted by the Paneth cells residing at the bottom of the crypts, in the colon by normal absorptive epithelial and the mucins by goblet cells.

In Crohn’s disease this mucus layer appears to be defective with respect to low defensin levels and lack of antibacterial activity. These deficiencies actually explain the Montreal phenotypes and the stable localization of disease in the terminal ileum with low α-defensins from Paneth cells and/or low β-defensins in colonic disease, respectively. In contrast, in ulcerative colitis the defensin production is normal or even induced but the mucus layer is thinner and patchy, more liquid and also chemically altered so that antibacterial peptides are not retained and lost into the luminal bacterial bulk. Therefore, both barrier problems allow slow bacterial attachment and invasion, ultimately triggering the massive response of adaptive immunity and tissue destruction. Therefore, leakiness should refer to the antibacterial barrier and not the general barrier against small molecules such as mannitol or lactulose which are not antigenic.

What to do? The most promising approach in ulcerative colitis seems to use the natural compound lecithin as a stabilizer of mucus structure to enhance the barrier. A phase II study has been positive and the results of the ongoing phase III study are eagerly awaited. It is quite possible that the protective effect of smoking in UC is related to mucus production also in the colon but this is not an option. Another alternative would be to shift cell differentiation in the colon towards goblet cells, the relevant differentiation factors are known.

In Crohn’s disease direct oral application of defensins might be effective if release and binding to the mucus is achieved. In the experimental colitis model this works quite well. Since recent data (Courth et al. PNAS 2005) suggest that the genetic defects in the Paneth cell may be bypassed by monocyte derived Wnt factors their application may be promising.

In conclusion, in a situation where enthusiasm about so called biologics is declining due to loss of response over time, searching for the primary defects in IBD and treating them may well be worthwhile, although it is unlikely to provide rapid relieve.
Session II

Unmet therapeutic needs:
Focus on intestinal fibrosis
Pathogenesis of intestinal fibrosis in IBD and perspectives for therapeutic implication

Florian Rieder
Department of Gastroenterology, Hepatology and Nutrition, Digestive Disease Institute, Cleveland Clinic Foundation, Cleveland, OH, USA

The inflammatory bowel disease (IBD) course is highly heterogenous. Intestinal fibrosis with stricture formation is a common feature of IBD and leads to a significantly impaired quality of life in affected patients, intestinal obstruction as well as need for surgical intervention. This constitutes a major treatment challenge. Fibrosis results from the response of gut tissue to the insult inflicted by chronic inflammation. Similarly to what occurs in other organs, the underlying fibrogenic mechanisms are complex and dynamic, involving multiple cell types, interrelated cellular events, and a large number of soluble factors. Owing to a breakdown of the epithelial barrier in IBD, luminal bacterial products leak into the interstitium and induce an innate immune response mediated by activation of both immune and non-immune cells. Damage-associated molecular patterns, intracellular components released by necrotic cells, can also induce mesenchymal cell activation and contribute to stricture formation. Finally, fat wrapping around the bowel wall, the so-called 'creeping fat' typical of Crohn’s disease, can drive fibrogenesis through the release of free fatty acids that induce intestinal muscle cell proliferation. Epigenetic signatures associated with fibrosis have been described, and environmental factors as well as chronic inflammation will certainly impact the quality and quantity of intestinal fibrosis. Finally, the composition of the intestinal extracellular matrix is dramatically altered in chronic gut inflammation and actively promotes fibrosis through its mechanical properties and interaction with infiltrating leukocytes.

The conventional view that intestinal fibrosis is an inevitable and irreversible process in patients with IBD is gradually changing in light of an improved understanding of the cellular and molecular mechanisms that underline the pathogenesis of fibrosis. In addition, clinical observations in patients that undergo strictureplasty have shown that stricture formation is reversible. If so, identification of the unique mechanisms of intestinal fibrogenesis should create a practical framework to target and blockade specific fibrogenic pathways, estimate the risk of fibrotic complications, permit the detection of early fibrotic changes and, eventually, allow the development of treatments customized to each patient’s type and degree of intestinal fibrosis.
Do we have a reliable marker of intestinal fibrosis in clinical practice? The role of biochemical markers and imaging methods

Peter D.R. Higgins
Director, IBD Program, Department of Gastroenterology, University of Michigan, Ann Arbor, MI, USA

Intestinal fibrosis in Crohn’s disease (CD) is induced by recurring cycles of inflammation and mucosal healing, ultimately resulting in irreversible organ damage, intestinal blockage, and surgical removal of damaged segments of intestine in more than 60% of patients. Current practice identifies strictures and obstruction at a late stage, when symptoms and signs (nausea, vomiting) occur, or when a stricture with upstream dilation is found at endoscopy or during cross-sectional imaging. Many investigators have sought methods for earlier detection of the progression of intestinal fibrosis.

Using a glycoproteomics approach, our group studied serum from 16 patients at the University of Michigan with Crohn’s disease who had fibrotic strictures removed at surgery. Serum was obtained prior to surgery, and post-operatively. High abundance proteins were removed and glycoproteins enriched with lectin binding. LC-MS-MS was used to identify biomarkers present pre-operatively that were significantly reduced post-operatively, corresponding to the burden of fibrotic bowel damage. These biomarkers were then validated in 20 paired samples of patients in the SWISSIBD cohort, selected for significant fibrosis vs. the absence of fibrosis.

We have also explored the role of shear wave ultrasound and magnetization transfer MRI in evaluating fibrotic vs. inflamed bowel. We have demonstrated that shear wave ultrasound can differentiate fibrotic vs. inflamed bowel in rodent models of Crohn’s disease, and that MT-MRI can quantitatively and reproducibly measure the collagen content of collagen phantoms and fibrotic bowel. Validation of these approaches in CD patients is ongoing, and could provide endpoints for future studies of anti-fibrotic medical therapies.
Surgical approach: Resection, strictureplasty and others

Yves Panis
Department of Colorectal Surgery, Beaujon Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Université Denis Diderot Paris VII, Clichy, France

In patients with Crohn's disease (CD), the main consequence of the progressive development of intestinal fibrosis is the occurrence of a localized stenosis. Because this intestinal stenosis is frequently symptomatic (i.e. abdominal pain, chronic intestinal obstruction, etc...), treatment is often mandatory. To date, besides medical treatment, which is considered to be poorly effective against non inflammatory fibrotic intestinal stenosis due to CD, there are two main options for the treatment of such intestinal stenosis: surgical approach, and endoscopic approach. Concerning endoscopic treatment, there are two solutions: balloon dilatation, and stenting. However, there are only very few reports with small numbers of patients reporting results of such approach for intestinal stenosis. Furthermore, only selected patients with short stenosis can be possibly treated by endoscopy. Finally, long term results of endoscopic treatment remains unknown, patient being exposed to early recurrence of the stenosis. For this reason, intestinal resection remains today the best option for localized symptomatic intestinal stenosis due to CD and refractory to medical therapy. By laparoscopic approach, short intestinal resection, frequently by ileocecal resection followed by ileocolonic anastomosis gives good short term results with almost no mortality and low rate of morbidity. Furthermore, surgery has no functional consequences in the majority of patients if resection do not exceed 50 cm, and it improves quality of life (in comparison with the preoperative status). However, because CD recurrence can be observed in the remaining small bowel and possibly indicate a second operation in up to 30% of the cases during the next 10 years, some surgeons have proposed, in order to reduce the risk of short bowel syndrome a more conservative surgical approach for intestinal stenosis: a stricturoplasty. The concept is to treat stenosis without intestinal resection, by opening the stenosis. Many reports have been published to date on different kind of stricturoplasty, with similar postoperative morbidity and same long term recurrence rate than after intestinal resection. Because no randomized study exists, it is difficult to know if one option is better than the other, but most of the surgeons propose intestinal resection in case of short stenosis, and primary surgery, and stricturoplasty only in case of recurrent cases and/or multiple stenosis.
Session III

Interactive Session: How to improve our care in IBD?
Case report: Perianal Crohn’s disease requiring complex management

Peter L. Lakatos, Zsuzsanna Vegh
1st Department of Medicine, Semmelweis University, Budapest, Hungary

Optimal management of perianal fistulizing patients is challenging and requires a close cooperation between gastroenterologists, imagine specialists and surgeons. Here we report the case of a 30-year-old nurse with complicated Crohn’s disease. The patient presented with perianal abscess and fistulas and a terminal ileum (TI) involvement in December 2005 at the age of 20 years. Abscess drainage was required metronidazole, mesalazine and azathioprine was started together with seton placement in March and June 2006. Infliximab induction was initiated due to draining fistulas in another institute. The patient presented in our unit in August 2008 with moderately active perianal disease. Abdominal CT and ileocolonoscopy revealed mild-TI involvement with only some aphthous ulcers together with active proctosigmoid inflammation. After initial seton placement and discussion with the patient adalimumab therapy was initiated in combination with metronidazole and ciprofloxacin for the first 8 weeks. Colonoscopy and pelvic MRI in October 2009 proved almost complete remission with mild rectal inflammation only. Adalimumab was temporarily stopped due to severe perioral HSV infection in December 2010, while pelvic MRI remained showed no active fistulas. Aciclovir was started. Adalimumab was recommenced in March 2011, pelvic MRI in February 2012 and January 2013 showed no active fistulas. Adalimumab has to be suspended again due to herpes infection until June 2013, again seton placement due to draining fistulas. Psoriatic lesions occurred in September 2013 in the armpits and pubic region. Dermatological consult and biopsy failed to confirm anti-TNF induced psoriasis. Local therapy was started. Colonoscopy showed mild inflammation in TI and throughout the colon with deep ulcers in the rectum. Adalimumab was intensified and metronidazole/ciprofloxacin was added. Abscess formation was diagnosed in May 2014 and MRI proved abscess with complex active fistulizing disease. Perianal surgery and seton placement was performed with abscess drainage. In August 2014 sigmoidostomy was performed due to recurrent abscesses. Adalimumab was re-started in October 2014 due to active perianal disease. Patient was re-admitted with abdominal abscess in November 2014 and after abscess drainage ileostomy was performed. Adalimumab level was measured and proved low trough/high antidrug antibody profile in March 2015. Fistula drainage was under control. Adalimumab was stopped and patients was treated with azathioprine and recurrent courses metronidazole. June 2015 MRI showed clear improvement with only mild rectal inflammation with 2 fistula tracts. February 2016 patient had only mild-perianal symptoms, well-functioning stoma at last follow-up. We would like to highlight the importance of close cooperation among different stakeholders and the need for tight control in patients with complex perianal Crohn’s disease.
What should be done in perianal CD? Surgeon’s statement

Z. Serclova
Surgical Department, NH Hospital, Prague, Czech Republic

**Introduction**: Perianal involvement shows up in 17–43% of patients with Crohn’s disease (CD) and 30% of patients have perianal fistulas (1). Fistulizing CD significantly decreases quality of life of these patients suffering from depression in 73% and in 13% from suicide tendency (2). Conservative treatment (biological therapy) could decrease symptoms (3), but surgical treatment consisting of drainages is essential. Complete eradication of fistulas by surgical methods in appropriate and good prepared cases is possible in up to 80–90% of patients (4). Following medical treatment is important to prevent recurrence rate increasing in long-term follow-up (5). Stoma creation and eventually proctectomy are solutions in cases with unfavorable progression or management of the disease. Particular steps of combined treatment are described in following case report.

**Methods**: 39-year-old woman with the history of fistulizing Crohn’s disease since 1999 (22-year-old) was treated by combination surgical and medical treatment. Primary manifestation was ileocecal disease, 2006 started perianal CD. Ano-vaginal abscess was drained. Due to failure of medical treatment (azathioprine, steroids, topical steroids and antibiotics) ileocecal resection with anastomosis was performed. Ano-vaginal fistula was successfully eradicated by advancement flap method next year. She continued with azathioprine therapy. Nine years later ano-vaginal abscess developed and was drained. No recurrence of luminal disease was found, therefore the second eradication of fistula by advancement flap was done. Fistula didn’t heal and fistula had to be drained again. Biological therapy was added to the medical therapy and fistula was eradicated by the 3rd advancement flap and patient continues with combination of azathioprine and infliximab.

**Results**: Long term remission (9 years) was achieved by combination conservative and surgical treatment in patient suffering from luminal and perianal CD.

**Conclusion**: Understanding of capability of combined conservative and surgical management of perianal disease could lead to successful treatment of patient with perianal CD (6, 7).

**References**:


An IBD (inflammatory bowel disease) patient has two incidence peaks at a young age of 20–30 years and the second half of his life at the age of 50–60 years. At this time, patients are cases of acute severe ulcerative colitis.

Patient P is a 57-year-old, male high medical education student who presents to the gastroenterologist with 8 days of bloody diarrhea and lower abdominal pain. He describes up to 3–5 urgent stool per day and 3–4 stool per night weight loss with dehydration. He is a lifelong nonsmoker and has no history of medical illness or surgeries, denies recent antibiotic or nonsteroidal anti-inflammatory drug use, and has had no known sick contacts or exposure to tainted foods. However, he has severe emotional stress.

The patient was hospitalized in gastroenterological. Stool culture is negative for infection, but fecal leukocytes are present. Flexible colonoscopy and biopsies was performed, which show friable and erythematous mucosa with erosions and ulcers in a diffuse circumferential distribution from the anal verge to the cecum. There are no pseudomembranes. Histological evaluation reveals acute inflammation without architectural distortion consistent with either acute infectious colitis or new inflammatory bowel disease, favoring ulcerative colitis.

At this point in work-up, treatment for presumed ulcerative colitis is initiated with mesalazine 8 g daily: 4 g orally, 4 g per rectum and prednisone at 40 mg orally daily. After 48 hours stool frequency were 12 times per day (2 per night) with urgency, blood in stool occasionally frank. IV steroids were prescribed – 16 mg of dexamethasone. Patient was consulted by coloproctologist. After 48 stool were 8 per day, 1–2 per night, trace blood in stool, general well being increased, but after 14 days condition did not significantly change. Infliximab 5 mg/kg were administered and after first infusion stool were 4 times per day without urgency and night diarrhea. Azathioprine 100 mg per day was prescribed after steroid (prednisone) withdrawal. But after third infusion of infliximab patient felt pain along the intercostal nerves, skin redness, itching. Varicella zoster virus infection was diagnosed. Famciclovir 750 mg per day was prescribed, azathioprine was stopped, infusions of infliximab were continuing and after 12 month patient obtained monotherapy of infliximab 1 time per 8 weeks and has stable remission.
Case report: Immunosuppressive therapy in patients with IBD and malignancy

G. Novacek
Klinische Abteilung für Gastroenterologie und Hepatologie, Universitätsklinik für Innere Medizin III, Medizinische Universität Wien, Vienna, Austria

This is the report of a man (born 1962) with Crohn’s disease of the colon who developed two cancers after the diagnosis of inflammatory bowel disease. Crohn’s disease was diagnosed in 2000. Due to a corticosteroid-dependent course infliximab was started in May 2007 but was switched to adalimumab in October 2008 because of loss of response to infliximab. After good clinical response a concomitant treatment with azathioprine was started in December 2013 due to moderate clinical activity. Under double immunosuppression the patient was in good clinical condition despite high values of fecal calprotectin. In September 2014 a superficial spreading melanoma was removed and in October 2014 the patient underwent a prostatectomy because of prostate cancer. The aim was to reduce the risk of recurrence of the malignancies due to exposure to double immunosuppression. Adalimumab was switched to vedolizumab and the dosage of azathioprine was reduced and should be withdrawn in the following months. In November 2015 the patient visited our out-patient department because of multiple focal liver lesions. The following diagnostic procedures and treatment decisions will be presented.
What should be done in IBD patients with prior malignancy?

Jacques Cosnes
Service de Gastroentérologie et Nutrition, Hôpital Saint Antoine, Paris, France

Treatment of IBD in patients with prior malignancy is challenging. On one hand, oncologists usually recommend avoiding immunosuppression, taking into account the risk of relapse or the worsening of the cancer while on immunosuppressive drugs, yet at the present time more than 50% of IBD patients are receiving antimetabolites or anti-TNF agents. On the other hand under-treatment of IBD may increase the risk of recurrent flares, poor quality of life, progressive digestive damage, and disability. The period, severity, and subtype of prior cancer and the IBD activity should be balanced before choosing the best therapeutic strategy. For example a recent multiple myeloma requires prolonged avoidance of immunosuppressive drugs whereas a non-melanoma skin cancer may not lead to modify an efficacious therapy, provided close skin surveillance is available. In contrast with the observations in the post-transplant population, retrospective observational studies of IBD patients with prior malignancy have not demonstrated that immunosuppressive drugs increased significantly the risk of new or recurrent cancer. However these studies are highly biased and underpowered and do not give a green light to the use of these drugs. In practice, in most cases of prior cancer, a step-up approach regarding IBD treatment should be preferred. Budesonide, low dose steroids, and limited intestinal resection should be considered on a case-by-case basis to increase the interval between completion of cancer treatment and immunosuppressive treatment for IBD. A 2- to 5-year pause for cancers with intermediate to high risk of recurrence needs to be respected. Another latent cancer should also be ruled out before starting immunosuppressants. Thiopurines should be avoided in case of prior EBV-related lymphoma, HPV-related carcinomas, and cancer of the urinary tract. Methotrexate and anti-TNF agents seem to be safe except for the risk of recurrent melanoma for the latter. Data regarding vedolizumab are too preliminary and it should be used with caution in case of prior cancer of the digestive tract.
Session IV

How to best use the drugs?
Impact of perioperative medical therapy on surgical outcome

Axel Dignass, MD PhD
Department of Medicine I, Agaplesion Markus Hospital, Goethe University, Frankfurt/Main, Germany

A majority of patients with Crohn’s disease will require surgical intervention during the course of their disease. Surgical resection is not curative and disease recurrence is relatively common. The decision to pursue surgical treatment for Crohn’s disease is highly personalized. In addition, the pre-operative and perioperative therapies and also the use of prophylactic medical therapy following surgery vary substantially and are also highly personalized. With more medications available, patients are frequently treated with several consecutive or simultaneous immnosuppressive regimens or go to surgery in a reduced nutritional status. In the past, medical maintenance therapy following surgical intervention has not been routinely recommended and patients were frequently treated on demand, with initiation of treatment at the time of symptomatic or endoscopic recurrence. Emerging evidence suggests that early postoperative initiation of medical therapy, especially in high-risk patients may reduce the need for additional operations.

Within the first year of surgery, 70–90% of CD patients develop endoscopic recurrence, increasing to 80–100% within three years. Severity of early endoscopic lesions can predict the symptomatic course of disease after surgery. Therefore, postoperative surveillance has been shown to be helpful to identify patients, who will benefit from early and intensive postoperative medical management. For example, early use of anti-TNFs after surgery has recently been demonstrated to significantly decrease the risk of endoscopic recurrence in patients with multiple previous surgeries, stricturing, or penetrating disease.

Especially in patients with complicated disease courses structured management of IBD patients within a coordinated multidisciplinary IBD team may improve the outcome with improved perioperative and postoperative results. Especially in the postoperative setting, patients should be referred back to their treating gastroenterologists to initiate early follow-up colonoscopy and/ or initiation of postoperative medical therapy to avoid a gap between endoscopic recurrence and clinical symptoms.

Also in patients with ulcerative colitis perioperative treatment within a multidisciplinary team is warranted, e.g. to reduce peri- and postoperative infectious or surgical complications caused by inappropriate medical treatment or nutritional status.

If possible pre-operative treatment with steroids should be short-term or tapered below 20 mg prednisolone-equivalent in patients with long-term steroid treatment. The dosing intervals and dosage of anti-TNFs, anti-adhesion molecules or other immnosuppressants and also co-medication with several immnosuppressants needs to be re-considered and discontinuation of certain therapies or prophylactic measures may be warranted.
Promise and danger of combination therapy

Wolfgang Kruis
Ev. Krankenhaus Kalk, University of Cologne, Cologne, Germany

Efficacy of treatment of IBD is limited. To redress this problem in principle two ways are possible, either to create new treatment modalities or to optimize current therapies. Optimisation may be accomplished by using combinations of established therapeutic strategies. Combination therapy comprises various strategies.

As concerns topically acting compounds such as 5-ASA it is common use to combine oral and rectal preparations. In ulcerative colitis this combination is clearly superior over exclusive oral or rectal therapy for induction as well as for maintenance treatment. Serious disadvantages or adverse events are not known of this combination therapy.

Another commonly used combination is the prescription of anti TNFα antibody modalities together with immunosuppressants (thiopurines, methotrexate). Several aspects favor those combinations. To encounter the immunogenicity of TNF antibodies with subsequent antibody formation and secondary loss of therapeutic effectivity is a major aim of the addition of immunosuppressants. Immunogenicity may also be a reason for paradoxe effects of TNF antibodies such as skin and skeletal reactions. Here, beneficial effects of the combination therapy have been reported. There is also a discussion on directly additive therapeutic effects, which has been demonstrated in some clinical trial. The combination of infliximab with azathioprine is most likely the most effective current treatment of Crohn’s disease. On the other side, combination therapy, both compounds affecting the immune system, has of course risks. For sure, the frequency of serious infectious complications is increasing. Furthermore, the number of patients experiencing malignancies such as hepato-splenic lymphoma or melanoma is strongly suspected to rise.

Enteral nutrition has some therapeutic effects in Crohn’s disease. There are some early attempts to combine anti TNF antibody therapy with elemental diets. Promising observations are existing. Enteral nutrition has also been used in patients with malnutrition and planned operations.

Treatment of the microbiota is a new strategy in IBD. Here, not only probiotics can be given but also combinations of pre- and probiotics. So called synbiotics. Early results from studies with synbiotics in inducing remission of ulcerative colitis are promising. As yet, specific adverse effects are not known.

In summary, combinations of current treatments for IBD are widely established. Various strategies have been studied and significant improvements of therapeutic effects have been demonstrated. Unfortunately, some of those proven combinations increase therapeutic risks, e.g. the frequency of serious infections and most likely also of some malignancies. Therefore, increased cautiousness is urgently needed when applying combination therapies.
Relevance of drug levels and antibodies in clinical practice

Prof. Ann Gils
Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium

Anti-tumor necrosis factor-alpha and anti-integrin monoclonal antibodies show great benefits for inducing and maintaining remission, healing the mucosa and restoring the quality of life of patients with inflammatory bowel disease. The therapeutic potential of these intrinsically powerful biologicals is reduced by a high variability in clinical response. Whereas primary non-response is defined as the lack of clinical response to the treatment, assessed 8–12 weeks after initiation, secondary loss of response is defined as loss of clinical benefit after initially responding which can be attributed to disease-related or drug-related factors. A drug can only exert its pharmacological effect when adequate concentrations of drug are achieved in the circulation and at drug’s site of action. Assays have been developed to determine the concentration of the therapeutic drug in serum. The trough concentration is the concentration just before the next administration and for practical reasons therapeutic drug monitoring is mainly based on measurement of these trough concentrations. Several studies have reported correlations between through concentration and clinical outcome leading to a number of prospective studies in which dosage regimens are adapted in order to achieve target trough concentrations that correlate with beneficial therapeutic outcomes. Immunogenicity is the capability of biologicals to elicit an unwanted immune response that results in the formation of anti-drug antibodies. Anti-drug antibodies can be non-neutralizing or neutralizing. Non-neutralizing antibodies do not impair the drug-target interaction but may increase clearance of the drug resulting in lower serum concentrations. Neutralizing anti-drug antibodies compete with the target for the antigen-binding site and modulate directly the activity of the drug in addition to the enhanced clearance of the drug. Combining drug and anti-drug antibody concentrations with relevant patient, disease and drug information will lead to adaptive dosing of biologicals based on covariates.
What can we learn from epidemiological studies in IBD?

D. Duricova
IBD Clinical and Research Centre, IS CARE, Prague, Czech Republic

Population based studies represent the whole spectrum of patient population and should represent the mainstay when evaluating patients’ prognosis. The disease course of both ulcerative colitis (UC) and Crohn’s disease (CD) is variable and still quite unpredictable. Up to one fourth of CD patients have bowel complications already at the time of diagnosis; the frequency increases with time and reaches more that 50% after 10 to 20 years of disease duration. Approximately one third of UC patients with proctitis or left-sided colitis experience disease progression during 10 years of follow-up. A high number of CD patients need surgical intervention during the disease course. According to older studies up to 60% of patients undergo at least one operation after 10 years of CD duration. Newer cohorts report lower cumulative probability of surgery of approximately 40% after 10 years. The colectomy rate in UC is approximately 10% after 10 years from diagnosis with a geographic difference. Similarly to CD, the colectomy rate seems to decrease over time. There is some evidence that the increasing use of immunosuppressive and/or biological therapy might have been responsible for this favourable trend. The relative risk of colorectal cancer in UC is approximately doubled compared to background population. However, the absolute risk in general is relatively low between 1.1 and 5.3% after 20 years of disease duration. Importantly, several factors such as disease extent, activity, age at UC onset, etc. may increase/modify an individual risk. Overall mortality in patients with UC seems to be comparable to background population. In contrast, patients with CD have approximately 40% increased risk of dying than background population. The highest mortality, both in UC and CD seems to be during the 1st year after diagnosis with subsequent decrease.
Session V

Biosimilars in clinical practice
State-of-the-Art Lecture

Does introduction of biosimilars change our understanding of track treatment?

B. Moum
Department of Gastroenterology, Clinics of Medicine, Oslo University Hospital Ullevaal & University Oslo, Norway

Therapeutic monoclonal antibodies for medical use are called biological medicines. Their manufacture is based on biological processes in which antibodies are produced in genetically modified cell colonies, with the challenges this entails.

When pharmaceutical manufacturers want to make “copies” of existing drugs, the manufacturer of the copy has to develop separate cell colonies and make synthetic genes that code for a protein that is as similar as possible to the original. A process of this nature will never be able to yield a result that is completely identical to the original drug, and therefore these copies are not called generic medicines, but “biosimilar” medicines. The products of this process are biochemically and clinically tested in collaboration with the European Medicines Agency (EMA) according to their own guidelines.

A biosimilar medicine must demonstrate equivalent efficacy and have the same safety profile as the drug that it has “imitated”. It is a matter of debate whether efficacy must be demonstrated for all diseases for which the original drug has been shown to be effective, or whether it should be sufficient to demonstrate efficacy for one or a few diseases, and then extrapolate to others. The argument for extrapolation is that development costs can be saved. The final result is that the medicines can be offered at a significantly reduced cost, which will naturally be advantageous.

There is an absence of good documentation on the use of biosimilar medicines for ulcerative colitis and Crohn’s disease. This creates uncertainty for decision-makers in national and international health policy and in medical communities. Unresolved questions about efficacy and safety are of concern to the medical community, and new studies are needed to clarify this.

The decision as to when biosimilar medicines should be chosen now lies with the individual specialist and hospital administration, with the responsibility that this entails. In the absence of a common decision-making arena regarding the medical stance on switching, registers that can follow up patients, and initiation of studies that requires that patients on established treatment switch under close monitoring should therefore be required.
Experience with biosimilar infliximab (Remsima®) in Norway

Jørgen Jahnsen
Department of Gastroenterology, Akershus University Hospital, Lørenskog, Institute of Clinical Medicine, University of Oslo, Nordbyhagen, Norway

Introduction: In response to the often high costs of originator biologics, interest has grown in biosimilars. Remsima® is a biosimilar of the reference medicinal product infliximab (Remicade®) and the first monoclonal antibody biosimilar to be approved by the European Medicines Agency (EMA). Documentation of clinical efficacy is based on studies performed in rheumatic diseases and there have been some concerns regarding extrapolation of indication to inflammatory bowel disease (IBD).

Aims and methods: In a prospective observational study we have evaluate tolerability and efficacy of treatment with Remsima® in patients with inflammatory bowel disease. Since January 2014 Remsima® has been the first line treatment at our hospital when starting biologic therapy in new IBD patients. Altogether 46 patients with Crohn’s disease (CD) (24 women) and 32 patients with ulcerative colitis (UC) (15 women) have participated in this study. Age, disease duration, disease extension and behavior, surgical treatment, co-medication and previous use of biologics were registered in addition to adverse events during treatment. In almost all patients the indication for starting treatment with Remsima® was on-going uncontrolled active inflammation. Disease activity was assessed using Harvey-Bradshaw index for CD and total and partial Mayo score for UC at the first infusion and at week 14. Calprotectin in faeces and C-reactive protein (CRP) in serum were measured at the same time points and trough level of infliximab at week 14 (before the fourth infusion). Anti-drug antibodies (ADA) was measured if trough level was < 1.0 mg/l.

Results: There was a significant clinical improvement in both CD and UC patients after induction therapy with Remsima® (p = 0.0001). At week 14, 79% of CD patients (34/43) and 56% of UC patients (18/32) were in clinical remission (HBI ≤ 4 or partial Mayo score ≤ 2). We also observed a significant reduction in faecal calprotectin and CRP from baseline in both patient groups. Four CD and four UC patients had trough level of 0 mg/l (seven with moderate to high levels of ADAs). No unexpected adverse events occurred during the study. One UC patient was colectomized and one CD patient was operated on with bowel resection before week 14.

Conclusion: Efficacy and tolerability of Remsima® in the treatment of IBD appears to be similar to the originator infliximab Remicade®.
Biosimilar infliximab interchangeability in clinical practice in the Czech Republic

M. Lukas, M. Kolar, D. Duricova, M. Lukas Jr., K. Mitrova, N. Machkova, V. Hruba
IBD Clinical and Research Centre, ISCARe Lighthouse and 1st Medical Faculty, Charles University, Prague, Czech Republic

Biosimilar infliximab (IFX) seems to have similar efficacy and safety to original preparation in patients with inflammatory bowel diseases (IBD) who are naive to anti-TNFα therapy. However, the evidence on switching from original to biosimilar preparation is very sparse.

Our aim was to evaluate efficacy and safety of switching from original to biosimilar preparation IFX in patients with Crohn’s disease (CD) and ulcerative colitis (UC).

Consecutive patients with CD and UC on maintenance IFX treatment at our center who were switched from original to biosimilar IFX during a period from January to March 2015 were included. Patients were followed prospectively in regular intervals coincident with infusion applications. At each visit disease activity was registered using Harvey-Bradshaw index (HBI) for CD and Simple clinical colitis activity index (SCCAI) for UC; blood sample taken for analysis of blood count, biochemistry and IFX pharmacokinetics (trough levels, TL and anti-drug antibodies, ATI) and stool sample obtained for measurement of fecal calprotectin (FC). Furthermore, adverse events were registered. All patients were evaluated at week 24 (W24) of treatment with biosimilar IFX.

Seventy-four patients with IBD, 56 with CD and 18 with UC, were switched to biosimilar IFX after mean time of 3 ± 2.2 years on original preparation. Almost half of individuals (34, 46%) were on concomitant azathioprine and one patient had systemic corticosteroids. Majority of patients, 51 (69%) were at the time of switch (week 0, W0) in clinical remission, 16 (22%) had mild to moderate active disease and 4 (5%) individuals had severe disease activity. Comparing W0 and W24, no significant difference in C-reactive protein levels (4.3 ± 8.0 mg/l vs. 3.6 ± 4.5; p = 0.78) and FC (135 ± 153 µg/g vs. 226 ± 297; p = 0.44) was observed. Likewise, no increase in immunogenicity was found (IFX TL: 3.4 ± 3.8 µg/ml vs. 3.8 ± 3.3, p = 0.23; ATI positivity: 9.5% vs. 10%, p = 0.79). Furthermore, disease activity was stable until the end of follow-up (remission at W0 vs. W24: 72% vs. 78%). Three patients discontinued IFX treatment up to W22 due to loss of response (n = 1), adverse event (n = 1) and low grade dysplastic lesion in colon (1 UC patients). None patient experienced infusion reaction and the frequency and type of adverse events were similar to that observed during treatment with original IFX.

Based on our results switching of IBD patients from original to biosimilar IFX is effective and safe. Importantly, no increase in immunogenicity was observed.
Immunogenicity and side effects of biosimilar infliximab treatment in Hungary

Zsuzsanna Vegh, Peter L. Lakatos
First Department of Internal Medicine, Semmelweis University, Budapest, Hungary

Recently, the use of biosimilar infliximab in IBD (inflammatory bowel diseases) has become more widespread in some European and non-European countries. Data on the efficacy and immunogenicity are limited so far. Korean authors\(^1\) reported high response and remission rates in both anti-TNF-naive and in patients who switched from the biologic originator to biosimilar IFX throughout week 54. Similar early efficacy data were reported from Norway\(^2\). Furthermore in a pediatric Polish CD cohort, switched to biosimilar IFX, no infusion reactions or change in the clinical activity were observed at around or after the switch\(^3\). Recently, a multicenter, nationwide prospective, observational study by Gecse et al.\(^4\) reported high response and remission rates were observed throughout week 30 in consecutive CD and UC patients (CD: clinical response: 67.2% of the week 14 responder patients, clinical remission: 53.4%; UC: clinical response: 80% clinical remission: 68%) from Hungary. Therapeutic drug level monitoring (including TL [trough level] and antidrug antibody [ADA] measurements) was serially performed. ADA positivity was observed in 9.1% and 21.3% of CD and in 8.8% and 23.8% of UC patients at baseline and at week 14 with significantly higher baseline ADA levels in patients treated with previous originator IFX in both CD and UC, coupled with a higher rate of infusion reactions. The side effects in the Hungarian, Norwegian and Korean study are in line with those reported in the previous studies of the originator infliximab – e.g. infections, pneumonia, with no tuberculosis or cancer case. In conclusion early real life data suggest that the efficacy, immunogenicity and side effect profile of the biosimilar infliximab is similar to that of the originator.

References:


Session VI

Transplantation procedures in the therapy of IBD
Randomised controlled clinical trial of autologous haemopoetic stem cell transplantation in Crohn’s disease

Prof. C.J. Hawkey
Nottingham Digestive Diseases Centre, University Hospital, Nottingham NG7 2UH, UK

**Aims:** Claims have been made that autologous haemopoetic stem cell transplantation (HSCT) can alter the natural history of refractory Crohn’s disease. We tested this hypothesis in a randomised controlled trial (RCT) with five year follow-up. Here we report two year controlled data.

**Methods:** Patients with clinical and endoscopic active CD who had failed at least 3 immunosuppressive drugs or biologics underwent cyclophosphamide mobilization and were randomized to immediate (4 weeks) or delayed (52 weeks) HSCT. Clinical (CDAI), endoscopic (SES-CD), and quality of life scores were compared immediately prior to (baseline) and one year after HSCT. An adjudication panel blinded to allocation and visit reviewed radiology and endoscopy to evaluate intestinal ulceration.

**Results:** 45 patients with successful mobilization were randomized to early (n = 23) or delayed (n = 22) HSCT. Data from baseline and 1 year after HSCT were available for 40 patients. Compared to baseline, there were significant improvements at 1 year for CDAI, PRO2, quality of life (IBDQ, and EQ5D) and SES CD (Table 1). Complete endoscopic regression (SES-CD score of 0 in all segments examined) occurred in 26%, with complete ulcer healing in 50% and partial healing (ulcers ≤ 5 mm in no more than 2 segments) in 82%. Clinical remission (CDAI < 150) at one year occurred in 46% patients (39% in remission > 3 months off steroids). On univariate analysis baseline factors associated with steroid free clinical remission at 1 year include colonic localization (p = 0.006), inflammatory phenotype (p = 0.009), high SES-CD (p = 0.005). Age, CRP and early vs delayed HSCT were not significant. On multivariate analysis high baseline SES CD was associated with steroid free remission at year 1 (OR = 1.21; 95% CI: 1.03–1.41; p = 0.017). SAEs were common following mobilisation (28 over 35 days), during and after conditioning (44 over 100 days, most commonly infective) and in follow-up, (35 over 271 days).

**Conclusion:** One year outcome in the largest reported cohort of patients undergoing HSCT for refractory Crohn’s disease shows a significant reduction in both clinical and endoscopic disease activity with an improvement in quality of life. Endoscopic severity at baseline predict outcome.

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<tr>
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<th>Baseline</th>
<th>One year</th>
<th>P values</th>
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<tr>
<td></td>
<td>N</td>
<td>Mean (IQR)</td>
<td>N</td>
</tr>
<tr>
<td>CDAI</td>
<td>40</td>
<td>332.6 (246–418)</td>
<td>37</td>
</tr>
<tr>
<td>PRO2</td>
<td>40</td>
<td>23.85 (15.6–30.8)</td>
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<tr>
<td>EQ5D</td>
<td>34</td>
<td>0.76 (0.7–0.8)</td>
<td>31</td>
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<tr>
<td>IBDQ</td>
<td>37</td>
<td>120.2 (101.5–141)</td>
<td>31</td>
</tr>
<tr>
<td>Total SES CD</td>
<td>36</td>
<td>14.1 (7–21.5)</td>
<td>36</td>
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Mesenchymal stromal cell therapy in Crohn’s disease

Geoffrey M. Forbes
Royal Perth Hospital and University of Western Australia, Perth, WA, Australia

Mesenchymal stromal cells (MSC) are multipotent adult stem cells with immunomodulatory properties. They uniquely express HLA class I antigen at low level, and do not express HLA class II. Hence for allogeneic administration, donor to recipient matching is not required, yet a prolonged chimeric state does not occur. In contrast to hematopoietic stem cell transplantation, cytotoxic drug therapy is not required to harvest, or administer cells.

MSC are obtained from marrow, adipose tissue or placenta. In our centre, MSC are isolated from a 10 ml donor marrow aspirate, by virtue of their adherence to plastic. They are expanded in culture, cryopreserved, and subjected to strict quality controls before release for intravenous administration. These activities occur in a dedicated, nationally accredited laboratory.

Initial observations of allogeneic MSC efficacy were in graft-versus-host disease. Both autologous and allogeneic MSC have since been evaluated in biologic refractory luminal and fistulising Crohn’s disease. Data from early phase studies have suggested efficacy for luminal disease when allogeneic MSC were given intravenously, and for fistulising disease when either allogeneic or autologous MSC were administered into fistulas. MSC treatment is not reported to have caused serious adverse events.

Although in-vitro criteria for defining MSC exist, a major challenge lies in how to define MSC for clinical use. MSC function in-vivo is likely to be dependent upon donor immunological characteristics, and widely varying manufacturing processes between laboratories. MSC dose, frequency of administration, stage of disease, and presence of concomitant immunosuppression also require defining.
Fecal transplantation

W. Reinisch
Department of Medicine, McMaster University Health Sciences Centre, Hamilton, ON L8S 4K1, Canada

The etiology of inflammatory bowel disease is unknown but it is thought to arise from an aberrant immune response to a change in colonic environment in a genetically susceptible individual. The intestinal microbiota is located at the complex interface of the epithelial barrier and sensitive to changes of environmental factors, such as diets, drugs or smoking and signals derived from the intestinal immune system and the gut-brain axis. In patients with inflammatory bowel disease an imbalance in the structural and/or functional configuration of the intestinal microbiota leading to the disruption of the host-microorganism homeostasis (dysbiosis) has been reproducibly reported. As animal models of inflammatory bowel disease require gut bacteria to induce inflammation it is hypothesized that the dysbiosis observed in patients is not only a surrogate of changes at the intestinal barrier but also a potential cause or at least enhancer of the mucosal inflammatory process. That burgeoning notion has stimulated thoughts to modify the intestinal microbiota and rekindled the interest in previous work on the efficacy of antibiotics in patients with IBD. The feasibility and tremendous success of faecal microbiota transplantation (FMT) to treat antibiotic resistant Clostridium difficile finally released the locks to embark with FMT also into the unchartered territory of IBD. Different routes and number of administrations, choices of donors, disease status and permitted might have contributed to mixed results, particularly from the so far published randomized controlled trials. However, microbiome analysis suggest that a durable transplantation of donor bacteria to the host appears feasible and might be associated with a higher likelihood of response. On the other site this raises the concern of not only transplanting anti-inflammatory active bacteria and their products, but also not yet known dispositions for other diseases including cancer. Attempts are being made to better characterize those components of the microbiome of healthy individuals which might mediate anti-inflammatory functions and assemble “synthetic stools” for more standardized treatment approaches.
Small bowel transplantation

Pavel Drastich
Department of Hepatogastroenterology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic

Most patients with Crohn’s disease (CD) require one or more operations over their lifetime. Repeated resections and complications of surgery may result in short gut in a subset of patients, typically those with an extensive small bowel disease or a penetrating CD phenotype. Short bowel syndrome (SBS) is a disorder that affects patients with CD as a result of three main conditions: as a consequence of complications of surgery for intra-abdominal sepsis, extensive inflammation of small bowel associated with severe loss of nutrient absorption or repeat resections in patients who have had large portions of their small bowel surgically removed. The effects of short bowel syndrome can range in seriousness from mild to life-threatening. CD is the second leading indication for small bowel transplantation (SBTx) worldwide after failure of total parenteral nutrition (TPN), but the overall incidence of SBTx is quite low. Currently TPN is the preferred option for patients with SBS due to its superior survival outcome. Failure of TPN can manifest as loss of venous access due to catheter-associated thromboses and as liver dysfunction. There are three types of transplantation available for CD patients, small bowel alone, liver plus small bowel and multivisceral that contains other organs (small bowel, stomach, duodenum, pancreas, liver and others). The choice of surgery depends on the presence of liver failure and the extend of abdominal pathology. Survival following SBTx currently appears worse than on TPN with 5 years survival around 55%, but outcomes in general are substantially improving because of surgical and technical progress and development of medical therapy. On the other hand intestinal transplants carry a high risk of complications, including rejection of the new organs, infections, postransplant lymphoproliferative disorders, adverse events of immunosuppression etc. Crohns disease recurrence has been reported in limited number of patients; however, this mainly histologic recurrence might not be of high clinical importance.

SBTx is an important part of therapeutical strategy which fortunately concerns a small proportion of CD patients but provides a reasonable survival and quality of life. Patients with a small bowel failure should receive their primary management through a center experienced in medical intestinal rehabilitation, nutrition and transplantation of other solid organs.
Session VII

Challenging clinical cases
Case reports: May both diseases (CD and UC) exist in one patient?

Martin Bortlik
Clinical and Research Center for IBD, Iscare I.V.F. a.s., Prague, Czech Republic

There is an increasing evidence that patients initially diagnosed with ulcerative colitis (UC) may develop Crohn’s disease (CD) after surgical therapy and ileopouch-anal anastomosis (IPAA) construction. Although some of them may have had CD prior to surgery, it seems that de-novo CD of the pouch and/or the afferent ileal limb may occur. Several risk factors for CD of the pouch development have been described in the literature, including clinical, endoscopic, and laboratory markers. Here we present two cases of patients with initial diagnosis of UC who underwent surgical treatment with eventual IPAA construction and occurrence of distinct patterns of CD several years thereafter.

Our first patient underwent a complicated disease course with IPAA performed at the age of 31. Within 3 years of IPAA, first attack of acute pouchitis occurred with subsequent signs of chronic pouch inflammation. Fifteen years after the IPAA construction, both clinical and endoscopic features changed. The patient developed obstructive symptoms with three segments of afferent limb affected by deep ulcers and strictures. Despite an intensive medical therapy including anti-TNF antibodies, the patient requires repeated endoscopic dilations to avoid pouch resection and permanent ileostomy construction. In second case, we describe a patient with severe UC and IPAA performed at the age of 23. Repeated pouchitis started 9 years after surgery. Within the next 8 years, multiple ulcers affected the distal part of the pouch and afferent limb with stricture at the orifice of afferent limb. Moreover, a typical features of perianal CD also occurred and required surgery with setton placement.

In both cases, the resected colonic specimens were re-evaluated in order to confirm the accuracy of initial diagnosis of UC. Appropriate diagnostic tools and management of de-novo CD of the pouch and afferent limb will be discussed during presentation.
Overview: Complications after IPAA

Tamas Molnár
First Department of Medicine, University of Szeged, Hungary

Approximately 30% of patients with relapsing, extensive ulcerative colitis require surgery. Total proctocolectomy with ileal pouch anal anastomosis (IPAA) represents the most common and potentially curative surgical procedure for intractable UC since 1978, although up to 50% of the patients undergoing surgery will develop pouchitis. Pouchitis is an idiopathic chronic inflammatory disease that may occur in the ileal pouch after restorative proctocolectomy with IPAA and seems to be the most frequent in the first 2–3 years after closure of the ileostomy. Finding routinely available risk factors predicting to the development of pouchitis is becoming more and more important for the selection of the appropriate treatment. Genetic polymorphisms, extraintestinal manifestations, the presence of serum perinuclear antineutrophil cytoplasmic antibodies, backwash ileitis, thrombocytosis, non-smoking behavior, extensive UC and the use of NSAIDs are some of the previously identified risk factors for pouchitis. During my presentation I will summarize the other possible predictive factors of pouchitis based on our data and I will review the other possible complications after IPAA. The quality of life of operated UC patients is influenced by several factors and also needs to be discussed. Experience with the treatment of chronic relapsing or refractory pouchitis is limited and efficacy of different therapeutic options will be presented.
Case report: Acute flare of ulcerative colitis during pregnancy is still a big problem

Marijana Protic¹, Dino Tarabar²
¹Department of Gastroenterology, University Hospital Zvezdara, Belgrade, Serbia
²Medical Military Academy, Belgrade, Serbia

Although severe flare of ulcerative colitis is uncommon, it significantly increases the risk of preterm delivery, low birth weight and other adverse fetal outcomes. It is critical to optimize aggressive medical treatment with both, mother and fetal health. Here we present a case of 30-year-old women with a severe flare of ulcerative colitis (UC) at the 16th gestational week. The diagnosis of extensive UC was established 8 years ago. Since diagnosed, she had 5 moderate flares successfully treated with oral and topical mesalamine. The relapses of disease were always a consequence of a poor compliance to maintenance therapy. The patient had a positive family history for ulcerative colitis and thrombophilia with homozygote mutation for C677T and heterozygote mutation for G1699A.

At the admission, she presented with 8-10 bloody diarrheas and moderate abdominal pain. She was afebrile (36.7°C), with increased hearth rate (96/min). Laboratory studies showed elevated C-reactive protein (42 mg/l), fecal-calprotectin (7223 μg/g), and anemia (hemoglobin 10.4 g/dl). Clostridium difficile and CMV infection were excluded. Intensive treatment with systemic steroids was started. Low-molecular weight heparin (nadroparin calcium 0.6 ml) was continued due to thrombophilia and acute severe flair of ulcerative colitis. Three days later, no response to the therapy was observed (8 bloody stools, CRP 40 mg/l). According to urgent indication, rescue therapy with infliximab (IFX) (5 mg/kg standard induction protocol) was administered, week later, at 17th gestational week. A partial clinical and laboratory response was achieved after 2nd dose of Infliximab (4 stools/day, CRP 12.2 mg/l and FCP 1078 μg/g). The patient received 3rd and least dose of IFX at 23th gestational week. She continued on corticosteroids and mesalamine with chronically active moderate disease. IFX trough levels obtained before the administration of 3rd dose was 20.6 μg/ml; antibodies to IFX were negative. The patient delivered trans-vaginally a healthy girl on the 36th gestational week (the newborn weight 3150 g, APGAR score 9). No live vaccines were administrated to newborn. It seems that our patient had happy outcome of the pregnancy despite the chronic active refractory disease with a primary non-response to biologics. There is a major question to be raised: will high drug concentration in the mother’s serum have a stronger and prolonged immunosuppressive effect on the newborn?

Key words: ulcerative colitis, pregnancy, infliximab, mesalamine, newborn
Overview: What should be done in pregnant women with severe UC?

Zuzana Zelinkova¹²
¹St. Michael’s Hospital, Bratislava, Slovakia
²IBD Center, Bratislava, Slovakia

Severe ulcerative colitis (UC) during pregnancy is an acute condition with high risk of unfavourable outcome for both, the mother and the child. When severe flare of UC occurs during pregnancy, the management should be prompt, usually on an inpatient basis. First steps include proper diagnostics, especially in a patient with first presentation of UC during pregnancy, should be focussed at the exclusion of an alternative diagnosis, such as infectious colitis and colorectal carcinoma. In a patient with known UC, also CMV infection should be considered. In the majority of cases, endoscopic evaluation is necessary in order to first, confirm the diagnosis and second, to determine the extent of the colitis. Endoscopy should be performed by an experienced endoscopist in a tertiary centre with multidisciplinary expertise in this field with obstetrician and surgeon actively involved in the management.

Subsequently, the treatment consisting of parenteral systemic corticosteroids, maintenance of adequate nutritional status and prevention of thromboembolism should be initiated. The evolution of clinical condition of the mother and the child should be closely monitored by the whole multidisciplinary team. If there is no improvement within 3 to 5 days, the decision about the second line treatment, such as cyclosporine or infliximab should be guided not only by the severity and extent of colitis but obstetric evaluation is equally relevant for the decision.

In conclusion, timely diagnosis and treatment with the involvement of gastro-enterologist, surgeon and obstetrician are the key elements of the management of severe UC during pregnancy.
Case report: Ileal Crohn’s disease in monozygotic twins

Mircea Diculescu, Corina Meianu, Alexandru Lupu
Department of Gastroenterology and Hepatology, Fundeni Clinical Hospital, Bucharest, Romania

The subject of the presentation is the diagnosis of limited ileal Crohn's disease in a pair of monozygotic twins. The disease developed with 6 months difference interval in the onset of symptoms, with the same localization, meeting the same pattern.

Twin A

36-years-old, non-smoker, non-appendicectomized with the diagnosis of irritable bowel syndrome (IBS) since 2013, was admitted in November 2015 for 12 kg weight loss in the previous year and the onset of 3–4 semi-solid stools per day with mucus and mild diffuse abdominal pain with improvement after defecation during previous weeks.

At diagnosis blood tests revealed inflammatory syndrome with increased values of CRP (32 mg/l), fibrinogen (626 mg/dl) and leukocytosis (12.640 U/l). No anemia. Stool tests were negative for infection.

Colonoscopy showed mucosal edema and aphthous ulcerations of the ileocecal valve and on 6–7 cm explored of the terminal ileum. Biopsies revealed non-granulomatous chronic active inflammation with foci of ulceration.

Budesonide 9 mg per day was initiated. After two months of corticoid treatment, the patient was asymptomatic, with 3 kg weight gain, the normalization of stools and normal range of blood tests inflammatory markers. For maintaining remission, azathioprine was added starting from 50 mg per day gradually increased with 50 mg per week until the therapeutic dose of 150 mg (2.5 mg/kg/day) with weekly hemogram and lipase monitoring. At the dose of 150 mg of azathioprine, the subject developed high lipase levels (1382 U/l).

Azathioprine was stopped and adalimumab will be initiated. Budesonide will be continued for one month in association with adalimumab at a dose of 9 mg with further tapering.

Twin 2

36-years-old, smoker (20 cigarettes per day for 10 years), non-appendicetomized, no significant medical history besides IBS-D since 2009 was admitted in January 2016 for weight loss (15 kg in the past 6 months) and 1–2 semi-solid stools a day no mucus or blood.

Increased values of inflammatory markers were detected (CRP 43.30 mg/l, fibrinogen 485 mg/dl, leukocytosis 13.000 U/l). No anemia. Stool tests were negative for infection.
Colonoscopy to the caecum showed normal aspect of the mucosa including normal aspect of the ileocecal valve. Pansdorff (barium follow-up of the small intestine) examination revealed multiple ileal stenosis with mild upstream dilatations and irregular outline of the intestinal loops interpreted as possible ulcerations.

Budesonide 9 mg per day was initiated in association with azathioprine starting from 50 mg per day gradually increased with 50 mg per week until the therapeutic dose of 150 mg (2.5 mg/kg) with weekly hemogram and lipase monitoring. After three weeks of treatment, the patient was asymptomatic, with 2 kg weight gain, the normalization of stools and normal range of blood tests inflammatory markers.

At the dose of 150 mg of azathioprine, the subject developed high lipase levels (458 U/l).

Azathioprine was stopped and adalimumab will be initiated. Budesonide will be continued for one month in association with adalimumab at a dose of 9 mg with further tapering.
Intestinal microbiome: Myths and facts

Institute of Microbiology, v.v.i., Academy of Sciences of the Czech Republic, Prague, Czech Republic
*Institute of Molecular Genetics, Academy of Sciences of the Czech Republic, Prague, Czech Republic

Most of our body surfaces covered by epithelial cells are populated by large numbers of microorganisms. Intestinal microbiota is composed mainly of bacteria but fungi, protozoa, archae and viruses are also present. Metagenomic approaches are currently being used to decipher the genome of the microbiota (microbiome), and, in parallel, functional studies are being performed to analyze the effects of the microbiota on the host. The interaction of macroorganism with commensal microorganisms substantially influences the development of the innate and adaptive arms of the mucosal immune system and development of systemic immunity. Numerous immunologically mediated chronic diseases may occur as a result of disturbance of intestinal microbiota composition ("dysbiosis"), impaired mucosal barrier function and changes in immuno-regulating mechanisms.

An irreplaceable role in the efforts to elucidate the role of microbiota in the development of immune and physiological mechanisms, as well as in the pathogenetic mechanisms of inflammatory and neoplastic diseases, is played by gnotobiology. Experimental animals as models of human disease (induction of disease or genetically manipulated models) reared in germ-free breeding isolators are used for comparison with conventionally bred experimental animals (colonized with normal microbiota) for the purpose of monitoring the participation of commensal bacteria in the development of diseases. Moreover, germfree animals can be colonized by defined strains of bacteria, and the participation of individual microbiota components in the development of diseases can thus be directly observed. By gnotobiological methods we have shown that gut microbiota transferred from intestinal biopsy samples of patients with IBD promotes intestinal inflammation. Moreover, we demonstrated the impact of gut microbiota composition on colitis-associated colon cancer development and the role of negative regulator IRAK-M in TLRs activation in this process (Tlaskalová-Hogenová et al. CMI. 2011; Klimešová et al. IBD. 2013).

Identification microbiota components and elucidation of molecular mechanisms of their action could help to influence microbiota composition and function by appropriate dietary interventions and/or to help finding such microbial components whose administrations would aid in disease prevention and treatment.
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List of Chairpersons, Speakers and Scientific Organizers

Dr. Martin Bortlik  
Clinical and Research Center for IBD  
Iscare I.V.F.a.s., Lighthouse  
Jankovcova 1569/2c  
170 04 Prague  
Czech Republic

Dr. Dana Duricova  
Clinical and Research Center for IBD  
Iscare I.V.F.a.s., Lighthouse  
Jankovcova 1569/2c  
170 04 Prague  
Czech Republic

Prof. Dr. Jacques Cosnes  
Service de Gastroentérologie et Nutrition  
Hôpital Saint Antoine  
184, rue du Faubourg St-Antoine  
75012 Paris  
France

Prof. Dr. Marc Ferrante  
Department of Gastroenterology  
University Hospitals Leuven  
KU Leuven  
Herestraat 49  
3000 Leuven  
Belgium

Dr. Mircea Diculescu  
Department of Gastroenterology and Hepatology  
Fundeni Clinical Hospital  
Sos Fundeni 258  
022328 Bucharest  
Romania

Prof. Dr. Geoffrey M. Forbes  
Department of Gastroenterology and Hepatology  
Royal Perth Hospital  
GPO Box X2213  
Perth, WA 6847  
Australia

Dr. Pavel Drastich  
Assoc. Prof. of Internal Medicine  
Department of Hepatogastroenterology Institute for Clinical and Experimental Medicine  
140 21 Prague  
Czech Republic

Prof. Dr. Andrey E. Dorofeyev  
National Medical University n.a.A.A. Bogomoletz  
Chair of Internal Diseases#1  
Shevchenko bul 17  
01030 Kiev  
Ukraine

Prof. Dr. Chris J. Hawkey  
Professor of Gastroenterology  
Nottingham Digestive Disease Centre University Hospital  
Nottingham NG7 2UH  
Great Britain

Prof. Dr. Marc Ferrante  
Department of Gastroenterology  
University Hospitals Leuven  
KU Leuven  
Herestraat 49  
3000 Leuven  
Belgium

Prof. Dr. Ann Gils  
Therapeutic and Diagnostic Antibodies O&N II  
KU Leuven  
Herestraat 49 – Box 820  
3000 Leuven  
Belgium

Peter D.R. Higgins, M.D.  
Associate Professor of Medicine  
Department of Gastroenterology  
University of Michigan  
Medical Science Research Bldg I  
1150 W Medical Ctr Drive  
Ann Arbor, MI 48109-0682  
USA
Prof. Dr. Tibor Hlavaty
Department of Internal Medicine
Subdepartment of Gastroenterology and Hepatology
University Hospital Bratislava
Ruzinovska 6
82606 Bratislava
Slovakia

Dr. Jørgen Jahnsen
Akershus
Universitetssykehus
Postboks 75
1474 Nordbyhagen
Norway

Prof. Dr. Wolfgang Kruis
Innere Medizin
Ev. Krankenhaus Kalk
Buchforststr. 2
51103 Köln
Germany

Prof. Dr. Peter L. Lakatos
1st Department of Medicine
Semmelweis University
Medical School
Koranyi u 2/a
1083 Budapest
Hungary

Prof. Dr. Milan Lukas
Clinical and Research Center for IBD
Iscare I.V.F.a.s., Lighthouse
Jankovcova 1569/2c
170 04 Prague
Czech Republic

Dr. Marc Martí Gallostra
Consultant Colorectal Unit
Digestive and General Surgery
Hospital Universitari Vall D’Hebron
Barcelona
Spain

Dr. Tamás Molnár
First Department of Medicine
University of Szeged
Korányi fasor 8–10
6720 Szeged
Hungary

Prof. Dr. Bjørn Moum
Department of Gastroenterology
Clinics of Medicine
Oslo University Hospital Ullevaal
& University Oslo
Kirkeveien 166
0424 Oslo
Norway

Prof. Dr. Gottfried Novacek
Klinische Abteilung für Gastroenterologie und Hepatologie
Universitätsklinik für Innere Medizin III
Medizinische Universität Wien
Währinger Gürtel 18–20
1090 Wien
Austria

Prof. Dr. Yves Panis
Service de Chirurgie Colorectale
Pôle des Maladies de l’Appareil Digestif (PMAD)
Hôpital Beaujon
100, bd du Général Leclerc
92118 Clichy Cedex
France

Dr. Marijana Protic
Assoc. Professor
Department of Gastroenterology
University Hospital Zvezdara
Dimitrija Tucovica 161
Belgrade
Serbia

Prof. Dr. Walter Reinisch
Department of Medicine
Health Sciences Centre
McMaster University
1280 Main Street West
Hamilton ON L8S 4K1
Canada
Florian Rieder, M.D.
Department of Gastroenterology,
Hepatology and Nutrition
Lerner Research Institute
Cleveland Clinic Foundation
Cleveland, OH 44195
USA

Prof. Dr. Dr. Gerhard Rogler
Klinik für Gastroenterologie
und Hepatologie
Universitätsspital Zürich
Rämistr. 100
8091 Zürich
Switzerland

Prof. Dr. Grazyna Rydzewska
Gastroenterologii MSWiA
Kierownik Kliniki
ul Wolowska 170
00-211 Warsaw
Poland

Bruce E. Sands, M.D.
Professor of Medicine
Department of Gastroenterology
Mount Sinai School of Medicine
One Gustave L. Levy Place
New York, NY 10029
USA

Prof. Dr. Jürgen Schölmerich
Klinikum der Johann Wolfgang
Goethe-Universität Frankfurt
Theodor-Stern-Kai 7
60596 Frankfurt
Germany

Dr. Zuzana Serclova
Surgical Department
University Hospital Bulovka
Prague
Czech Republic

Prof. Dr. Eduard F. Stange
Abteilung für Gastroenterologie,
Hepatologie und Endokrinologie
Robert-Bosch-Krankenhaus
Auerbachstr 110
70376 Stuttgart
Germany

Prof. Dr. Helena Tlaskalová-Hogenová
Department of Immunology
and Gnotobiology
Institute of Microbiology
Academy of Sciences of the
Czech Republic
Prague
Czech Republic

Dr. Zuzana Zelinkova
IBD Center
5th Department of Internal Medicine
Tomaskikova 50/C
831 04 Bratislava
Slovakia
POSTER ABSTRACTS

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Clinicians’ knowledge about the ionizing radiation of the common investigations used in inflammatory bowel disease

Laith Alrubaiy, MBChB, MSc, MRCP (UK)¹, Sinan Al-Rubaye², Ibtihal Rikaby³, Chin Lye Ch'ng²
¹College of Medicine, Swansea University, UK
²Abertawe Bro Morgannwg University Health Board, Swansea, UK
³Boots Druggist and Chemist, London, UK

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

Laith Rubaiy\textsuperscript{1}, Ian Arnott\textsuperscript{2}, Aimee Protheroe\textsuperscript{3}, Michael Roughton\textsuperscript{3}, John Williams\textsuperscript{1}  
\textsuperscript{1}College of Medicine, Swansea University, Swansea SA2 8PP, UK  
\textsuperscript{2}Western General Hospital, Edinburgh, UK  
\textsuperscript{3}Clinical Effectiveness & Evaluation Unit, Royal College of Physicians, London, UK

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

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

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

Discussion/Conclusion: The results show clear evidence of improvement in most aspects of the quality of care for IBD inpatients over the last five years.
Evaluation of fecal calprotectin to differentiate inflammatory bowel disease (IBD) from irritable bowel syndrome (IBS) in Qena, Egypt

Mohamed Alsenbesy¹, Ahlam Sabra¹, Samar Sayed³, Mansour Kabbash²
¹Internal Medicine Department, Qena University Hospital, South Valley University (SVU), Qena, Egypt
²General Surgery Department, Qena University Hospital, South Valley University (SVU), Qena, Egypt
³Public Health and Community Medicine Department, South Valley University (SVU), Qena, Egypt

Introduction: lower bowel symptoms (e.g. abdominal pain, diarrhea, constipation and tenesmus) can be overlapping in both inflammatory bowel diseases (IBD) and irritable bowel syndrome (IBS). Fecal calprotectin showed promising results in differentiating IBD from IBS. Qena is located in upper-Egypt with high prevalence of parasitic infestation. The prevalence of Entamoeba histolytica and Giardia intestinalis is variable and reached up to 57% and 34.6% respectively in some regions of Egypt.

Aim: To evaluate the diagnostic value of fecal calprotectin as a non-invasive marker in differentiating patients with IBD from those with IBS in Qena.

Method: 28 patients with IBD (group A) and 32 patients with IBS (group B) were recruited from Qena University Hospital between September 2014 and October 2015. Fecal calprotectin level using an ELISA technique (PhiCal®) was measured. ESR and stool analysis were also detected.

Results: At the recommended cut-off value of 50 Ug/g, the sensitivity of calprotectin to differentiate IBD from IBS was 50% while the specificity was 62.50. In addition, the positive predictive value (PPV), the negative predictive value (NPV) and the diagnostic accuracy were 36.84%, 74.07% and 59% respectively. The level of fecal calprotectin in group A showed statistically insignificant elevation compared to group B. ESR was elevated in 19% of patients in group B. Also, E. histolytica cyst and G. intestinalis were detected in 15% and 12% respectively, in patients previously fulfilled the criteria for IBS (group B).

Conclusion: Although fecal calprotectin level had shown promising results in previous studies, our study didn’t support its validity in differentiating IBD from IBS. The NPV of calprotectin level can’t be considered reliable in excluding the need for colonoscopy. The high incidence and prevalence of parasitic infestation in the region of Qena is partly responsible for the overlap of symptoms.
Predictive factors for surgery and postoperative complications in patients with chronic inflammatory bowel disease

S. Ayadi, M. Cheikh, R. Ennaifer, H. Romdhane, W. Bougassas, H. Ben Nejma, N. Belhadj
Department of Gastro-enterology, Mongi Slim University Hospital, Tunis, Tunisia

Background: Surgery keeps an important place in the treatment of inflammatory bowel disease (IBD), but it is not without risk. Postoperative complications (POC) are often observed. This study aimed to precise clinical, biochemical and evolutive characteristics of patients operated for IBD and to precise frequency and predictive factors of POC.

Methods: Retrospective study including patients with IBD followed in our department between 2010 and 2015. Surgery was defined as any act of intestinal resection. Drainage of perianal fistulae and abscess were excluded. POC included complications inherent to surgery. General anesthesia complications were excluded.

Results: Sixty-five patients were included, 47 Crohn disease (CD) and 18 ulcerative colitis. Surgery was required in 23 patients (35.4%). Mean age of operated patients was 40.8 years with a sex ratio male/female of 1.87. Forty-three percent of patients were smokers. Mean disease duration was 101 months. Surgery was inaugural in 47.8% of cases. Surgical procedures were ileocecal resection (13 cases), total or subtotal colectomy (5 cases), ileum resection (3 cases), stricturoplasty, sigmoid resection and discharge ileostomy each in one case only. Surgical indications were variable, dominated by acute intestinal obstruction (56.5%). Smoking and CD were significantly correlated to surgery. The duration of postoperative follow-up was 89 months [3–288]. POC were observed in 21.7% of patients, represented by: anastomotic dehiscence (20%), intra-abdominal collections (40%) and fistulas (40%). Only an age < 20 years at diagnosis was correlated with the occurrence of POC.

Conclusion: In our series, surgery is more common in CD patients and smokers. POC were observed in 20% of cases. The young age at diagnosis was the only risk factor for POC. This could be explained by severe evolutive genius of these forms.
Role of the mean platelet volume as a marker of inflammation in Crohn’s disease

N. Ben Mustapha¹, O. Gharbi¹, I. Gheribi¹, A. Laabidi¹, M. Serghini¹, L. Kallel¹, M. Fekih¹, J. Boubaker¹, A. Filali¹
¹Department A of Gastroenterology, Rabta Hospital, Tunis, Tunisia

Introduction: Many inflammation markers have been studied to assess the activity of inflammatory bowel diseases mainly Crohn’s disease (CD), and predict relapse during follow-up. The aim of this study was to determine the capacity of the mean platelet volume (MPV) to evaluate inflammation in CD.

Methods: We investigated 29 patients with CD enrolled during a flare and then followed up during 12 months of remission. Platelet count, MPV, white blood cells count and C-reactive protein (CRP) were measured for every patient at enrollment, 6 months and 12 months of follow-up. Severity of flare was assessed based on Truelove and Witts criteria.

Results: Among the 29 enrolled patients, 8 were males and 21 were females. The median age was 28.6 years. 19 patients had an ileal form of CD, while the 10 others had a pure colic form. Thrombocytosis (above 350*10³/mm³) was found in 20/29 patients (68.96%) at enrollment with a mean platelet count at 564.8*10³/mm³, and in only 2/23 patients (9.09%) with clinical remission after 12 months of follow-up. 4 patients had a relapse during the study, only a half had a thrombocytosis. The MPV was decreased under 10 fl in 24/29 patients (82.75%) on flare at enrollment with a mean value at 9.03 fl. After 12 months, 12/23 with clinical remission (52.17%) had a MPV above 10 fl, the mean value after follow-up was around 9.37 fl. These results suggest that total platelet count was significantly increased (p = 0.02) and MPV was significantly reduced (p = 0.015) during flare compared to clinical remission.

Conclusion: Mean platelet volume declines significantly in CD on flare compared to clinical remission, while the total platelet count increases significantly. These two markers could be considered as useful markers in order to evaluate the inflammatory activity in CD.
Mucosal expression of microRNAs in pediatric patients with inflammatory bowel disease

Nóra Judit Béres¹, Zoltán Kiss¹, Dániel Szűcs², Katalin Eszter Müller¹, Áron Cseh¹, Zsófia Sztupinszki¹, Gábor Lendvai³, András Arató¹, Erna Sziksze¹,4, Ádám Vannay¹,4, Attila J. Szabó¹, Gábor Veres¹

¹1st Department of Pediatrics, Semmelweis University, Budapest, Hungary
²Department of Pediatrics and Pediatric Health Care Center, University of Szeged, Szeged, Hungary
³MTA-SE Tumor Progression Research Group, Semmelweis University, Budapest, Hungary
⁴MTA-SE Pediatrics and Nephrology Research Group, Budapest, Hungary

Introduction: MicroRNAs (miRs) came recently into focus as promising novel research targets offering new insights into the pathogenesis of inflammatory bowel diseases (IBD). Since the diagnosis of IBD is often challenging, there is a need to determine new disease biomarkers. Therefore, the aim of the present study was to identify a pediatric IBD characteristic miR profile serving as potential Crohn’s disease (CD) and ulcerative colitis (UC) specific diagnostic pattern. Our next aim was to further analyze the related target genes of the miRs to reveal their complex role in the pathomechanism of IBD.

Methods: Illumina sequencing was performed on macroscopically inflamed (CD inflamed, n = 4) and intact (CD intact, n = 4) colonic biopsies of therapy-naive children with CD and controls (C, n = 4). Selected miRs were further investigated by real-time PCR using an extended number of patients (CD inflamed, n = 15; CD intact, UC, C, n = 10). To analyze network connection of differentially expressed miRs and their target genes in pediatric IBD according to the MiRTarBase database and previous microarray data used.

Results: Sequencing analysis identified 148 miRs, dysregulated in the inflamed mucosa compared to the intact mucosa of IBD patients or controls. Twenty-two miRs were differentially expressed in the intact mucosa of CD patients compared to controls. Subsequent analysis by RT-PCR revealed differently expressed miRs which could discriminate between the inflamed mucosa of CD and UC (miR-31, -142-3p, -146 and -125a). Moreover, the expression of miR-20a, -100, -185, -204, and -221 was elevated in the intact mucosa of CD patients compared to controls, referring to the differences between the non-inflamed mucosa. The target gene screening, annotation and enrichment analysis identified several IBD-related functional groups (inflammation, fibrosis and angiogenesis).

Discussion/Conclusion: We demonstrated a characteristic colonic miR pattern in pediatric patients with IBD which could facilitate the deeper understanding of the pathomechanism of IBD.
Iron deficiency anaemia in inflammatory bowel disease – The psychological, clinical and financial impact of first line intravenous iron therapy

A.J. Boal, S.I. Squires, G.D. Naismith
Royal Alexandra and Vale of Leven Hospitals, Paisley, UK

Introduction: It is estimated that 60–80% of patients with inflammatory bowel disease (IBD) can be affected with iron deficiency anaemia¹ (IDA). 10–40% of patients can be intolerant and experience gastrointestinal side effects. European guidelines² recommend consideration of Intravenous (IV) replacement as first line treatment in patients with active IBD or intolerance to oral iron.

Our hospitals have an IBD population of approximately 2500 patients. There is no dedicated service for IV iron replacement. The impact of IV iron administration in this population was investigated. Clinical outcomes, patient perception of treatment vs. fatigue and financial implications were analysed.

Methods: 24 consecutive IBD patients with subnormal haemoglobin (Hb) with iron deficiency pattern or symptomatic with low ferritin were administered IV ferric carboxymaltose 1 g. Hb was re-checked at 4 weeks with follow up Hb and ferritin at 12 weeks. Patients completed quality of life questionnaires relating to fatigue following treatment.

Results: 24 patients were included (Crohn’s disease: n = 12, ulcerative colitis: n = 7, IBD unclassified: n = 5). 12 had active disease. Pre infusion: 19 patients had Hb < normal. Mean Hb = 104 g/dl. 20 Ferritin recorded, 19/20 < normal (20–300). Mean ferritin = 14. Post infusion: 4 week mean Hb = 119 g/dl and 12 week mean Hb = 126 g/dl. Mean ferritin at 12 weeks = 138 µg/l. Local guidelines recommend Hb ≤ 90 g/dl to transfuse, therefore 8 day-case admissions were avoided. (total = 17 units red blood cells) Total cost savings of £4000 can be demonstrated in this cohort. (day case transfusion³ vs. IV iron.) There was a 50% response rate to questionnaires, with 100% positive experience and improvement of fatigue symptoms. Average time for symptom improvement was 3 weeks. No adverse events were reported.

Discussion/Conclusion: Administration of IV iron appears safe in this IBD population. There are clear benefits with improvements in serological values, symptom improvement and quality of life. There are cost savings and potential transfusion complications are avoided.
References:


Four-year efficacy and safety of azathioprine treatment in the maintenance of steroid-free remission in inflammatory bowel disease patients

Claudio Cassieri¹, Roberta Pica¹, Eleonora Veronica Avallone¹, Giovanni Brandimarte², Maddalena Zippi¹, Pietro Crispino¹, Giusi Lecca², Claudia Corrado¹, Piero Vernia¹, Paolo Paoluzi¹, Enrico Stefano Corazziari¹

¹Internal Medicine and Medical Specialties, "Sapienza" University of Rome, Italy
²Internal Medicine, “Cristo Re” Hospital, Rome, Italy

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

Methods: Aim of this study has been to investigate its efficacy and safety in maintaining steroid-free remission in steroid dependent IBD patients four year after the institution of treatment. Data from consecutive IBD outpatients referred in our Institution, between 1985 and 2013, 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 2556 consecutive IBD outpatients, AZA was prescribed to 376 patients, 198 (52.7%) were affected by Crohn's disease (CD) and 178 (47.3%) by ulcerative colitis (UC). One hundred and four patients with a follow-up < 48 months were excluded. Two hundred and seventy-two patients were evaluated, 146 (53.7%) with CD and 126 (46.3%) with UC. One hundred and forty-nine (54.8%) were male and 123 (45.2%) female (average age of 33.56 ± 14.34 SD years, range 14–74 years). Four year after the institution of treatment, 149 (54.8%) patients still were in steroid-free remission (89 CD vs. 60 UC, 61% and 47.6%, respectively, p = 0.0288), 71 (26.1%) had a relapse requiring retreatment with steroids (42 UC vs. 29 CD, 33.4% and 19.8%, respectively, p = 0.0130), 52 (19.1%) discontinued the treatment due to side effects (28 CD vs. 24 UC, 19.2% and 19%, respectively). Loss of response from 1st to 4th year of follow-up was low, about 15%.

Discussion/Conclusion: Four year after the onset of treatment 55% of patients did not require further steroid courses. After the first year loss of response was low in three 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.
Digestive strictures complicating Crohn’s disease: Clinical and therapeutic features

M. Cheikh, I. Ben Aounallah, R. Ennaifer, H. Romdhane, W. Bougassas, H. Ben Nejma, N. Belhadj
Department of Gastro-enterology, Mongi Slim University Hospital, Tunis, Tunisia

Introduction: Intestinal stricture is a severe complication of Crohn’s disease (CD) that often leads to repeated resections. It may result from purely inflammatory, fibrotic or malignant lesions. The aim of our study was to describe clinical features and management modalities of digestive strictures complicating CD.

Methods: Retrospective study including patients with intestinal strictures complicating CD, hospitalized in our department between 2011 and 2015.

Results: Twenty-nine patients were enrolled, 19 men and 10 women. Average age was 29 years. The most frequent circumstances of discovery were Koenig syndrome in 51.3% of cases and right iliac fossa pain with fever in 17.2% of cases and 5 patients presented an authentic acute intestinal obstruction. The site of intestinal obstruction was: ileum (n = 28); anal canal (n = 2), colon (n = 1) and jejunum (n = 1). An inflammatory syndrome, anemia and severe hypoalbuminemia (< 30 g/l) were found in respectively 82.8%, 44.8% and 31% of patients. Sectional imaging showed signs of activity in 93.1% of cases and complications such as abscess in 27.6% of cases. The treatment was medical in 23 patients: corticosteroid in 21 patients and anti-TNF in only 2 patients. Thiopurines were involved in the attack treatment in 16 patients. For the rest of patients (n = 6), surgical treatment was adopted. Among patients who received medical treatment, a clinical response was achieved in 15 patients (65.2%), 2 of them had relapsed after an average period of 6.2 months and 4 patients did not respond to medical treatment. Complications occurred in 4 patients: abdominal abscess (n = 2) and acute intestinal obstruction (n = 2). Clinical response to surgical treatment was initially favorable in all patients (n = 6) and 2 patients had recurrences on the control colonoscopy at 6 postoperative months.

Conclusion: The inflammatory strictures complicating Crohn's disease is a good indication to medical treatment in the first intension in combination with other measures including smoking cessation.
Tolerance and efficacy of azathioprine in the treatment of chronic inflammatory bowel disease

M. Cheikh, S. Ayadi, H. Romdhane, R. Ennaifer, W. Bougassas, H. Ben Nejma, N. Belhadj
Department of Gastro-enterology, Mongi Slim University Hospital, Tunis, Tunisia

Introduction: The use of Azathioprine (AZA) is well established in the management of inflammatory bowel disease (IBD). AZA remains a relatively safe therapy in the majority of IBD patients. This study aimed to determine the frequency and predictive factors of adverse events secondary to AZA, and to evaluate efficacy of AZA in patients with IBD.

Methods: We conducted a retrospective study, including patients with IBD seen in our department between January 2010 and December 2015.

Results: Sixty-five patients were included, 47 CD and 18 UC. They were 33 men and 32 women. The mean age was 38 ± 13 years. Mean duration of disease was 68 months ± 79. Forty-one patients (63%) were treated with AZA. Mean dose of AZA was 2.33 mg/kg/day and mean duration of treatment was 20.7 ± 24.18 months. Indications of AZA were severe acute colitis in 12 patients, corticosteroid in 8 patients, prevention of postoperative recurrence in 10 cases, postoperative recurrence in 6 cases, extensive ileum involvement in 4 cases and severe profile disease in 4 cases. Adverse events were observed in 13 patients (31.7%), represented by digestive disorders in 4 patients, leukopenia in 6 patients, 2 patients had neutropenia and 3 patients had lymphopenia. An elevation of liver enzymes was noted in 3 cases, and was greater than 10-fold the upper normal limit in one case. Thirteen treated patients presented at least one relapse. These relapses were severe in 69% of cases. None of the following factors were correlated with the development of adverse events: age > 50 years, gender or type of IBD.

Conclusion: In our series, nearly third of patients with IBD treated with AZA developed adverse effects. AZA was ineffective in about 10% of patients.
Clinical outcomes of ulcerative colitis patients treated with 5-aminosalicylates after a first course of corticosteroids

Department of Gastroenterology, Fattouma Bourguiba Hospital, Monastir, Tunisia

Introduction: 5-Aminosalicylic acids (5-ASA) remain the first line treatment for the induction and the maintenance of remission in mild to moderate ulcerative colitis (UC). Its efficacy as a maintenance treatment after a first flare treated with corticosteroids has not been specifically studied. The aim of our study was to analyze the clinical outcomes of patients with UC treated with 5-ASA after a course of oral systemic corticosteroids and to identify predictive factors of relapse.

Methods: We studied retrospectively a cohort of UC patients admitted to our unit, who never received immunosuppressive drugs, and treated for the first time with oral corticosteroids for a flare. Among patients responding to corticosteroids, we studied the group treated by 5-ASA after the flare.

Results: A total of 65 patients with ulcerative colitis were treated with oral corticosteroids. Of these, 27 (41.5%) received oral 5-ASA. They were 49% female and 51% male with a mean age of 39 years (range: 23–56 years). The mean duration of disease was 6 years and the mean number of previous relapses before study was 3. Most of the patients presented with pancolitis (66.7%) followed by left-sided colitis (27.8%) and proctitis (5.6%). Fifteen (55%) patients treated by 5-ASA relapsed after a median period of 14 months (range: 3–36 months), 8 (29.6%) of them presented with an acute severe colitis. Thiopurines were started in 51% of subjects. Only one (3%) patient required a colectomy. No predictors of thiopurine use or colectomy were found.

Discussion/Conclusion: Approximately half of the ulcerative colitis patients responding to a first course of corticosteroids will require immunosuppressors during the course of their disease.
Risk factors for colectomy in ulcerative colitis patients with severe flare-up

Department of Gastroenterology, Fattouma Bourguiba Hospital, Monastir, Tunisia

Introduction: Surgery continues to play an important role in acute severe ulcerative colitis (ASUC). Determining risk factors predisposing to colectomy could help the clinicians to indicate surgical intervention at the appropriate time in patients with ulcerative colitis (UC). The aim of the present study was to investigate different factors which may predispose to colectomy in ASUC.

Methods: In this retrospective study, we evaluated every hospital admissions due to acute exacerbation of UC and requiring intravenous corticosteroid treatment between 2000 and 2015. Two groups of patients were individualized: those who underwent colectomy (G1) and those who avoided surgery (G2). Different parameters were compared and statistically analyzed between the two groups. P < 0.05 was considered statistically significant.

Results: Of the 105 UC patients hospitalized during the study period, 43 (41%) met the criteria of severe ulcerative colitis (44% male and 56% female; median age: 37 years). The median disease duration was 48 months. Twenty-four patients (55.4%) had pancolitis, 15 (34.8%) had left-sided colitis and 4 (9.3%) had proctitis. Overall 30.2% of the patients underwent colectomy. Patients of G1 were characterized by the following features when compared to those of G2: younger age at UC diagnosis (median age 30 years vs. 44 years, p = 0.02), more frequently pancolitis at diagnosis (44% vs. 26%, p = 0.026), with lower albumin level at admission (24.2 g/l vs. 35 g/l, p = 0.01). No difference was found between the two groups when analyzing disease duration, body mass index, extraintestinal manifestations presence and inflammatory laboratory parameters.

Discussion/Conclusion: Our results suggest that severe UC patients with younger age at diagnosis, pancolitis and hypoalbuminemia have a higher likelihood of requiring colectomy.
Cigarette smoke modulates the effect of dextran sulfate sodium (DSS)-induced colitis on subpopulation of T cells in blood and colon in mice

Jaroslaw Daniluk¹, Urszula Daniluk², Malgorzata Rusak³, Joanna Reszec⁴, Milena Dabrowska³, Andrzej Dabrowski¹
¹Department of Gastroenterology and Internal Medicine, ²Department of Pediatrics, Gastroenterology and Allergology, ³Department of Haematological Diagnostics, ⁴Department of Medical Pathomorphology, Medical University of Białystok, Poland

Introduction: Cigarette smoke (CS) induces protective anti-inflammatory effect during ulcerative colitis and improves the course of the disease. The mechanism of this phenomenon remains unknown. Recent reports showed marked increase in CD4 and CD8 colonic T cells in animal model of DSS-induced colitis. However, the effect of CS on these cells in mice with DSS-induced colitis has not been studied yet. The aim of this study was to evaluate the effect of CS on the course of intestinal inflammation and differences in complete blood count (CBC) and subpopulations of lymphocytes in blood (CD4+, CD8+, CD4+CD25+CD127- Treg, and CD4+ cells expressing IL-4, IL-13 and IFNγ) and colon (CD4+, CD8+, CD20+) in animal model of DSS-induced colitis.

Methods: C57BL6/cdmb mice were divided into 4 groups: the control group, the colitis group treated with 2.5% DSS, the cigarette smoking group and group exposed both on CS and 2.5% DSS. Mice were exposed on CS for 4 weeks using the Teague smoking exposure system reproducing human smoking habit. Colitis was induced with 2.5% DSS added in drinking water for 7 days, starting from week 4. Peripheral subpopulations of lymphocytes were assessed using flow cytometry. The intestinal infiltration by T cells was evaluated by immunohistochemistry.

Results: Comparing to control, mice exposed to CS alone demonstrated significant increase in red blood count (p = 0.007), hemoglobin level (p = 0.007) and decrease of lymphocytes count (p = 0.031) in CBC with concomitant increase of percentage of CD4+ cells (p = 0.007) and T cells producing IFNγ (p = 0.007). On the contrary, treatment with 2.5% DSS alone enhanced blood lymphocytes percentage in comparison to control (p = 0.015), but without significant differences in lymphocytes subpopulations. Interestingly, combination of CS exposure and DSS treatment, resulted in similar effect to CS exposure alone, i.e. decrease of peripheral lymphocytes count with increased percentage of CD4+ subpopulation (p = 0.007) and T cells producing IFNγ (p = 0.007) compared to mice treated with DSS alone. Histology evaluation revealed enhanced lymphocytic infiltration of submucosal and muscular layers of the intestine of CS+DSS+ mice with predominance of CD8 cells compared to other groups.

Discussion/Conclusion: Our results demonstrate that CS exposure prevented increase of peripheral lymphocyte number after DSS treatment and enhanced the percentage of CD4+ cells and T cells producing IFNγ in blood and CD8+ cells in colon. These mechanisms may be involved in protective action of smoking in ulcerative colitis, however further investigations are required.
Non-invasive markers for diagnosis and determination of the severity of Crohn’s disease in children – Preliminary study

Urszula Daniluk¹, Irena Werpachowska¹, Jaroslaw Daniluk², Joanna Maria Lotowska³, Dariusz Lebensztejn¹
¹Department of Pediatrics, Gastroenterology and Allergology, Medical University of Bialystok, Poland
²Department of Gastroenterology and Internal Medicine, Medical University of Bialystok, Poland
³Department of Medical Pathomorphology, Medical University of Bialystok, Poland

Introduction: The aim of our study was to determine the usefulness of new non-invasive markers representing gut mucosal damage (metalloproteinase-9, MMP-9) and remodeling (tissue inhibitor of metalloproteinase-1, TIMP-1), gut wall fibrosis (galectin-3) and gut wall inflammation (calprotectin) in diagnosis, and severity assessment of Crohn’s disease (CD) in children.

Methods: Serum and fecal MMP-9, TIMP-1 and Galectin-3 and fecal calprotectin concentrations were measured with ELISA in 10 children with CD and 15 controls. Disease activity was determined with pediatric Crohn’s disease activity index (PCDAI). The performance of each marker with references to serum C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) complete blood count, albumins concentration, endoscopic activity and clinical activity index was assessed by computing correlations. The cut-off levels, specificity and sensitivity were calculated using receiver operating characteristic (ROC) analysis.

Results: CD children demonstrated significantly higher levels of serum MMP-9, TIMP-1 and fecal MMP-9, TIMP-1 and calprotectin compared to controls (all p < 0.05). Among fecal markers the best discriminators for CD patients were calprotectin and MMP-9, with the area under curve (AUC) of 0.963 (95% CI: 0.884–1) for MMP-9, followed by TIMP-1 with AUC of 0.943 (95% CI: 0.774–1). The best serum marker for CD group was TIMP-1 with AUC of 0.943 (95% CI: 0.853–1), followed by MMP-9 with AUC of 0.85 (95% CI: 0.677–1) and galectin-3 with AUC of 0.718 (95% CI: 0.474–0.963) compared to controls. No association between tested markers and clinical and endoscopic activity index, and CRP or ESR was found in CD group. However, the serum level of TIMP-1 inversely correlated with albumins and MPV (p < 0.05), the known inflammatory indicators.

Discussion/Conclusion: The increased level of serum MMP-9, TIMP-1 and fecal MMP-9, TIMP-1 and calprotectin differentiate children with CD from controls. Further studies to evaluate the usefulness of these markers are required for larger group of CD patients.
Evaluation of angiogenesis in colorectal cancer associated with ulcerative colitis

Cristina Ionela Deliu, Maria Cristina Bezna, Amelia Genunche-Dumitrescu, Daniela Neagoe, Diaconu Oana, Nicusor Deliu
University of Medicine and Pharmacy of Craiova, Craiova, Romania

Patients with long-standing inflammatory bowel disease have higher risk for developing dysplasia and colorectal cancer.

Introduction: The purpose of this study was to determine the neoangiogenesis in colorectal cancer associated with ulcerative colitis with endothelial cells markers CD31, CD34 and CD105, and tried to observe the differences between these three antibodies

Methods: The study group included a total of 35 patients diagnosed from June 2008 to September 2014 with colorectal cancer and ulcerative colitis from which was taken a fragment of tumor tissue either by colonoscopy with biopsy. For immuno-location of blood vessels, fixed paraffin tissue sections were subjected to immunostaining for CD31, CD34 and CD105.

Results: Analyzing the overall results, we found CD4 values to be almost double, compared with CD31 or CD105. As for CD31 and CD105, they have similar values, but CD31 is mean values are significantly higher than CD105 values (p Student = 0.00515 < 0.05). We couldn’t find a statistically significant correlation between CD 34 and CD 31; Pearson’s correlation coefficient was $r = 0.001$, which corresponds to a $p \approx 1$. Calculating the Pearson correlation coefficient for the relationship CD31-CD105 we obtained a value $r = 0.440$, which corresponds to $p = 0.0013 < 0.05$, indicating a statistically significant direct correlation between the two factors.

Discussion/Conclusion: In conclusion the CD 31 increases in parallel with the CD105 for cases analyzed in this study. An important number of vessels (around 40%) that can be found in tumor area are neoformation vessels, fact that is an important observation for the choice of the correct and effective treatment in colorectal adenocarcinoma associated with ulcerative colitis.
Prevalence of articular disorder in patients with inflammatory bowel disease

Cristina Ionela Deliu, Maria Cristina Bezna, Amelia Genunche-Dumitrescu, Nicusor Deliu, Daniela Neagoe
University of Medicine and Pharmacy of Craiova, Craiova, Romania

Inflammatory bowel disease is the most common extraintestinal manifestation.

**Introduction**: The aim of this study was to evaluate the articular involvement present in inflammatory bowel disease, mainly in Crohn’s disease and ulcerative colitis.

**Methods**: The group of 146 patients that were monitored, consisted of two subgroups: 47 patients with Crohn’s disease, and 99 patients with ulcerative colitis and have been enrolled in a prospective longitudinal study. The patients were included in the study group according to strictly established criteria, taking into account the underlying inflammatory bowel disease that triggered the respective articular disorders, have been assessed according to a protocol including both individual parameters (clinical, biological), endoscopic, histopathologic, radiographs, RMN, CT evaluation.

**Results**: 74 patients had joint manifestations. 55 of them had developed due articular lesions in ulcerative colitis and 19 Crohn’s disease. In ulcerative colitis joint damage occurred as follows: 52.72% sacroiliitis (29 cases), ankylosing spondylitis 21.81% (12) 25.45% acute arthritis (14). In Crohn’s disease were detected: sacroiliac 26.31% (5 patients), 36.84% peripheral arthritis (7), acute arthritis 15.78% (3 cases), reactive arthritis 21.05% (4) with germs Salmonella (3) and Shigella (1). In 53 patients from those with articular manifestations of detecting the presence of HLA B27.

**Discussion/Conclusion**: Joint damage was correlated with the severity, type of inflammatory bowel disease (IBD) reflecting the state of activity. Joint manifestations were detected mainly in ulcerative colitis increased, unlike the literature.
**Frequency of adverse skin reactions in patients treated with the anti-TNF therapy**

Cristina Ionela Deliu, Maria Cristina Bezna, Amelia Genunche-Dumitrescu, Oana Diaconu, Daniela Neagoe  
University of Medicine and Pharmacy of Craiova, Craiova, Romania

Biological therapies using anti-tumor necrosis factors have represented a major advance in treatment of inflammatory bowel disease (IBD) patients in the last few years. The use of infliximab in inflammatory bowel disease has been associated with a variety of adverse skin reaction including psoriasiform eczema, eczema, xerosis cutis, palmoplantar pustulosis, psoriasis and other.

**Introduction:** The objective of our study was to investigate the frequency and characteristics of adverse skin reaction at the patients diagnosed with ulcerative colitis and Crohn’s disease treated with infliximab.

**Methods:** Forty-eight patients diagnosed with inflammatory bowel disease and received biological therapies using infliximab between January 2011 and August 2013 were enrolled in this study. The changes in their clinical manifestations after 24-months treatment were analyzed retrospectively.

**Results:** During the study period of 24 months, skin lesions associated with the use anti-TNF therapy – infliximab developed in 31 of 48 (64.5%) patients. Nineteen of this was women and twelve men. Psoriasiform eczema was the most commonly described skin manifestation 30.6%, followed by eczema, 23.5% and xerosis cutis, 10.6%; palmoplantar pustulosis, 5.3%; psoriasis, 3.8% and other, 26.1%). Lesions typically developed at flexural regions, genitalia, and the scalp, especially the psoriasiform lesions. One case of alopecia were reported after infliximab therapy. Seven patients were successfully managed without needing to stop therapy because of lesions.

**Discussion/Conclusion:** Skin lesions complicatione involve frequently in association with anti-TNF therapy but rarely require discontinuation of therapy.
The condition of the intestinal microflora in patients with ulcerative colitis combined with hepatic steatosis

L. Demeshkina, E. Zygalo, V. Didenko
State Institution "Institute of Gastroenterology of National Academy of Medical Sciences of Ukraine", Dnipropetrovsk, Ukraine

It is known that small intestinal bacterial overgrowth (SIBO), which is observed in patients with ulcerative colitis (UC) and hepatic steatosis, reduces the adaptation mechanisms of the small intestine and increases the risk of liver disorders.

The aim of the study: To identify the incidence of SIBO in patients with UC and hepatic steatosis.

Materials and methods: 29 patients with UC and hepatic steatosis were included in this study. Fibroscan examination of liver and ultrasound diagnostics were used to estimate liver state, especially the degree of fatty liver. Controlled attenuation parameter (CAP) was used for diagnosis. All patients underwent colonoscopy with biopsy for diagnosis. SIBO was identified with the hydrogen breath test with lactose (1 g lactose per 1 kg of body weight, no more than 50 g). Sampling of a patient's exhaled air was taken every 30 min for 3 hours with a cut-off of 20 ppm compared to baseline.

Results: According to Fibroscan examination of liver all patients were divided into 4 groups: S0 – 58.6% patients with CAP from 112 to 175 dB/m; S1 – 13.8% patients 175 to 197 dB/m; S2 – 13.8% patients with CAP from 197 to 244 dB/m; S3 – (13.8%) patients with CAP from 250 to 310 dB/m.

Using the hydrogen breath test SIBO was revealed in 34.5% of the patients. The average level of hydrogen evolution was increased in all patients, who had S3 (the result of Fibroscan examination), and was equal to (17.3 ± 4.2) ppm, which indicated SIBO presence. These indices after 30, 45 and 180 minutes were (18.0 ± 1.1) ppm, (16.5 ± 1.2) ppm, and (17.6 ± 3.2) ppm, correspondingly. At the same time indices of level of hydrogen evolution were statistically lower in patients without hepatic steatosis (p < 0.01): these patients had (6.1 ± 2.2) ppm, (2.2 ± 1.0) ppm, (1.1 ± 1.3) ppm, correspondingly.

It was found that lactase deficiency on the background of SIBO was observed in 75.0% of patients, who had S3 (Fibroscan result) and high content of hydrogen to (17.3 ± 4.2) ppm. One patient with S1 (Fibroscan result) had was positive test for SIBO and lactose deficiency.

Conclusion: SIBO revealed more often in patients with UC and hepatic steatosis than in patients with UC without one. Lactase deficiency on the background of SIBO was observed in 75.0% patients with S3 compared to 25.0% patients with S1.
Ulcerative proctitis patients presenting with minimal rectal bleeding may be overlooked

Aylin Demirezer Bolat¹, Huseyin Koseoglu¹, Oyku Tayfur Yurekli², Sumeyye Ulutaş¹, Fatma Ebru Akin¹, Naciye Semnur Buyukasik¹, Osman Ersoy²
¹Ankara Ataturk Research and Teaching Hospital, Gastroenterology Department
²Yıldırım Beyazıt University, Faculty of Medicine, Gastroenterology Department, Ankara, Turkey

Introduction: Patients with ulcerative colitis (UC) confined to the rectum are classified as ulcerative proctitis (UP). Patients with UP can present with minimal rectal bleeding (MRB; intermittent bleeding in the form of transfer to the toilet paper or dripping) or with overt rectal bleeding, mucus discharge, mild cramping abdominal pain and less than 4 stools per day soft consistency. UP diagnosis may be overlooked in patients presenting with MRB. The aim of this study is to compare the duration of symptoms, extent of colonic involvement and laboratory data of UP patients presenting with MRB or other complaints.

Methods: Patients laboratory, clinical data and colonoscopy reports were evaluated retrospectively. Patients were classified according to the presenting symptoms into 2 groups as MRB group and other complaints group (OCG) (significant amount of rectal bleeding, bloody defecation or bloody diarrhea, mucus discharge, abdominal pain). Patients were compared in terms of symptom duration, colonoscopic and laboratory findings.

Results: Among 378 UC patients who had been followed in our inflammatory bowel disease clinic 101 had UP (26.7%). 36 of them were male (35.6%). Among 101 UP patients 55 were classified as MRB group (54.4%). When we reviewed the colonoscopy or rectosigmoidoscopy reports of the patients with MRB UC activity was found to be prominent up to 8th cm of distance from the dentate line. Mean age of the patients were 47 ± 14.20 years. Mean white blood cell count (WBC) were 6653 ± 2291 K/ul, hemoglobin (Hb) level 14.1 ± 1.73 g/dl, sedimentation (SED) rate 15.65 ± 13.57 cm/h and CRP levels were 1.35 ± 2.74 mg/dl. There were 46 patients (45.5%) with other complaints (overt rectal bleeding and/or abdominal pain, diarrhea, tenesmus) and in these patients UC activity was found to be prominent up to 18th cm of distance from the dentate line. Mean age of these patients were 46.91 ± 14.4 years, WBC 7043 ± 2108 K/ul, Hb 13.8 ± 1.8 g/dl, sedimentation 25.4 ± 16 mm/h and CRP levels were 3.03 ± 2.32 mg/dl. There were no significant differences between the groups in terms of age, WBC and hemoglobin but sedimentation rate, CRP, duration of symptoms in months and extension of colonic involvement were significantly higher in OCG (table 1).

Discussion/Conclusion: MRB incidence were found to be 15% from studies based on patient surveys and only 15% of them admit to hospital. Hemorrhoids, anal fissures, proctitis, solitary rectal ulcer and colon cancer should be considered in differential diagnosis. UP has been reported to be between 30–50% of UC patients. Our UP ratio was 26.7% among our UC group which suggest that we might be missing some patients with UP. UP patients may either present with MRB or with overt rectal
bleeding, mucus discharge, mild cramping abdominal pain and less than 4 stools per day soft in consistency. 54.4% of our UP patients presented with MRB and these patients inflammatory disease markers were found to be significantly lower than patients in OCG. There may be significant delays in diagnosis in patients with MRB due to vague and intermittent nature of the symptoms and low levels of inflammatory markers. These patients usually undergo rectosigmoidoscopy after a few rounds of treatment for hemorrhoids. Symptom duration was significantly longer in our patients with MRB supporting this observation. Our findings remind us that patients with MRB should be examined endoscopically even at first admission and attention should be given especially to the last few centimeters of the rectum.

<table>
<thead>
<tr>
<th></th>
<th>MRB (n = 55)</th>
<th>OCG (n = 46)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>47.11 ± 14.20</td>
<td>46.91 ± 14.49</td>
<td>0.94</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>36 (65.5%)</td>
<td>32 (69.6%)</td>
<td>0.66</td>
</tr>
<tr>
<td>Symptom duration (months)</td>
<td>8.29 ± 5.5</td>
<td>4.3 ± 2.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Extent of colonic involvement (cm)</td>
<td>8.82 ± 7.43</td>
<td>18.39 ± 7.34</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>WBC</td>
<td>6653 ± 2291</td>
<td>7043 ± 2108</td>
<td>0.38</td>
</tr>
<tr>
<td>Hb</td>
<td>14.11 ± 1.73</td>
<td>13.8 ± 1.88</td>
<td>0.52</td>
</tr>
<tr>
<td>CRP</td>
<td>1.35 ± 2.74</td>
<td>3.03 ± 2.32</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sedimentation rate</td>
<td>15.65 ± 13.57</td>
<td>21.78 ± 14.64</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Adverse reactions versus benefits of anti-TNF agents in inflammatory bowel disease

Oana Mihaela Diaconu, Ana-Maria Bedelici, Cristina Deliu, Amelia Genunche-Dumitrescu
University of Medicine and Pharmacy of Craiova, Craiova, Romania

The treatment with anti-TNF agents proved to be useful long term in patients with inflammatory bowel disease because decrease the number of relapses and complications.

Introduction: The objectives of our study was to investigate the frequency and characteristics of adverse reactions at the patients diagnosed with inflammatory bowel disease (Crohn’s disease and ulcerative colitis) and treat with anti-TNF agents.

Methods: We analyzed 58 patients diagnosed with inflammatory bowel disease (Crohn’s disease and ulcerative colitis) from January 2013 to December 2014 and treated with adalimumab and infliximab. Data included age, sex, origins, diagnosis, infliximab and adalimumab therapy duration and adverse reactions.

Results: There were fifty-eight patients with inflammatory bowel disease who were treated with infliximab and adalimumab during the study period. Thirty-five had Crohn’s disease and twenty-three had ulcerative colitis. About origins 69% patients are from urban areas and 31% from rural areas. 55.2% patients received Infliximab therapy and 44.8% Adalimumab therapy. Four patients (6.9%) developed rash, swelling and pain at the injection site, two patients (3.4%) headache, seven patients (12%) increased serum liver enzymes and three patients (5.1%) hematological reactions adverse (anemia and leukopenia). Full remission was see in 38 patients (65.5%) aiming at the reduction of CDAI score and MAYO score.

Discussion/Conclusion: In inflammatory bowel disease the treatment with anti-TNF biological agents is beneficial to 65.5% of the patients. The occurrence of adverse reactions of infliximab and Adalimumab therapy imposed switching and reverse.

Adalimumab is an anti-TNF drug used to induce and maintain remission in patients with immune-mediated diseases, such as Crohn’s disease.
The prevalence of extraintestinal manifestations in patients with inflammatory bowel disease

Oana Mihaela Diaconu, Cristina Deliu, Ana-Maria Bedelici, Amelia Genunche-Dumitrescu
University of Medicine and Pharmacy of Craiova, Craiova, Romania

Osteoporosis and mucocutaneous manifestations are examples of variable extraintestinal manifestations of the inflammatory bowel disease.

Introduction: The aim of our study was to evaluate the prevalence of extraintestinal manifestations associated with patients diagnosed with inflammatory bowel disease and treated with anti-TNF agents.

Methods: We analyzed 40 patients diagnosed with inflammatory bowel disease (Crohn's disease and ulcerative colitis) from May 2013 to December 2014 and treated with adalimumab. All patients were evaluated with magnetic resonance imaging (MRI) of sacroiliac joints and dual energy X-ray absorptiometry (DEXA) scanning at neck femur and L4–L5 spine.

Results: Forty patients were analyzed, 18 had Crohn's disease and 22 had ulcerative colitis. Twenty-five percent had at least one while 20% suffered from multiple extraintestinal manifestations. Mucocutaneous manifestations, aphthous stomatitis and pyoderma gangrenosum were seen in 10% patients. None had erythema nodosum or primary sclerosing cholangitis. Fifty percent of patients had eight osteopenia and twenty-five osteoporosis on DEXA. Multivariable analysis revealed female gender, severe disease and steroid usage were significantly associated with the presence of extraintestinal manifestations.

Discussion/Conclusion: Osteoporosis and mucocutaneous manifestations occurred in a significantly higher proportion of inflammatory bowel disease patients. Female sex, severe disease and steroid usage were significantly associated with the presence of extraintestinal manifestations.
Tumor necrosis factor-α, resistin, leptin and ghrelin in ulcerative colitis

Ola El-Segai,* Hassan Elbatae,** Ayaman Wageeh,* Ghada Ismail*, Mervat Eldomery**
*Tanta University Hospital, Tanta, Egypt
**Khafr Elsheikh University Hospital, Khafr El-Sheikh, Egypt

Introduction: Adipokines could play an important role in modulating body metabolism, appetite and immune-inflammatory response, which were considered among the hallmarks of acute phase of ulcerative colitis. The present work aimed to study the serum levels of tumor necrosis factor-α (TNF-α), resistin, leptin and ghrelin in patients with ulcerative colitis to clarify their role in the inflammatory process and the associated anorexia and body weight loss in those patients.

Methods: The study was conducted on 30 patients with ulcerative colitis (UC). Patients groups included 15 patients with acute ulcerative colitis (AUC – GII), and 15 patients with chronic ulcerative colitis (CUC – GIII). In addition 15 healthy subjects served as control group (GI). Serum levels of TNF-α, resistin, leptin, and ghrelin, were measured using enzyme linked immunoassay (ELISA) technique.

Results: There is significant increase in serum level of TNF-α (pg/ml), resistin (ng/ml), and ghrelin (pg/ml) in acute ulcerative colitis (AUC) compared to control and chronic ulcerative cholitis (CUC) (12.67 ± 3.56, 20.25 ± 4.27, 24.96 ± 6.87 vs. 6.39 ± 2.03, 9.83 ± 2.62, 6.6 ± 2.9 vs. 7.56 ± 3.93, 9.89 ± 2.56, 6.27 ± 3.37; p < 0.5). There is significant decrease in serum leptin (ng/ml) in AUC patients compared to the other two groups (4.09 ± 1.95 vs. 9.79 ± 3.07 vs. 9.40 ± 2.80). There is insignificant difference between different parameters under study in CUC patient compared to control using student t test.

Discussion/Conclusion: Adipokines could play a significant role in the pathogenesis of inflammatory processes of ulcerative colitis and in the associated anorexia. Further study should be conducted to investigate the effectiveness of ghrelin as antileptin anti-inflammatory in treatment of ulcerative colitis.
Management of intra-abdominal abscesses in Crohn’s disease: A monocentric Tunisian experience

Department of Gastroenterology, Mongi Slim University Hospital, Tunis, Tunisia

Introduction: Intra-abdominal abscesses are challenging dilemma for gastroenterologists and surgeons. There are several treatment options where the role and timing of medication and surgery are conflicting.

Methods: Retrospective study including patients with Crohn’s disease admitted in our department between January 2011 and December 2015 for intra-abdominal abscess.

Results: Among 58 patients followed for Crohn’s disease, 10 had spontaneous intra-abdominal abscess. Mean age was 34 years; they were 7 men and 3 women. The abscess was associated with perforating ileocecal Crohn’s disease in all but one who had rectosigmoid fistula. The abscess was inaugural in 3 cases while Crohn’s disease was diagnosed since a mean time of 12 months [extremes: 3–36] for the others. 4 patients were on immunosuppressive therapy (corticoids, thiopurines or anti-TNF) for active luminal disease.
Tomography was the initial imaging performed. It disclosed single abscess in 7 cases and multiples abscesses in 3 cases with a mean diameter of 35 mm [extremes: 10–200]. Fistula was demonstrated in all cases associated with stenosis in 8 cases. All patients were started on intravenous antibiotic therapy during 21 days, alone in 8 cases and associated with percutaneous drainage in 2 cases. Total parenteral nutritional therapy was prescribed in 5 cases. Only one patient required immediate surgery. Patients with persistent fistula or stenosis after successful medical treatment underwent planned surgical resection, while patients with extensive ileal disease had anti-TNF therapy. No recurrence of the abscess was noted with a follow up ranging from 1 to 12 months.

Conclusion: In this small case series, management was mostly non-surgical according to the characteristics of the abscess and the availability of percutaneous drainage. Following medical therapy, surgery was required only when the disease was localized with persistent fistula or obstruction. Biotherapy are now useful when the disease is extensive.
Efficacy and safety of tumor necrosis factor antagonists in Crohn's disease: A Tunisian monocentric study

Department of Gastroenterology, Mongi Slim University Hospital, Tunis, Tunisia

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

Methods: Retrospective study including patients with CD receiving anti-TNF therapy and followed in our department between 2011 and 2015. Indication, result of therapy and adverse events were determined.

Results: We included 66 patients with CD. Eleven patients received anti-TNF therapy: 4 men and 7 women with a mean age 33.6 years [19–57]. Localization was ileocolic, colonic and ileal respectively in 9 (81.8%), one (9%) and one case (9%). The indication of anti-TNF therapy was complex anoperineal fistulas in 4 cases (36.3%), prevention of postoperative recurrence in 3 cases, intolerance to purines in two cases, a luminal form dependent to steroids in 1 case (9%) and for extraintestinal manifestation in one case. IFX was prescribed in 6 cases (54.5%) and ADA in 5 cases (45.4%). All the 6 patients who received IFX completed their induction treatment with a response in five of them (83.3%). A response to the maintenance treatment was observed in 3 of 5 patients (60%). Adverse reactions to treatment were early allergic reactions in 2 patients and tuberculosis reactivation in one case. All patients receiving ADA completed their induction treatment and had an adequate response in four cases. A response to the maintenance treatment was observed in 3 out of 4 patients (75%). The adverse effects of ADA were allergic reaction in one case.

Conclusion: In our series, results of anti-TNF-alpha therapy for Crohn's disease were similar to those reported in the literature. The main side effects were allergic reactions and infections especially tuberculosis reactivation.
Tuberculous versus Crohn's anal fistula: Diagnostic difficulties in endemic area

Department of Gastroenterology, Mongi Slim Universitary Hospital, Tunis, Tunisia

Introduction: In spite of new emerging diagnosis techniques and recent advances in the exploration, Crohn’s disease and intestinal tuberculosis are frequently misdiagnosed due to their high similarity. In tuberculosis endemic countries, careful differentiation is required. The aim of the study was to illustrate diagnosis difficulties of tuberculous versus Crohn's anal fistula.

Methods: We describe four cases of isolated anal fistula without past medical history of tuberculosis or Crohn’s disease. Clinical, laboratory, endoscopic, radiographic and pathologic features and therapeutic issue were analyzed.

Results:

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25</td>
<td>34</td>
<td>50</td>
<td>52</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Male</td>
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<tr>
<td>Presenting symptoms</td>
<td>Non-healing complex fistula with anal abscess</td>
<td>Non-healing simple perianal fistula</td>
<td>Non-healing complex fistula</td>
<td>Non-healing complex fistula</td>
</tr>
<tr>
<td>Symptoms of active tuberculosis (fever, night sweat)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Type of surgery</td>
<td>Fistulotomy</td>
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<td>Seton suture</td>
<td>Seton suture</td>
</tr>
<tr>
<td>Pathology</td>
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<td>Non-caseating granulomas</td>
<td>Non-caseating granulomas</td>
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<tr>
<td>TST</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>IGRA</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>Normal</td>
<td>Typical lesions of active tuberculosis</td>
<td>Normal</td>
<td>Normal</td>
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<tr>
<td>Colonoscopy</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
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<td>Initial diagnosis</td>
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<td>Perianal Crohn's disease</td>
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<tr>
<td>Treatment</td>
<td>Antituberculous therapy</td>
<td>Antituberculous therapy</td>
<td>Infliximab with preemptive therapy</td>
<td>Antituberculous therapy</td>
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</table>
**Results**

<table>
<thead>
<tr>
<th>Results</th>
<th>Incomplete healing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>New biopsies planned</td>
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<tr>
<td>Healing</td>
<td></td>
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<tr>
<td>Clinical deterioration</td>
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<table>
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<th>Final diagnosis</th>
<th>Perianal tuberculosis</th>
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<tbody>
<tr>
<td>Perianal tuberculosis</td>
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<tr>
<td>Crohn’s disease</td>
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</table>

<table>
<thead>
<tr>
<th>Treatment adjustment and outcome</th>
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</thead>
<tbody>
<tr>
<td>Antituberculous therapy with clinical remission</td>
<td>Infliximab with clinical remission</td>
</tr>
</tbody>
</table>

**Conclusion:** Differentiation between perianal tuberculosis and Crohn’s disease is a challenge, particularly in endemic country. Clinical pictures of both are similar and any test can distinguish between them with sufficient sensibility and sensitivity. Therefore, as in our series, we need constant re-evaluation of the diagnosis in the face of deterioration.
**Tuberculosis screening before anti-TNF-α therapy in an endemic country**

Department of Gastroenterology, Mongi Slim University Hospital, Tunis, Tunisia

**Introduction:** Screening for latent tuberculosis (LTB) is recommended before starting anti-TNF-α therapy especially in our country which is an endemic area. The aim of our study was to compare the results of interferon-gamma release assay (IGRA) and the tuberculin skin test (TST) for the screening of LTB in a population of inflammatory bowel disease (IBD) patients who were candidates for anti-TNF-α therapy and to assess the risk of tuberculosis reactivation under this treatment.

**Methods:** Retrospective study including all patients candidates to anti-TNF-α therapy and followed in our department between 2011 and 2015. We studied screening modalities for LTB before starting anti TNF therapy (search for a TB contagion, chest X-ray, TST, IGRA), indications and results of chemoprophylaxis. TST was considered positive when > 5 mm.

**Results:** A total of twelve patients were included, all of them had TST, IGRA and chest X-ray. At the moment of screening, two patients were under immunosuppressive therapy and 2 under corticosteroids. On patient had chest X-ray showing lesions suggestive of tuberculosis, considered as sequelae at tomography. Agreement between the two tests was observed in 83.4% of patients (10% +/+ , 90% -/-), IGRA+/TST- was observed in 8.3% (n = 1), and IGRA-/TST+ was observed in 8.3% (n = 1). All disagreements were observed in immunosuppressed patients. The agreement analysis showed moderate strength among the patients (p = 0.455). Patients with positive TST and/or IGRA (n = 3) were considered having LTB and received rifampicin-isoniazid chemoprophylaxis during three months. One patient with fistulizing Crohn's disease developed a pulmonary tuberculosis reactivation despite chemoprophylaxis.

**Conclusion:** In this series, screening for LTB was positive in 25% of patients candidates for anti-TNF-α. IGRA and TST showed good agreement, except for patients under immunosuppressive therapy. Chemoprophylaxis is mandatory for LTB but it does not rule the risk of reactivation, involving a rigorous follow-up during anti-TNF-α therapy.
Toxicity of thiopurines in patients with inflammatory bowel disease: Frequency and risk factors

M. Fekih, A. Labidi, L. Kallel, M. Amri, N. Ben Mustapha, J. Boubaker, M. Serghini, A. Filali
Department of Gastroenterology “A”, La Rabta Hospital, Tunis, Tunisia

Introduction: The aim of our study was to assess safety of thiopurine therapy in inflammatory bowel disease patients and to determine risk factors of adverse effects (AE) through a retrospective series.

Patients and methods: We have conducted a retrospective study including patients treated with thiopurines from 2006 to 2014. Epidemiologic, clinical and therapeutic characteristics were abstracted from medical records. Thiopurine-related (AE) were sought in each patient.

Results: We colligated 210 patients (98 males and 112 females) of mean age of 29.8 years old. One hundred sixty-nine patients (80.5%) patients had Crohn’s disease, 27 (12.9%) had ulcerative colitis and 12 (5.7%) had unclassified colitis. AZT and 6-MP were prescribed respectively in 206 (98.1%) and 19 (9%) patients. Indications for thiopurines were mainly as maintenance therapy after severe acute colitis in 79 patients (37.6%), prevention of postoperative recurrence of CD in 51 patients (24.4%) and steroid-dependent IBD in 37 patients (17.6%). During a mean follow-up period of 28.4 months, digestive intolerance (DI) of AZT was noted in 14 patients after 5 months of treatment leading to a switch to 6-MP in 10 patients. Immunoallergic reactions occurred in 8 patients (acute pancreatitis [n = 5], cutaneous rash [n = 3]). Hematologic toxicity was seen in 25 patients after 20 months (2–80) of treatment: lymphopenia (n = 19), neutropenia (n = 11), anemia (n = 15) and thrombopenia (n = 11). Six patients had hepatic toxicity: cholestasis at 3 times the upper limit of normal (ULN) resulting in a dose reduction in 3 patients. Acute hepatic cytolysis at 3 to 9 times ULN occurred in 4 patients after ruling out a viral origin. Regenerative nodular hyperplasia was seen in only 1 patient. There have been one case of acute myeloid leukemia diagnosed 3 months after AZT onset. In univariate analysis, CD patients had significantly less AE (30% vs. 70%, p = 0.008). Patients with steroid-resistance profile had less AE with trend to marginal significance (6% vs. 94%, p = 0.08). Patients who had extensive ileal involvement and who were more than 20 years old at disease onset developed (DI) less rapidly (respectively p = 0.06 and p = 0.04). Immunoallergic reactions seem to occur less commonly among patients who had been previously treated with steroids (p = 0.09).

Conclusions: Use of thiopurines in patients with IBD is overall safe. Hematologic and hepatic toxicities are the most common adverse effects. These effects seems to be less frequent in patients who were more than 20 years old at disease onset.
Comparison of severe acute colitis inaugurating inflammatory bowel disease to followed IBD complicated by SAC

M. Fekih, A. Labidi, L. Kallel, M. Hafi, M. Serghini, N. Ben Mustapha, J. Boubaker, A. Filali
Department of Gastroenterology “A”, La Rabta Hospital, Tunis, Tunisia

Introduction: Severe acute colitis occurs in 10% of patients with inflammatory bowel disease (IBD) and could inaugurate IBD in 21% of cases. In this study, we aimed to compare outcome of SAC inaugurating IBD with SAC occurring in patients treated for IBD.

Material and methods: We have conducted a retrospective chart review of patients who were admitted to hospital for severe acute colitis over 7 years. Demographics, characteristics of the disease, clinical presentation, laboratory and morphologic investigation and management were all abstracted from medical records. Patients were divided in two groups: SAC inaugurating IBD (A) and SAC occurring in IBD patients (B). Items of outcome including: response to therapy, need for colectomy and recurrence of SAC were compared between both of the groups.

Results: 62 patients were included in the study. There were 23 males and 39 females. Mean age at the onset of SAC was 36 years old (range 14–78 years old). There were 34 patients of group (A) and 28 patients of group (B). Overall, there were 28 patients with Crohn’s disease, 31 patients with UC and 3 others with undetermined colitis. There was no difference between both of the groups with regard to sex, age at the onset of SAC, smoking status, family history of IBD, body mass index and laboratory findings including full blood count and C reactive protein. Mean Truelove and Witts score was higher in group A than group B (4 vs. 3, p < 0.0001). Erythrocyte sedimentation rate was slightly higher in group A than group B (68 vs. 53, p = 0.07). Overall, endoscopic signs of severity were significantly more common in among patients from group A than group B: deep colonic ulcerations (p = 0.05) and diffuse mucosal abrasions (p = 0.04). Patients from group B seem to respond better to steroid therapy than patients from group A (68% vs. 58%, p = 0.5). There was no difference between both of the groups with regard to use of cyclosporine (p = 0.7), colectomy (p = 1) and recurrence of SAC (p = 0.7).

Conclusion: Patients with severe acute colitis inaugurating inflammatory bowel disease seem to present more severely than patients followed for IBD and complicated by SAC. However, response to therapy seems to be the same in both of the groups. Larger studies are necessary to confirm the aforementioned data.
Can we predict response to cyclosporine as second-line therapy in patients with severe acute colitis of inflammatory bowel disease?

M. Fekih, A. Labidi, M. Serghini, M. Béjaoui, J. Boubaker, L. Kallel, A. Filali
Department of Gastroenterology A, La Rabta Hospital, Tunis, Tunisia

Background: The aim of our study was to determine predictive factors for response to cyclosporine as second-line therapy in patients with severe acute colitis refractory to steroid therapy.

Methods: We conducted a retrospective study including patients admitted in our department for severe acute colitis of inflammatory bowel disease (IBD) between 2000 and 2015. Diagnosis of severe acute colitis was made on the basis of Truelove and Witts criteria. Response to cyclosporine therapy was assessed clinically and biologically after 3 and 7 days of treatment and was defined as a Lichtiger score less than 10/20.

Results: One hundred and sixteen patients were referred for severe acute colitis. Cyclosporine was administered in 40 patients after failure of intravenous steroid therapy. There were 18 males and 22 females with a mean age of 31.4 years old (17–55). There were 12 Crohn's disease cases and 28 of ulcerative colitis cases. Response to cyclosporine was obtained in 20 patients (50%). In univariate analysis, presence of mucosal bridges during initial colonoscopy (p = 0.033), absence of anterior maintenance therapy (p = 0.021) and a decrease of platelet count > 65,000/mm³ after 7 days of treatment (p = 0.013) were associated to response to cyclosporine. In multivariate analysis, presence of mucosal bridges during initial colonoscopy was independently associated with response to cyclosporine (p = 0.0001).

Conclusion: Cyclosporine is effective in preventing surgery in patients with severe steroid resistant colitis. Response rate of 50% encourages selecting candidates to this treatment with similar benefit in case of Crohn's disease or ulcerative colitis.
Smoking status and response to thiopurines in inflammatory bowel disease patients

A. Filali, N. Ben Mustapha, L. Kallel, H. Hassine, J. Boubaker, M. Serghini, J. Boubaker
Department of Gastroenterology “A”, La Rabta Hospital, Tunis, Tunisia

Aim: The aim of our study was to assess impact of smoking habits on response to thiopurine therapy in inflammatory bowel disease (IBD) patients.

Patients and methods: We conducted a retrospective study including inflammatory bowel disease patients who received thiopurines (azathioprine or mercaptopurine) from 2005 to 2015. Epidemiologic features, characteristics of the disease, indications of thiopurines and response to treatment were abstracted from medical records. Univariate analysis was conducted so as to assess impact of smoking status on response to thiopurines.

Results: We colligated 210 patients of mean age at disease diagnosis of 29.8 years. There were 98 males and 112 females. There were 169 patients having Crohn’s disease, 27 patients with ulcerative colitis and 12 patients with unclassified colitis. Indications of thiopurines were as follows: young age at disease onset (n = 20), steroid-dependence (n = 37), steroid-resistance (n = 84), extended ileal involvement (n = 28), prevention of postoperative recurrence (n = 51), severe course disease (n = 68), proximal location of the disease (n = 8) and anoperineal lesions (n = 12). There were 57 smoking patients. Maintenance of clinical remission was noted in 163 patients (77.6%) over a mean follow-up period of 34 months. Loss of response was noted in 36 patients (17.1%) and failure of the treatment occurred in 11 patients (5.2%). In univariate analysis, maintenance of clinical remission was significantly more common among non-smoking patients (85.7% vs. 72.5%, p = 0.034). Loss of response and failure of treatment were as common in smoking patients as in non-smoking patients (p = 0.57).

Conclusion: Smoking habits seem to reduce chances of maintenance of clinical remission among inflammatory bowel disease patients. However, there is not yet a clear ethiopathogenic link between both facts.
The role of the innate immune components in predicting the risk of early relapse of Crohn’s disease

A. Galushkin, L. Mamedova, G. Tarasova
Department of Propaedeutics of Internal Medicine, Rostov Medical State University, Rostov-on-Don, Russia

Introduction: Currently defined new concept of the nature of immune inflammatory process. Role of toll-like (TLR) receptors in the development of inflammatory bowel disease (IBD) is discussed. The study of TLR has a value in understanding the pathogenesis of ulcerative colitis (UC) and Crohn’s disease (CD).

Methods: We studied 38 patients with CD aged 21–70 years (38.5 ± 1.7 years). We divided patients into two groups: I – 12 patients with colon damage (31.6%), II – 26 patients with combined colon damage and small intestine (68.4%). The control group consisted of 20 healthy volunteers aged 26.2 ± 8.3 years. TLR expression on peripheral blood monocytes was determined by immunofluorescence assay with monoclonal antibodies TLR 2 (CD 282), TLR 4 (CD 284), TLR 6 (CD 286), conjugated with FITC (Hycultbio, the Netherlands).

Results: Expression of TLR 2,4,6 during relapse CD was 81.1 ± 2.4%, 12.8 ± 1.3% and 7.2 ± 0.8% respectively, in clinical remission: 56.0 ± 2.9%, 6.9 ± 1.4%, 4.1 ± 0.8% respectively. In the control group these index were 66.7 ± 0.8%, 3.7 ± 0.3% 3.4 ± 0.2% respectively. The expression of TLR 2,4,6 depending on the severity of the inflammatory process and long term morbidity revealed significant differences. We calculated the risk of relapse of CD based on the values of TLR 2,4,6 using non-linear regression. We got a table for calculating the risk of relapse of CD based on the expression TLR 2,4,6.

Discussion/Conclusion: Expression of TLR 2,4,6 represents phase severity and activity of inflammation in CD. Rise expression of TLR 2,4,6 leads to an increased risk of relapse CD. Composite increase in the expression of TLR 2,4,6 associated with the development of early relapse. Determination of the expression of TLR 2,4,6 can be used as a marker of clinical and endoscopic remission and early prediction of relapse CD.
Quality of life and late diagnosis of inflammatory bowel disease

O. Gavrilescu¹, M. Dranga¹, I. Popa¹, M. Palaghia¹, M.A. Badea¹, C. Mihai¹, C. Cljevschi Prelipcean²
¹Grigore T. Popa University of Medicine and Pharmacy, Iasi, Romania

Introduction: Accurate diagnosis of inflammatory bowel disease (IBD) can often be difficult. Delaying the diagnosis can have several negative consequences for these patients. The presence of clinical manifestations and uncertainty of a clear diagnosis can adversely affect the quality of life of patients with IBD.

The aim of this study was to assess the period between onset of symptoms and the date of certain diagnosis and to correlate this period of evaluation using quality of life scores.

Methods: We performed a prospective study, conducted over a period of 35 months (1 October 2011–30 September 2014). The study enrolled 254 patients diagnosed with IBD who addressed the Institute of Gastroenterology and Hepatology of the Hospital "St. Spiridon" Iasi. Quality of life was assessed by the IBDQ-32 (Inflammatory Bowel Disease Questionnaire – 32).

Results: In the study group, patients with ulcerative colitis (UC) had a significantly shorter period of time until a positive diagnosis was established (< 6 months), compared with Crohn disease (CD) patients (87.7% vs. 58.2%).

Among CD patients, 19.4% had a 2 year delay time period until positive diagnosis was established after the onset of symptoms (p = 0.001). In the UC subgroup the period between onset of symptoms and diagnosis date was not significantly correlated with quality of life assessment scores (p > 0.05), but in the CD subgroup of patients the period from onset of symptoms to diagnosis was significantly correlated with quality of life scores (p < 0.05).

Discussion/Conclusion: For patients with UC there were no delays in diagnosis, therefore their quality of life was not influenced by the time period between onset of symptoms and diagnosis. On the other hand, for patients with CD diagnosis was established late and the quality of life in these patients was significantly influenced by the delay in diagnosis. These results confirm that late diagnosis of IBD setting causes a negative impact on quality of life.
Anemia and quality of life in inflammatory bowel disease

O. Gavrilescu¹, I. Ungureanu¹, R. Popa¹, A. Didita¹, M. Dranga¹, C. Mihai¹, C. Cijevschi Prelipcean¹
¹Grigore T. Popa University of Medicine and Pharmacy, Iasi, Romania

Introduction: Chronic inflammation of the intestinal mucosa is the basic pathogenic mechanism in inflammatory bowel disease (IBD). Several studies have shown that intestinal inflammation can cause structural and functional changes that result in symptoms which affect the patient even after remission of the inflammatory process was obtained. The aim of the study was to assess the presence of anemia in IBD patients and to see if any type of correlation can be made using quality of life evaluation score.

Methods: We performed a prospective study conducted over a period of 35 months. The study enrolled 254 patients diagnosed with IBD who addressed the Institute of Gastroenterology and Hepatology of the Hospital "St. Spiridon" Iasi. The presence of anemia was considered according to the limits reference laboratory of the hospital "St. Spiridon" from a hemoglobin < 11 g/dl for female patients and < 13 g/dl for male patients. Quality of life was assessed by the IBDQ-32 (Inflammatory Bowel Disease Questionnaire – 32).

Results: In the study group, the presence of anemia was found to be greater among patients with CD (66.1%) compared with UC patients (52.2%). In both groups, the presence of anemia adversely affected the quality of life. Serum hemoglobin values were statistically significant and a strong positive correlation was established with the total score values IBDQ-32, even though apparently these parameters are independent (p = 0.027).

Discussion/Conclusion: The presence of anemia caused a negative influence on quality of life for both study groups. According to these results, the correction of anemia in IBD patients may result in improvement of quality of life.
The distinctive features of the therapy for induction of remission of the moderate UC in patients with HBV or HCV infection

Amelia Genunche-Dumitrescu, D. Badea, M. Badea, P. Mitrut, A. Badea, C. Deliu, O. Diaconu
University of Medicine and Pharmacy, Clinical Hospital of Emergency, Craiova, Romania

Introduction: We retrospectively assessed the efficacy and tolerability of mesalazine-budesonide combined therapy versus azathioprine in inducing remission in mild to moderate UC in patients who associated UC with HBV or HCV infection.

Methods: This retrospective study was performed, in a five years period, on 42 patients with UC: the A group composed of 17 patients who associated UC with viral B or C infection and B group consist of 25 patients without viral infection. In A group 10 patients were treated with oral mesalazine (Salofalk®, 2–3 g/day) and oral budesonide (3 mg x 3 times/day), for 6–8 weeks and 7 patients were treated with azathioprine (1–1.5 mg/kg/day). In B group 13 patients were treated with oral mesalazine and budesonide and 12 patients were treated with azathioprine. We evaluated the Powell-Tuck index and endoscopic classification at baseline, after 1, 3, 6 and 12 months. Also, we monitored the liver function tests.

Results: The distinctive features in patients with viral infection consists in the high incidences of: rectal bleeding (64.71%), diarrhea or paradoxical constipation (82.36%) and extraintestinal manifestation (58.83%). Also, they have a lower incidence of abdominal pain (35.30%) or weight loss (11.77%).

The rate of rapid response to associated treatment was higher in patients without viral infection: 60.0% in B group versus 11.77% (only two case) in the A group. The rate of clinical and colonoscopically confirmed remission after three months mesalazine-budesonide therapy was: 58.83% in A group and 52.00% in B group. Comparatively, the remission rate after azathioprine monotherapy was: 29.42% in A group and 48.0% in B group. Four patients with HBV or HCV infection (23.53%) discontinued azathioprine treatment due to leuco-trombocytopenia (one case) and increased aminotransferases levels (3 cases). We observed increases of the levels of HCV-RNA (one case) and HBV-DNA (3 cases). The diminution of the mean Powell-Tuck score at 3 and 6 months suggest a more slowly response in patients with viral infection. In a five years period after treatment we not identified a relationship between the immunosuppressive therapy in inducing or maintenance remission of UC and the development a new or recurrent cancer in patients with HBV or HCV infection.

Discussion/Conclusion: The combined therapy with budesonide and mesalazine remains the first-line therapy in patients who associate UC with HBV or HCV infection and assure a high remission rate in short term treatment in moderate UC.
The immunosuppressive therapy in induction of remission of the steroid-refractory ulcerative colitis in elderly patients

Amelia Genunche-Dumitrescu, D. Badea, M. Badea, P. Mitrut, A. Badea, C. Deliu
University of Medicine and Pharmacy, Clinical Hospital of Emergency, Craiova, Romania

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

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

Results: Most of the older patients (58.33%) present left-sided UC, 4 patients had proctitis and only one extensive colitis. In B group the localization was: left-sided UC in 11 cases and proctitis in 14 cases. The distinctive features in elderly patients consist in the high incidences of: rectal bleeding (66.66%), diarrhea or paradoxical constipation (83.33%) and extraintestinal manifestation (58.33%). Also, they have a lower incidence of abdominal pain (33.33%) or weight loss (8.33%).

Rapid response to associated treatment was observed in most young patients (60.0%) and only in one case (20.0%) in A group. Two older patients discontinued treatment with budesonide due to osteoporosis. At 3 months, the rate of clinical and 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: 57.10% in older patients and 50.0% in B group. Two patients discontinued azathioprine treatment due to leuco-trombocytopenia (A group) and increased aminotransferases levels (B group). The diminution of the mean Powell-Tuck score at 3 and 6 months compared with baseline suggest a more slowly response in elderly patients.

Discussion/Conclusion: The immunosuppressive therapy can represent a effective and safe alternative for the induction of remission in the elderly and steroid-refractory or steroid-dependent UC patients. Mesalazine associated with budesonide achieved high remission rate in short term treatment in moderate UC and assured better result in young patients.
Metabolic syndrome is also prevalent in inflammatory bowel disease

O. Gharbi¹, I. Gheribi¹, N. Ben Mustapha¹, A. Laabidi¹, M. Serghini¹, L. Kallel¹, M. Fekih¹, J. Boubaker¹, A. Filali¹
¹Department A of Gastroenterology, the Rabta Hospital, Tunis, Tunisia

Introduction: The prevalence of metabolic syndrome (MS) is constantly increasing in the adult population worldwide. However, it has not been evaluated in some categories, in fact, it is still unknown in inflammatory bowel disease. The aim of this study was to determine the prevalence of MS in a Tunisian population of inflammatory bowel disease.

Methods: We investigated all the IBD patients admitted in our department in the period between July 2015 and December 2015. We determined for each patient the body mass index (BMI) and blood pressure (BP). We performed blood samples to evaluate total cholesterol (TC) in blood, triglycerides (TG), HDL-cholesterol (HC) and fasting blood glucose (FBG). A MS was confirmed if two of the following criteria were present: BMI > 25 kg/m², BP > 13.5/8.5, CT > 2 g/l, TG > 1.5 g/l, HC < 0.5 g/l in women or 0.4 g/l in men, FBG > 1 g/l.

Results: A total of 62 patients, including 46 Crohn’s disease (CD) and 16 ulcerative colitis (UC) patients, were studied. The prevalence of MS was 40.32% of all IBD patients. In CD, it was present in 34.78% with a sex ratio of 1.28, while in UC, it was diagnosed in 56.25% of patients, with a mild female predominance (sex ratio = 0.8). The difference between CD and UC was not statistically significant (p = 0.9). The mean age of patients having a MS was 41.84 years, and for those who didn’t have it it was around 33.13 years. The presence of a MS was significantly higher in older patients (p < 0.001). We also compared the evolution of IBD between patients having or not a MS. There was no significant correlation between MS and severe course of the disease in both groups of UC and CD.

Conclusion: According to this study, the prevalence of MS is comparable between UC and CD. Furthermore, it seems to occur more in older patients, but, no impact on the course of the disease were noticed. However, our study was limited by the absence of waist size in MS criteria, and the exclusion of outpatients due to lack of information.
Mean platelet volume: A predictor of therapeutic response to azathioprine in Crohn’s disease

O. Gharbi¹, I. Gheribi¹, N. Ben Mustapha¹, A. Laabidi¹, M. Serghini¹, L. Kallel¹, M. Fekih¹, J. Boubaker¹, A. Filali¹
¹Department A of Gastroenterology, The Rabta Hospital, Tunis, Tunisia

Introduction: The mean platelet volume (MPV) has been recently considered as a useful marker of inflammation and activity in inflammatory bowel disease. The aim of this study was to correlate the MPV to the response to treatment in Crohn’s disease (CD) and its ability to predict sustained clinical remission under azathioprine (AZA) based-therapy.

Methods: We investigated 21 patients with CD enrolled during a flare and then followed up during 12 months. They were treated by azathioprine as a maintenance treatment, and MPV was determined at baseline, at 6 months and at 12 months during the study.

Results: We found a clinical remission at 12 months in 15 patients, and relapse in 6 patients. Among the subgroup of clinical remission, the MPV increased at 6 months in 12 cases with a mean difference compared to baseline estimated to 1.31 fl. The other 3 cases had a decline of 0.1 fl in the MPV.
In clinical relapse, the MPV remained unchanged in 3 patients, and decreased by 0.95 fl compared to baseline in 3 patients.
These results suggest that there was a statistically significant difference in the change of MPV from baseline to 6 months treatment of azathioprine between clinical relapse and remission (p < 0.001).

Conclusion: Mean platelet volume at 6 months of azathioprine based-therapy and change compared to baseline is a good predictor of sustained response at 12 months of treatment. Further studies on larger populations should be performed to assess its predictive role in other therapies.
Role of the neuropeptides in ulcerative colitis before treatment and in remission

Dr. Zeynep Gök Sargin¹, Prof. Dr. Nuray Erin², Prof. Dr. Bülent Yildirim², Prof. Dr. Özlem Elpek², Dr. Erhan Alkan³
¹Gazi University Medical Faculty Hospital, Ankara, Turkey  
²Akdeniz University Medical Faculty Hospital, Antalya, Turkey  
³Burdur State Hospital, Burdur, Turkey

Introduction: Ulcerative colitis (UC) is a chronic relapsing inflammatory bowel disease. Intestinal mucosa is heavily innervated with peptidergic neurons. Substance P (SP) and Calcitonin gene-related peptide (CGRP), which are largely co-expressed in sensory neurons, have dual role in mucosal healing and inflammation while VIP has anti-inflammatory effects. In this research, we tried to explain the role of SP, CGRP and VIP levels over UC pathogenesis and clarify the importance of the change after treatment.

Methods: Biopsies of involved mucosa from 74 patients with UC were obtained. Patients who underwent colonoscopy because of cancer screening and had pathology was used as control (n = 28). Biopsies were obtained from 33 of UC who were in clinical remission after treatment. Study was approved by Committee of Ethics at Faculty of Medicine, Akdeniz University, and informed consents were obtained from patients. Changes in neuronal and non-neuronal peptide levels were determined using two-step acetic acid extraction of colonic mucosa followed by ELISA.

Results: Both neuronal and non-neuronal SP levels were increased in patients after treatment. Neuronal SP levels in the inflamed mucosa of the pancolitis were repressed considering healthy tissue. Besides, only neuronal CGRP levels were increased in treated patients. Neuronal VIP levels were significantly lower in colonic mucosa of patients with UC compared to healthy control group. We also observed that VIP levels were lower in inflamed mucosa to compare non-inflamed mucosa in distal colitis. Furthermore in patients who are in remission neuronal and non-neuronal VIP levels were increased.

Discussion/Conclusion: Consequently, we found that SP, CGRP and VIP levels increased in treated patients, it is likely that these neuropeptides have protective effects in UC. Further studies are needed to clarify the role of these peptides in inflammatory bowel disease.
Tissue telomerase activity and plasma basic fibroblast growth factor as markers for early detection of dysplasia in chronic ulcerative colitis patients

*Tanta University Hospital, Tanta, Egypt  
**Khafr El-Sheikh University Hospital, Khafr El-Sheikh, Egypt  

Introduction: Ulcerative colitis is a highly premalignant condition, particularly with long duration. Screening of appropriately selected individuals at risk for colon cancer by periodic surveillance for colonic dysplasia which, is considered as premalignant marker for carcinoma, appears to be useful in detecting those lesions at an early treatable stage. The present study was carried out to investigate the validity of tissue telomerase activity and blood levels of basic fibroblast growth factor as markers for colonic dysplasia in cases of ulcerative colitis.

Methods: 55 human subjects were grouped as control group, ulcerative colitis group and ulcerative colitis with dysplasia group. Control group included 10 patients who underwent colonoscopy for investigative purpose, ulcerative colitis patients group included 33 patients and group of ulcerative colitis with dysplasia composed of 12 patients. Tissue biopsies and blood samples were taken from all patients.

Results: Tissue samples from the three studied groups showed telomerase activity. This activity was in its highest level in samples of ulcerative colitis patients with dysplasia (11.5 ± 4.2 U/µg protein compared to the corresponding activity in ulcerative colitis patients (6.4 ± 3.1 U/µg protein) and control groups (7.3 ± 2.71 U/µg protein). Plasma level of basic fibroblast growth factor (bFGF), also, showed a statistically significant higher levels only in ulcerative colitis patients with dysplasia (7.1 ± 0.8 pg/ml) compared to its level in the plasma of ulcerative colitis patients and control groups (3.1 ± 0.28 pg/ml) and (2.6 ± 0.3 pg/ml) respectively, with insignificant elevation of its level in ulcerative colitis patients.

Discussion/Conclusion: These findings suggest that tissue telomerase activity as well as plasma basic fibroblastic growth factor (bFGF) could be used as markers for early detection of the development of dysplasia in patients with ulcerative colitis.
Extraintestinal manifestations in 112 cases of inflammatory bowel disease: Prevalence, types, predisposing factors

L. Hamzaoui¹, M. Medhioub¹, O. Ghannei¹, H. Sahli², M.M. Azouz¹
¹Gastroenterology Department, ²Internal Medicine Department, Mohamed Taher Maamouri Hospital, Nabeul, Tunisia

Introduction: Extraintestinal manifestations (EIM) in inflammatory bowel disease (IBD) occur frequently and may present themselves before or after IBD diagnosis. They most commonly affect the eyes, skin, and joints, but can also involve other organs such as the liver. Some EIM are associated with intestinal disease activity and ameliorate by treatment of the underlying IBD.

Methods: Epidemiologic, clinic, therapeutic and risk factors were reported in patients with EIM associated to IBD. It was a retrospective and descriptive study including 64 patients with EIM and analytic study comparing these patients to the other 48 without MEI (period of 5 years).

Results: They were 31 man and 33 women (sex ratio 1.06) with a median age of 43.5 years (16–77 years). Ulcerative colitis (UC) was reported in 54% of cases. Most frequent EIM were osteoarticular manifestations (40.6%) and hepatobiliary lesions (26.5%). Cutaneo-mucosal and ocular manifestations were seen in respectively 11% and 9.3% of cases. Patients had peripheral arthritis in 11 cases (42.3%), axial arthritis in 9 cases (34.6%). Seventeen patients had abnormal liver tests: 5 cases of steatosis and 4 cases of primary sclerosing cholangitis. Seven patients had cutaneo-mucosal manifestations consisting in erythema nodosum. Ocular manifestations were seen in 6 patients: anterior uveitis in 5 cases and episcleritis in one case. A colorectal cancer occurred in one patient who had a PSC. No significant difference was reported between the 2 groups for the sex, body mass index, smoking and the type of IBD. Patients with EIM were younger (44.3 years vs. 36.4 years, p = 0.015), had more frequently anoperineal lesions (43% vs. 19%, p = 0.003) and an active disease. Multivariate analysis showed independent predisposing factors of EIM: family history of IBD, anoperineal lesions and an active IBD.

Discussion/Conclusion: EIM are frequent in IBD. Their prevalence was 57.1% in our serie. They were more seen in UC, in case of family history of IBD and in active disease.
Iatrogenic colorectal Kaposi sarcoma complicating a refractory ulcerative colitis in a human immunodeficiency virus-negative patient

L. Hamzaoui\textsuperscript{1}, M. Mahmoudi\textsuperscript{1}, M. Bouassida\textsuperscript{2}, E. Chelbi\textsuperscript{3}, MM. Azouz\textsuperscript{1} \\
\textsuperscript{1}Gastroenterology Department, \textsuperscript{2}General Surgery Department, \textsuperscript{3}Histopathology Department, Mohamed Taher Maamouri Hospital, Nabeul, Tunisia

Introduction: Kaposi’s sarcoma (KS) is a mesenchymal tumor, arising predominantly in the skin but which can affect any organ system. It’s associated to human herpes virus-8 (HHV8). Patients with inflammatory bowel disease (IBD), in particular ulcerative colitis (UC), are often treated with immunosuppressive therapy and can develop colorectal iatrogenic KS.

Methods: We report the case of a human immunodeficiency virus (HIV)-negative man, with a severe refractory UC, who was treated with steroids, azathioprine and infliximab (IFX). Failure of medical treatment indicated surgery.

Results: A 30-year-old heterosexual man was diagnosed with rectosigmoid ulcerative colitis (UC) since 2010. He had a 3 pack-year history of smoking (stopped 3 years ago). He was initially treated with oral and local mesalamine with a good response. In 2011 he was treated 2 times with steroids (1 mg/kg/day of prednisone) for a moderately active disease without a complete relief of diarrhea. In December 2011, he was admitted for an acute relapse. At physical exam, the patient was apyretic. His body mass index was 17 kg/m\textsuperscript{2}. Abdominal exam was normal. There was no skin lesion. Laboratory data revealed iron deficiency anemia (11 g/dl), signs of inflammation: erythrocyte sedimentation rate (ESR) 37 mm, C-reactive protein (CRP) 74 mg/l, hypoalbuminemia (25 g/l). Ileocolonoscopy showed large superficial ulcerations, spontaneous bleeding and pseudo-polyps. Histology found clear signs of active UC with no signs of malignancy. Intravenous corticosteroids (1 mg/kg/day of prednisone) and parenteral nutrition were prescribed during 1 week after failure of oral corticotherapy with initial good response. Corticosteroids were prescribed (1 mg/kg/day of prednisone) with a good initial clinical and biological responses: At week 5 of corticosteroid therapy, another relapse occurred and we had considered that it was a refractory severe UC. Medical treatment with immunomodulators was indicated. Assessment before immunosuppressive therapy was done and was normal. After improvement in health status, anemia (9 g/dl) and albumin concentration (37 g/l), azathioprine (2.5 mg/kg/day, total of 3 months of treatment) and IFX (induction regimen with 5 mg/kg, weeks 0, 2 and 6) were prescribed with unchanged disease activity. Drug failure led to a surgical treatment. A subtotal colectomy with double stomy of the ileum and of the sigmoid colon was performed. Colon macroscopic examination revealed multiple polypoid red lesions associated with a large ulcerations. Histologic examination of polypoid lesions showed a fusocellular spindle cells proliferation with a slit like vascular channels and extravased red blood cells consistent with the diagnosis of KS, associated with a typical features of UC. Immunolabelling for HHV8 stained the nuclei of the spindle cells. The patient underwent mucosal proctectomy and ileoanal anastomosis. The patient is asymptomatic three years after surgery.
Discussion/Conclusion: Although it is rare, it is important to consider a concomitant KS in patients with refractory severe ulcerative colitis, on immunosuppressor therapy, independently of HIV status.
Acute abdomen in Crohn’s disease patients: Comparative study between first diagnosed at surgery and known Crohn’s disease

Department of Gastroenterology, Habib Thameur Hospital, Tunis, Tunisia

Introduction: Crohn’s disease (CD) is a heterogeneous entity with unpredictable behavior. Bowel resection is common during the course of the disease. The aim of this study is to compare features of patients with CD first diagnosed at surgery for acute abdomen and patients who complained surgery with known CD.

Methods: We have conducted a retrospective study from January 2002 to May 2015 including patients with CD who underwent surgery for acute abdomen. They were divided into two groups: group A (GA): CD first diagnosed at surgery for acute abdomen and group B (GB): acute abdomen occurring in already known CD patients. Were assessed personal history, clinical parameters and medical/surgical treatment during the follow-up, Data were obtained by consulting the chart of each patient.

Results: We included 74 patients, 55 males and 19 females of mean age of 37 years [16–61]. CD was already diagnosed in 71.6% of cases (GB), and first diagnosed at surgery for acute abdomen in 28.4% of cases (GA). They were intestinal obstruction in 60.8%, acute peritonitis in 24.3%, and appendicitis in 14.8%. There was no statistical difference between the two groups in sex, extra intestinal manifestations, perineal involvement as well as disease location. Behavior was predominantly penetrating and/or stricturing in GA (penetrating: GA 52.4%; GB 15.1%; p = 0.0031; stricturing: GA 71.4%; GB 26.4%; p = 0.022). In GB, 67.9% of patients were taking corticosteroids where occurred acute abdomen.

Conclusion: CD first diagnosed at surgery for acute abdomen was associated with family history of inflammatory bowel disease, active smoking and penetrating and/or stricturing behavior. Acute abdomen in known CD patients was associated with corticosteroids intake.
Clinical features of elderly-onset ulcerative colitis

Department of Gastroenterology, Habib Thameur Hospital, Tunis, Tunisia

Introduction: Ulcerative colitis (UC) has a bimodal age distribution and increasingly recognized as a disease affecting the elderly. It is unclear whether elderly-onset UC is a different phenotypic subgroup, requiring different treatment strategies. Information on disease course and treatment response of elderly-onset UC patients is scarce and conflicting. Therefore, we aimed to compare disease course and treatment response between adult- and elderly-onset UC in our population.

Methods: We enrolled a retrospective study from 2004 and 2014 including patients who were hospitalized to treat first flare UC. They were divided into two groups: adult onset UC (AO): < 50 years of age at diagnosis) and elderly onset UC (EO) (> 50 years of age at diagnosis). Epidemiologic, clinical and therapeutic characteristics were abstracted from medical records.

Results: We colliged 92 patients (52 males, 40 females). Mean age was 39 years [18–69]. 21 patients were identified having EO (22.8%) and 61 having AO (66.2%). In elderly, they were males in 61.9% of cases, more left-sided disease (57.1% vs. 44.2%) and less rectal disease (23.8% vs. 36%) were observed at diagnosis. The risk of more hospitalizations, the risk of colectomy, and the risk of progression of disease extent did not differ between groups. EO patients were less likely to receive immunosuppressive or anti-TNFα treatment.

Conclusion: Elderly-onset UC behaved differently compared to adult-onset UC, reflected by a reduced use of immunosuppressive and anti-TNFα treatment, without consequent increased need for multiple hospitalizations or colectomy.
Predictive factors of postoperative morbidity and mortality in acute severe colitis

Department of Gastroenterology, Universal Hospital, Monastir, Tunisia

Introduction: Inflammatory bowel diseases are characterized by a life-long chronic course with remissions and exacerbations. Approximately 15% of patients have a severe attack during their illness. The aim of our study is to identify the predictors of postoperative morbidity and mortality in patients operated on for ASC.

Materials and methods: A retrospective study was conducted, including all patients hospitalized for ASC in our department of Gastroenterology (between 2004 and 2014). Surgical treatment was considered either because of the occurrence of complications or after the failure of second-line rescue therapy.

Results: 47 patients were included (28 women and 19 men) with a mean age of 36 years [16–81]. Surgical treatment was decided because of: The relapse of ASC and failure of maintenance therapy in 2 (4%), the severity of endoscopic lesions associated with impaired general condition in 4 cases (8%), resistance to medical treatment of first line and second line in 29 cases (62%) and 6 cases (13%), respectively, and the occurrence of surgical complications (n = 6). In the postoperative course, medical complications were observed in 29 cases (62%), the major cause was sepsis (n = 23, 49%). Surgical complications appeared in 11 cases (23%). The mortality rate was 21%. Univariate analysis showed that the only factor associated with postoperative morbidity was the presence of severe anemia requiring blood transfusion (p = 0.01, OR = 5.33, 95% CI: 1.26–22.47). Predictors of early postoperative mortality were: tachycardia (p = 0.002, OR = 0.67, 95% CI: 0.53–0.86), ESR > 30 mm (p = 0.007, OR = 0.18, 95% CI: 0.1–0.34), a severe anemia requiring blood transfusion (p = 0.032, OR = 4.86, 95% CI: 1.06–22.17), a revision surgery (p = 0.004, OR = 11.66, 95% CI: 1.73–78.43), and the occurrence of postoperative complications (p = 0.001, OR = 0.66, 95% CI: 0.51–0.85). In a multivariate analysis, it was noticed that the IBD revealed by a Severe flare (p = 0.025, OR = 10.34, 95% CI: 1.34–79.78)) and the revision surgery (p = 0.005, OR = 33.2, 95% CI: 2.95–373.22) were associated with a higher risk of mortality.

Conclusion: Patients with severe or fulminant colitis who are refractory to medical therapy or who develop disease complications (such as toxic mega colon) should be considered for colectomy. Early surgical referral in severe or refractory UC is crucial, and colectomy may be a life-saving procedure.
The economic burden and prevalence of inflammatory bowel disease (IBD) from 2010 to 2014 in Korea

Hyo Jong Kim, Chang Kyun Lee, and Sang Youl Rhee
Kyung Hee University Hospital, Seoul, Korea

Introduction: IBD poses a significant economic burden on the utilization of healthcare resources. Although the incidence and prevalence of IBD in Korea are steadily increasing, data regarding healthcare expenditures for IBD are limited. This population-based study examined the time trends of IBD-attributable healthcare costs and utilization and to estimate the nationwide prevalence of IBD in a Korean population from 2010 to 2014.

Methods: We performed a longitudinal analysis on the public dataset from the Korean National Health Insurance claims data and calculated age-standardized prevalence rates of IBD using the population census data from Statistics Korea.

Results: The nationwide prevalence rate of IBD increased from 0.085% in the general population (0.059% for ulcerative colitis [UC], 0.073% for Crohn's disease [CD]) in 2010 to 0.105% in the general population (0.069% for UC, 0.036% for CD) in 2014 (p for trend < 0.001). There was an approximately two-fold increase in the overall annual direct healthcare costs for IBD from $23.0 million in 2010 to $50 million in 2014 (p for trend < 0.001). The proportion of outpatient costs increased from 45.5% in 2010 to 66.6% in 2014 (p for trend < 0.001). The proportion of hospital inpatient days significantly declined from 26.9% in 2010 to 23.1% in 2014 (all p for trend < 0.001).

Discussion/Conclusion: This cost-of-illness study showed an increasing trend for total healthcare costs as well as prevalence of IBD in Korea. The huge increase in total healthcare costs seems to be partly attributable to increasing use of biologics for maintenance therapy. Thus, cost-effective maintenance strategies are recommended to lower the economic burden of IBD in Korea.
The clinical features of patients with newly diagnosed ulcerative colitis (UC) in Korea: A population-based inception cohort study

Hyo Jong Kim, and Chang Kyun Lee
Kyung Hee University Hospital, Seoul, Korea

Introduction: There is limited data for UC in Asia. We report first interim analysis regarding the baseline features of the patients who were enrolled during the first year of study from nationwide hospital inception cohort study in Korea.

Methods: We have prospectively enrolled patients with newly diagnosed moderate to severe UC at 30 tertiary referral hospitals since 2014, and collected clinical, epidemiologic and patient-reported outcomes data regarding health-related QOL.

Results: Of 131 patients enrolled, 128 were analyzed. Of these, 67.2% were male with a male to female ratio of 2.0. The median of age was 34.5 years; the peak age of onset of symptoms was 20–29 years (28.1%). Five patients had family history of IBD, and one patient had a history of appendectomy. The disease extent was 12.7% for E1, 39.7% for E2 and 47.6% for E3. Systemic corticosteroids as an initial treatment were used for 46.1% of patients, and their uses were associated with the disease extent (p < 0.001) and activity (p = 0.03). With respect to patient-reported outcomes, a high percentage of overall work impairment (48.5%), daily activity impairment (48.6%), anxiety (11.0%) and depression (13.3%). A clinically significant depression was more common in patients aged over 40 (23.6% vs. 5.5%, p = 0.01).

Discussion/Conclusion: The first interim analysis of the MOSAIK cohort shows a male predominance, a peak occurrence in the third decade, and a high proportion of left-sided and extensive colitis. Our data suggests that both assessment of psychosocial distress and adequate psychological support should be integrated into an initial management plan for patients with newly diagnosed moderate to severe UC.
Enhanced atherogenesis and altered high-density lipoprotein in patients with Crohn’s disease

David Janelidze, Nino Omanidze
National Medical Academy of Postgraduate Education named after P.L. Shupyk, Kiev, Ukraine

Introduction: In the last decade, it has become increasingly clear that inflammation plays a pivotal role in the pathogenesis of atherosclerosis. Inflammation can induce changes in lipoprotein metabolism. Particularly, inflammation can decrease HDL concentrations as well as qualitatively affect HDL. In several chronic inflammatory disorders, dyslipidemic changes have been linked to enhanced atherogenesis. Our study was designed to evaluate whether Crohn's disease (CD) is associated with an increased progression of the atherosclerotic process and whether inflammatory exacerbations are associated with alterations in HDL metabolism.

Methods: The aim of our study was to explore whether Crohn's disease (CD), characterized by recurrent inflammatory episodes, is also associated with accelerated atherogenesis. Ultrasound and laboratory measurement, lipoprotein composition, HDL antioxidant score and statistical analyzes were done. In 60 CD patients and 122 matched controls, carotid intima media thickness (IMT), a validated marker for the burden and progression of atherosclerosis, was assessed ultrasonographically (CIMT test). Additional subgroup analyses, including plasma levels of acute phase reactants and HDL protein profiling, were performed in 11 consecutive patients with CD in remission, 10 patients with active CD, and 15 healthy controls.

Results: Carotid IMT in patients with CD was increased compared with healthy volunteers: 0.71 (0.17) versus 0.59 (0.14) mm ($p < 0.0001$), respectively. In the subgroup analysis, HDL levels in controls and patients in remission were identical [1.45 (0.48) and 1.40 (0.46) mmol/l; $p = 0.797$], whereas HDL during exacerbation was profoundly reduced: 1.02 (0.33) ($p = 0.022$). HDL from patients with active CD and CD patients in remission was characterized by a reduced ability to attenuate oxidation compared with controls ($p = 0.008$ and $p = 0.024$ respectively). Patients with CD have increased IMT compared with matched controls, indicative of accelerated atherogenesis.

Discussion/Conclusion: In the current analysis, we show that CD is associated with an acceleration of the atherosclerotic process, as illustrated by an increased carotid IMT in CD patients compared with healthy controls. In addition, CD patients were characterized during an inflammatory exacerbation by profoundly decreased levels of HDL combined with biochemical changes of the HDL particle. These data suggest that early detection of atherosclerosis and subsequent cardiovascular prevention in patients with CD might be warranted.
Latent TB in IBD patients receiving anti-TNF therapy

M. Jelaković1, D. Baričević1, M. Brinar1, D. Gržinić1, A. Kunović1, R. Prijić1, N. Turk1, Ž. Krznarić1,2, B. Vucelić1,2, S. Čuković-Čavka1,2
1University Hospital Center, Zagreb, Croatia
2School of Medicine, University of Zagreb, Croatia

Introduction: Tumor necrosis factor (TNF)-α inhibitors increase the risk of tuberculosis (TB) reactivation. The objective was to evaluate the effectiveness of chemoprophylaxis (ChP) for tuberculosis (TB) in IBD patients receiving anti-TNF therapy who tested positive on QuantiFERON TB Gold test (QFT-G).

Methods: This is a retrospective observational study on IBD patients receiving anti-TNF therapy in a single IBD referral center. We recorded the test results of QFT-G testing and the rate of TB reactivation in patients who received isoniazid ChP.

Results: From June 2009 to July 2015 a total of 137 IBD patients underwent anti-TNF therapy. Eight out of 137 (5.84%) patients had a latent TB infection, 3 males and 5 females. Five (62.5%) patients received infliximab and three (37.5%) received adalimumab. Four (50%) patients were on concomitant immunosuppressive therapy with azathioprine. Their mean duration of anti-TNF therapy was 14 (14.25 ± 9.42) months. All of them received isoniazid ChP for a mean period of 6 (5.75 ± 1.58) months. During the mean follow-up period of 20 (20.75 ± 16.01) months we have not identified a single case of active TB among these patients.

Discussion/Conclusion: Based on our results we can conclude that the ChP of TB is effective in QFT-G positive patients which is in concordance with other similar studies. One patient who initially tested negative for latent TB infection, later developed an active TB meaning that despite of latent TB screening with QFT-G, the risk of developing active TB infection persists. It is very important to monitor patients on biologics very closely.
FXR-mediated induces expression of miR29a3p in colonic epithelial cells: Implications for therapy of inflammatory bowel disease

Stephen J. Keely, Aoife M. O’Dwyer
Molecular Medicine Laboratories, Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin 9, Ireland

Background: Inflammatory bowel disease (IBD) is a group of disorders that affects the GI tract and results in chronic intestinal inflammation. Although the etiology of IBD is not yet fully understood, it is thought to arise due to dysregulated epithelial barrier function in genetically susceptible individuals. MiRNAs are small, single stranded RNA molecules that regulate gene expression. The colonic epithelium of IBD patients has a unique miRNA expression profile, indicating the involvement of these endogenous molecules in disease pathogenesis. FXR is a nuclear bile acid receptor, activation of which has been shown to alleviate symptoms in animal models of colitis by preserving the integrity of the epithelial barrier. The aim of this study was to investigate the effect of the FXR agonist, GW4064 on the miRNA expression profile of colonic epithelial cells.

Methods: Isolated colonic crypts and T84 colonic epithelial cells, were treated with GW4064 [5 µM] for 6 hrs. Use of human tissue was approved by the Beaumont Hospital Ethics Committee. RNA was extracted and miRNA profiling was performed by Nanostring Technologies. nCount software was used to detect miRNAs that were up- or down-regulated 1.5-fold or more compared to control. TargetScan was used to identify miRNA targets.

Results: FXR activation increased expression of miR 29a3p by 3.9 ± 0.8 fold (n = 4; p < 0.05). miR 29a3p is predicted to target PTEN, a pro-apoptotic protein, with a 92% context score as ascertained by TargetScan. Treatment of colonic epithelial monolayers with GW4064 resulted in decreased PTEN mRNA (n = 8; p < 0.05) and decreased PTEN protein levels (n = 3; p < 0.05).

Conclusion: By virtue of its ability to increase expression of miR29a3p and reduce expression of its target PTEN, our data suggest that FXR agonists may promote epithelial barrier function by inhibiting apoptosis-induced epithelial cell death. Such actions may contribute to the beneficial effects that have been previously reported for FXR agonists in animal models and patients with IBD. We conclude that drugs which activate the FXR may represent a new avenue for therapeutic development in IBD.
Inflammatory bowel disease patients’ group with hepatobiliary manifestation. Results of 5-year experience

Nataliia Kharchenko, Igor Lopukh, David Janelidze
National Medical Academy of Postgraduate Education named after P. L. Shupyk, Kiev, Ukraine

Introduction: Diseases of the liver and biliary tract are common extraintestinal manifestations of inflammatory bowel disease (IBD). The most commonly associated liver and biliary diseases with IBD are: cholelithiasis, non-alcoholic steatohepatitis (NASH) primary sclerosing cholangitis (PSC), autoimmune hepatitis (AIH) and primary biliary cirrhosis (PBC).

Methods: We offer the results of 351 IBD patients (including both ulcerative colitis [UC] and Crohn’s disease [CD]) during last 5 years in Kyiv. Hepatobiliary manifestation was observed in 101 (28.77%) cases. Clinical, biochemical, serological, instrumental and histological methods of investigation were used for diagnosis.

Results:

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<th>Patients with IBD (n = 351)</th>
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<td></td>
<td>UC (n = 266)</td>
<td>CD (n = 85)</td>
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<td>Female (n)</td>
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<td>PSC</td>
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<td>AIH</td>
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<td>PBC</td>
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The liver enzymes transient increase was observed in 205 patients (58.4%) during the exacerbation of the disease and was correlated with the severity of episodes. During the period of follow-up, 30 patients (8.55%) performed cholecystectomy, 2 patients (0.57%) with PSC was diagnosed colorectal cancer and was performed a colectomy, in 5 patients (1.42%) was observed cirrhosis and they were put on a waiting list for transplantation.

Discussion/Conclusion: Liver damage is one of the most common extra intestinal manifestations of IBD. It worsens the severity of the disease, quality of life and prognosis of survival. The most common liver pathology in case of IBD patients is NASH. It highlights the importance of liver function test in subjects with IBD and they should be more closely observed for liver and biliary complications.
Management of intra-abdominal collections complicating Crohn's disease: Experience of a Tunisian center

A. Khsiba, M. Fekih, M. Hafi, I. Ghribi, J. Boubaker, L. Kallel, A. Filali
Department of Gastroenterology “A”, La Rabta Hospital, Tunis, Tunisia

Introduction: Intra-abdominal collections represent a fairly common complication during Crohn’s disease (CD). They can be of poor prognosis, especially since they can occur in malnourished patients or ones under immunosuppressive therapy. They can also be a diagnostic problem in case of atypical clinical presentation and represent a treatment challenge given that their care is not yet codified. The aim of our study was to evaluate the intra-abdominal collections support through a single-center study.

Materials and methods: This is a retrospective study that included all patients managed for an intra-abdominal abscess complicating Crohn's disease in our department. We excluded from the study intra-abdominal abscesses that occurred in the postoperative (30 days) of abdominal surgery for Crohn's disease, pelvic abscesses, perineal abscesses, liver and splenic abscesses.

Results: We included 65 patients: 35 women and 30 men, average age 28.6 years. Intra-abdominal collection was discovered per operatively in 11 patients (17%). For other patients: 54 (83%), abdominal pain associated with fever, was the most frequent presentation. In radiological assessment, intra-abdominal abscesses were sitting at the right iliac fossa in 36 patients (66.6%), at the left iliac fossa in 5 patients (9.2%) at the psoas muscle in 10 patients (18.5%) and hypogastric level in 3 patients (5.5%). The abscess was single in 48 patients (89%) and the average size was 3.4 cm (1.5–14 cm). Internal fistulas were observed in 21 patients (39%).

Three therapeutic methods have been used for the treatment of abscesses. Exclusive antibiotic therapy was prescribed in 31 patients with an initial success rate of 51.6% with a gain of 28.4% after extension or modification of antibiotic therapy (80%). Radiological drainage of the abscess was performed in 11 patients with a success rate of 72%. Surgical drainage was selected for 12 patients with a success rate of 50%. Only a size greater than 5 cm was a factor associated with the failure of the initial treatment.

Surgical treatment of Crohn's disease consisted of intestinal resection in 34 patients and a medical treatment with azathioprine in 4 patients. At follow-up, recurrence of the abscess was observed in 6 patients. Factors associated with recurrence of the abscess were age at diagnosis of abscess less than 25 years (p = 0.001), an initial polynuclear neutrophils rate higher than 8000/mm³ (p = 0.018), platelet rate at baseline greater than 600,000/mm³ (p = 0.0002), an initial hemoglobin less than 10.25 g/dl (p = 0.038) and the non-use of bowel resection (p < 0.0001).

Conclusion: Intra-abdominal abscesses are a frequent complication in Crohn’s disease. Non-surgical treatment (exclusive antibiotics or radiological drainage) has 72% efficiency in the treatment of abscesses. The use of elective surgery carrying the sick intestinal segment after the disappearance of the abscess is a predictor of the absence of recurrence of this complication.
MicroRNA expression in the colonic mucosa of pediatric patients with eosinophilic colitis in comparison with Crohn’s disease

Zoltan Kiss1, Nóra Judit Béres1, Erna Sziksz1,2, Ádám Vannay1,2, András Arató1, Katalin Eszter Müller1, Áron Cseh1, Attila J. Szabó1,2, Gábor Veres1
11st Department of Pediatrics, Semmelweis University, Budapest, Hungary
2MTA-SE Pediatrics and Nephrology Research Group, Budapest, Hungary

Introduction: Allergic/eosinophilic colitis (EC) is a common cause of hematochezia in infants and young children. The disease pathomechanism is not well understood. Noninvasive tests are unavailable, and the diagnosis can be difficult in severe cases having overlapping features with Crohn’s disease (CD). The primary aim of the present study was to test whether a set of microRNAs (miRs) having major roles in the posttranscriptional regulation in pediatric CD is dysregulated also in EC, in order to find potential biomarkers. The secondary aim was to analyze the expression of different miRs suggested to be relevant in eosinophilic esophagitis (EOE) to assess the similarities in the epigenetic factors.

Methods: Real-time reverse transcription PCR was carried out on fresh-frozen biopsy specimen from young children with EC (n = 14) and control patients (n = 10). Bioinformatics analysis was used to compare the results with publicly available miR profile data of pediatric CD and EoE patients and to retrieve potential miR-target interactions.

Results: Expression of miR-17, -18a, -20a, -21, -99b, -184, -216a, -221, and -223 was elevated in the colonic mucosa of children with EC compared to controls. However the expression of miR-150 and -559 showed decreased expression in the EC group. MiR-20a, -125a, -126, -142 changes were opposite in EC than measured in CD. Amongst the previously reported miRs in EoE miR- 20a, -21, -223, -221 expression changes were similar in EC, whereas miR-126 and -142 showed an opposite change compared to EoE. Bioinformatics analysis of EC-related miR-target interactions revealed functional groups connected to inflammation, leukocyte activation, leukocyte trafficking and the regulation of apoptosis.

Discussion/Conclusion: Differentially dysregulated miRs in EC and CD may serve as early potential biomarkers in severe form of EC. Several miRs reported to be relevant in EoE were dysregulated also in EC patients, suggesting similar epigenetic elements in the pathomechanism.
One year experience in treating patients with severe ulcerative colitis with biosimilar (infliximab) – Remsima®

Asiyana Koleva, Miglena Stamboliyska, Iskren Kotzev, Angel Angelov
Clinic of Gastroenterology, Hepatology and Nutrition, St. Marina University Hospital of Varna, Varna, Bulgaria

Introduction: Biosimilar versions of infliximab (Remsima®) showed clinical efficiency and immunogenicity similar to infliximab in the treatment of ulcerative colitis. In Bulgaria was approved the treatment with biosimilar infliximab (Remsima®) from 2014 (July). We have set ourselves the task to investigate the efficacy and safety of infliximab biosimilar (Remsima®) in patients with severe ulcerative colitis.

Methods: Over a period of one year in Clinic of Gastroenterology of University Hospital “St. Marina” seven patients with severe ulcerative colitis were treated: four women and three men middle-aged-39, with a starting total Mayo score between 11 and 12. Five of the patients were naive (anti-TNF) and two had previous treatment with another anti-TNF drug and had no clinical response. Efficiency criterion: clinical response, clinical remission (corticosteroid free remission) mucosal healing, level of fecal calprotectin and CRP, and quality of life (by IBD-questionnaire) was observed on week 6, 14 and 24. The dose of Remsima® 5 mg/kg body weight with induction at 0, 2 and 6 weeks, and maintenance treatment of 8 weeks.

Results: All patients had an early clinical response at week 6 and very good improvement (decrease number of defecation and without blood stool) at the week 2. At week 14 there is a clinical remission in 4 of 7 patients (57%) At week 24 there is a clinical remission in 6 of 7 patients (86%). Completed mucosal healing (Mayo score = 0) in 3 of the patients at week 52 was established. The level of CRP was decreased of average 57 mg/l at week 14. Side effects were observed in one female patient, assessed as mild, such as headache, dizziness, hair loss. These side effects did not lead to discontinuing the treatment. A good clinical response at week 6 and clinical remission was achieved in both patients with previous treatment with anti-TNF agent. After the treatment carried out, the patients had improved quality of life.

Discussion/Conclusion: Our primary results with infliximab biosimilar (Remsima®) showed a very good efficiency to the achievement of clinical remission (corticosteroid-free remission) in induction period in the treatment of patients with severe ulcerative colitis. It is well tolerated with rare and mild side effects.
Our experience with the application of biosimilar infliximab to IBD patients

M. Konečný
2nd Internal Clinic of Gastroenterology and Hepatology, Olomouc University Hospital, Olomouc, Czech Republic

Introduction: Biological therapy (BT) represents a major breakthrough in the treatment of the most severe forms of inflammatory bowel disease (IBD). Besides the original molecules, copies of them have been developed, i.e. biologically similar (biosimilar) drugs.

Methods: The aim of this study is to present the current positive experience, which has been gained over a period of two years, with the application of biosimilar IFX as a form of BT IBD. From January 2014, we began BT administration of biosimilar IFX to eleven BT-naive patients, seven men and four women with an average age of 31.9 and with more severe forms of IBD, namely Crohn's disease in nine cases (the inflammatory type in six cases and the fistulizing type in three cases) and ulcerative colitis in two cases (pancolitis and the sinistral type). All the patients responded to the induction therapy by remission of their intestinal inflammation and proceeded to maintenance therapy.

Results: So far IFX has been applied 128 times to the eleven patients, always at a dosage of 5 mg/kg of personal weight. We noticed side effects (headache, paresthesia of the limbs) only in ten cases of IFX administration. Upon deceleration of the infusion complete reconstitution occurred in all cases. The whole group of patients is currently still in clinical, laboratory, and endoscopic remission.

Discussion/Conclusion: On the basis of our experience so far with a small group of patients, we can conclude that, in the case of a correct indication and proper monitoring of the patients, the administration of biosimilar IFX to patients with IBD is an effective and safe treatment.
Significance of serological markers in the disease course of ulcerative colitis

Gyorgy Kovacs, M.D.¹, Nora Sipeki, M.D.¹, Karoly Palatka, M.D., Ph.D.¹, Istvan Altorjay, M.D., D.Sc.¹, Kai Fechner, Ph.D.², Gary L. Norman, Ph.D.³, Zakera Shums, M.Sc.³, Gabor Veres, M.D., D.Sc.⁴, Peter Laszlo Lakatos, M.D., D.Sc.⁵, Maria Papp, M.D., Ph.D.¹

¹Department of Internal Medicine, Division of Gastroenterology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary
²Institute of Experimental Immunology, Euroimmun AG, Luebeck, Germany
³Inova Diagnostics, Inc., San Diego, CA 92673, USA
⁴1st Department of Pediatrics, Semmelweis University, Budapest, Hungary
⁵1st Department of Medicine, Semmelweis University, Budapest, Hungary

Background and aim: Data are few and conflicting regarding the association of serological markers to the disease behavior, medical treatment and response to therapy in patients with ulcerative colitis (UC). We aimed to determine the prognostic potential of serological antibodies regarding long-term disease course of an adult prospective UC patient cohort. The association between serological markers and requirements for immunosuppressant or anti-TNF therapy was also evaluated.

Patients and methods: One hundred and eighty-seven consecutive patients (male: 46.0%, median age: 40 years, extensive colitis: 33.3%) were studied from a single referral IBD center. Sera were tested for a panel of different IgA/IgG type autoantibodies (anti-neutrophil cytoplasmic [ANCA], anti-lactoferrin [aLFS], anti-goblet cell and anti-pancreatic [anti-GP2 and anti-CUZD1] antibodies) by IIFT and for anti-microbial antibodies (ASCA IgG/IgA and anti-OMPPlusTM IgA) by ELISA. Clinical data were available on unfavorable disease outcome as well as disease activity and medical treatment during the prospective follow-up (median: 104 months).

Results: A total of 73.6%, 62.4% and 11.2% of UC patients were positive for IgA/IgG type of pANCA, aLFS and anti-goblet cell antibodies, respectively. Both type of anti-pancreatic antibody occurred in 9% of the patients, while ASCA and anti-OMP in 17.7% and 19.8%. Serological antibody status was stable over time. There was no significant association between antibody positivity and gender, age at onset or disease extent. Presence of certain antibodies was negatively associated to the occurrence of extraintestinal manifestations: aLFS IgA/IgG to current smoking status (OR = 0.26, p = 0.01) and ocular disease (OR = 0.16, p < 0.01), while pANCA IgA/IgG to the arthritis (OR = 0.36, p = 0.026). During the follow-up period, UC-related hospitalization occurred in 34.2% and requirement for colectomy was 3.7%. Exposure to steroids, azathioprine or anti-TNFs was 77.0%, 37.4% and 13.4%, respectively. IgA type ASCA and anti-CUZD1 antibody but not other serological markers were associated to an increased likelihood of requirements for immunosuppressant in Kaplan-Meier analysis (pLogRank < 0.01 for both), however only ASCA IgA was identified as an independent predictor in multivariate Cox-regression model (HR = 2.74, 95% CI: 1.46–5.14,
p < 0.01) comprising age at onset, gender, disease extent as covariates. At the same time, clinical factors, such as extensive colitis and male gender were exclusively associated with UC related hospitalization, HR = 1.8 (95% CI: 1.09–2.95, p = 0.019) and HR = 6.7 (95% CI: 1.6–27.9, p < 0.01), respectively.

**Conclusion:** Present prospective study displays limited role of serologic markers in the prediction of disease course in UC.
Predictive factors for severe Crohn’s disease. Results of a Tunisian survey

M. Labbane, K. Torjmane, S. Zarrouk, Y. Bouteraa, S. Ouerdiane
Department of Gastro-enterology, Menzel Bourguiba Hospital, Bizerta, Tunisia

Background: Severe Crohn’s disease (CD) may be defined as stricturing or fistulating disease, disease requiring surgery secondary to CD complications and disease requiring immunosuppression with anti-TNF-α inhibitors and purine analogue therapy for maintenance of remission. The aim of this study was to determine the risk factors related to severe CD in Tunisian patients.

Methods: Retrospective study including patients seen in our department for CD. We defined severe CD as the development of penetrating or stricturing disease, need for surgery or patients requiring immunosuppressive therapy. Demographic characteristics, smoking, family history of CD, disease location, hemoglobin and C-reactive protein were analyzed. Statistical analysis was performed using SPSS version 19. A p-value of less than 0.05 was considered statistically significant.

Results: Forty patients were recruited, 22 men (55%) and 18 women (45%). The mean age was 32.8 ± 10.5 years (12–58). Fifteen patients (37.5%) had non-stricturing, non-penetrating disease, 12 patients (30%) had stricturing disease, 13 patients (32.5%) had penetrating disease and 3 patients (7.5%) had anoperineal fistulas. Fifteen patients (37.5%) underwent bowel surgery because of CD complications. Immunosuppression with azathioprine and infliximab was required respectively in 17 (42.5%) and 4 (10%) patients. A statistically significant correlation was observed between severe CD and smoking (p = 0.04), high level of C-reactive protein (p = 0.03), ileocolonic location (p = 0.04). Young age was associated with an increased risk of requiring immunosuppression with anti-TNF-α but this association was not statistically significant. There was no correlation between gender, family history of CD, hemoglobin and severe CD.

Conclusion: In this study, smoking, ileocolonic location and high level of C-reactive protein are markers of severe CD. Smoking is a modifyable environmental agent and smoking cessation should be actively encouraged.
Natural history of non-severe inflammatory bowel disease at onset

M. Labbane, S. Zarrouk, K. Torjmane, Y. Bouteraa, S. Ouerdiane
Department of Gastro-enterology, Menzel Bourguiba Hospital, Bizerta, Tunisia

**Background:** Inflammatory bowel diseases (IBD) are progressive diseases characterized by the occurrence of complications requiring immunomodulators and surgery. Few data are available for the prevalence and the factors associated with long-term non-severe (NS) Crohn’s disease (CD) and ulcerative colitis (UC). Our aim was to assess the natural history of NS IBD at diagnosis and to identify predictive factors of mild evolution over the long term.

**Methods:** A retrospective study including the IBD patients seen in our department. NS CD was defined as the absence of stricturing, penetrating or perianal disease, no treatment with immunomodulators and anti-TNF, no need for surgery in the course of the disease. NS UC was defined as no requirement for immunomodulators, anti-TNF and colectomy. Patients were assessed at 1 year and at the maximum follow-up. Patients with less than one year of follow-up were excluded.

**Results:** Among 56 patients, a subgroup of 14 CD and 9 UC were included with a mean follow-up of 4.7 and 6.8 years respectively. One year after the diagnosis, 78.6% of CD patients had NS CD. At the maximum follow-up 57.1% of patients still had NS CD. Complications were strictures (7.1%), fistulizing disease (14.2%), perianal disease (7.1%). Immunomodulators were required in 35.7% of patients. Prognostic factors for persistent NS CD were older age at diagnosis and no corticosteroid during the first year. In UC, 8 patients (88.9%) had NS disease one year after the diagnosis. Five patients (55.6%) had NS UC at the maximum follow-up. No patient required surgery. Immunomodulators were needed in 3 patients (33.3%). Statistical analysis did not found predictive factors for persistent NS UC.

**Conclusion:** In our series, nearly the half of CD patients and UC with NS disease at diagnosis became severe with time. Old age at diagnosis and absence of steroid use during the first year was associated with NS CD outcome.
High-resolution anorectal manometry in IBD patients: A pilot study

Agata Ladic, Nadan Rustemovic, Jelena Skunca, Silvija Cukovic-Cavka
Department of Gastroenterology and Hepatology, University Hospital Center, Zagreb, Croatia

Introduction: High-resolution anorectal manometry (HRAM) offers a unique, reliable and comfortable measurement of anorectal function. In inflammatory bowel disease (IBD) patients, anorectal manometry is usually performed prior to ileal pouch surgery – in order to evaluate the strength and tone of anal sphincter. The aim of our study was to evaluate whether HRAM measurements differ between IBD and other patients.

Methods: Ten patients underwent HRAM procedure. Reusable solid state HRAM catheter (MMS, the Netherlands) with 8 circumferential pressures and one balloon pressure was used. Following tests were analyzed: resting pressure, squeeze pressure, rectal sensations (first sensation, defecation desire and maximal tolerable volume) and RAIR. The comparisons between groups were analyzed with a two-sample t-test, with a significance set at p < 0.5. The statistical package “R” was used for the analysis.

Results: 10 patients were included in the study (6 F, 4 M). Five of them were IBD patients (3 MC, 2 UC), the other five patients entered for some other medical condition. The mean age of the study population was 50.1 years. There was no statistically significant difference in pressure values between the groups: p = 0.955, p = 0.9161 – for resting and squeeze pressures, respectively. Rectal sensations didn’t show difference either: p = 0.1876, p = 0.1881 and p = 0.422 for the first sensation, defecation desire and maximally tolerable volume, respectively. RAIR test was negative in two IBD patients, but didn’t reach statistically significant difference (p = 0.6541).

Discussion/Conclusion: Our results with the HRAM solid state catheter show that there is no difference in anorectal function between IBD and other patients. Considering the fact that we had a very small number of patients, as well as that normative values on solid state catheter still have to be standardized, results might not be sufficient. However, we believe that HRAM offers a very acceptable, quick and patient-friendly approach, contrary to conventional manometry. This is very important for IBD patients who are often subjected to painful and long endoscopic procedures.
Bile acids regulate intestinal epithelial restitution: Implications for pathogenesis and therapy of IBD

Natalia Katarzyna Lajczak¹, Magdalena Mroz¹, Vinciane Saint-Criq¹, Stephen Keely¹
¹Molecular Medicine, Royal College of Surgeons in Ireland, Dublin, Ireland

Introduction: Epithelial restitution is an essential process for maintenance of intestinal barrier function. Increased levels of colonic bile acids have been proposed to be involved in the pathogenesis of inflammatory bowel disease (IBD) but their roles in regulating restitution are not yet known. Here, we investigated the effects of bile acids on epithelial restitution and molecular pathways involved in colonic epithelial healing.

Methods: T84 colonic epithelial cells, grown as monolayers on transparent permeable supports, were wounded by scratching with a pipette tip at T = 0. Cells were treated with either the most abundant colonic bile acid, deoxycholic acid (DCA; 150 μM), the “therapeutic” bile acid, ursodeoxycholic acid (UDCA; 100 μM), a farnesoid X receptor (FXR) agonist, GW4064 (5 μM), or a cystic fibrosis transmembrane conductance regulator (CFTR) channel blocker, CFTR(inh)-172 (10 μM). Restitution was measured as wound area after 48 h expressed as % T = 0 wound area. HEK-293 cells were transfected with vector expressing luciferase gene under control of the CFTR promoter and vectors expressing FXR. Protein expression was assessed by western blotting and cell migration by Boyden chamber assay.

Results: After 48 h post-wounding, wound closure in untreated cells was 63.3 ± 13.5% of that at T = 0, while in cells treated with DCA (150 μM) it was reduced to 24.5 ± 13.1% (n = 5; p < 0.001), whereas UDCA enhanced healing to 88 ± 4 (n = 5; p < 0.001). Furthermore, UDCA prevented inhibition of wound closure by DCA. The effects of DCA are mediated via a decrease in cell migration to 0.7 ± 0.1 fold (n = 5, p < 0.05) of that in untreated controls, rather than inhibition of cell growth. Furthermore, DCA decreased cell surface CFTR expression to 23 ± 5% of controls (n = 3, p < 0.001), while a CFTR inhibitor, CFTR(inh)-172 (10 μM), attenuated wound closure to 37 ± 2% (n = 5; p < 0.01), compared to control. Moreover, DCA decreased CFTR promoter activity, in a concentration-dependent manner that was also dependent on co-expression of FXR. Finally, GW4064 (5 μM), an agonist of FXR, mimicked DCA effects on wound healing and CFTR expression.

Discussion/Conclusion: Our data suggest that colonic bile acids differentially regulate intestinal epithelial restitution and that UDCA promotes healing and protects against the detrimental effects of DCA. Thus, manipulation of the colonic bile acid pool may prove to be a useful approach for promoting intestinal barrier function in IBD.
Involvement of PARK7 in the pathomechanism of inflammatory bowel diseases

Rita Lippai¹, Erna Sziksz¹,², Domonkos Pap¹,², Réka Rokonay¹, Apor Veres-Székely¹,², Andrea Fekete³, Attila J. Szabó¹,², Ádám Vannay¹,²
¹1st Department of Pediatrics, Semmelweis University, Budapest, Hungary
²MTA-SE, Pediatrics and Nephrology Research Group, Budapest, Hungary
³MTA-SE, Lendulet Diabetes Research Group, Budapest, Hungary

Introduction: The incidence of inflammatory bowel disease (IBD), including Crohn’s disease (CD) and ulcerative colitis (UC) is almost doubled during the last two decades. Recently, the immunoregulatory, antioxidant role of Parkinson’s disease 7 (PARK7) was suggested, however its role in the pathogenesis of IBD is completely unknown.

Methods: mRNA expression, protein level and localization of PARK7 were determined in colon biopsies of children with IBD, in colon of wild type and IL-17 KO mice with dextran sodium sulphate (DSS)-induced colitis and in IL-17-treated HT-29 colonic epithelial cells by real-time PCR, western blot, flow cytometry and immunofluorescence staining, respectively.

Results: The expression of PARK7 increased in the colonic mucosa of children with IBD, and in the colon of wild type mice with DSS-induced colitis. The expression of PARK7 remained unchanged in DSS treated IL-17KO mice. IL-17 treatment of colon epithelial cells increased the amount of PARK7 in vitro.

Discussion/Conclusion: Increased expression of PARK7 in the mucosa of children with IBD suggests its involvement in the disease pathogenesis. Our data also suggest that IL-17 is an important inducer of PARK7 production in the colon. Although further studies are needed to elucidate the exact role of PARK7 in IBD, our results suggest that it may be an important element of the IL-17 mediated signalling in IBD.

Support: OTKA PD105361, -K108688, -K116928, LP2011-008
Ileal inflammation at the resection margin may be predictive for increased risk of postoperative Crohn’s disease recurrence over a 10 year follow-up

Lucy Lynch, Iain Hay, Eliana Saffouri, Annette Riley, Raj Burgul, David Watts
Gastrointestinal Unit, Forth Valley Royal Hospital, Larbert, Scotland, UK

Introduction: Crohn’s disease recurrence following ileocolonic resection is a well recognised clinical complication of surgical management. The ideal therapeutic strategy for preventing recurrent Crohn’s postoperatively is widely debated. Many studies have reported conflicting data with regard to the preventive efficacy of immunosuppressive therapy and as such there is no accepted standard of postoperative treatment. Identifying specific risk factors for postoperative disease recurrence may allow an opportunity to treat high risk patients effectively. Ileal inflammation at the surgical resection margin may be such a risk factor for disease recurrence but there is little published data to support this.

Methods: A retrospective review of ileal marginal histologic inflammatory activity was undertaken for all ileocolonic resections for Crohn’s disease in Forth Valley from 2005–2012. This data was then correlated to radiological and endoscopic outcomes in this patient cohort. Chi-squared statistical analysis undertaken across the groups with no marginal disease against those with evidence of marginal disease activity.

Results: 91 patients were identified to have undertaken ileocolonic resection for Crohn’s between 2005–12. Of those with no marginal disease (n = 70) 59% went onto have colonoscopic reassessment and 36% were shown to active ileal disease compared to the positive ileal marginal disease group (n = 21) in whom colonoscopic reassessment was required in 76% with 52% exhibiting ileal disease recurrence (p = 0.17). MR enterography (MRE) was undertaken in 43% of the negative marginal group with 24% demonstrating features of ileal disease compared to the positive marginal disease group (52% reassessed by MRE) in whom 38% had radiological signs of ileal activity (p = 0.21). The combined recurrence data for both endoscopic and radiographic disease (table 1) yields a recurrence rate of 62% (13/21) in the positive marginal cohort against 40% (28/70) in the negative marginal group (p = 0.07).

Table 1

<table>
<thead>
<tr>
<th>P 0.07</th>
<th>No recurrence</th>
<th>Recurrence</th>
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</thead>
<tbody>
<tr>
<td>Negative margin</td>
<td>42</td>
<td>28</td>
</tr>
<tr>
<td>Positive margin</td>
<td>8</td>
<td>13</td>
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</tbody>
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Discussion/Conclusion: This study confirms that the rate of postoperative disease recurrence is higher in those patients with inflammatory disease activity at the ileal resection margin at index surgery (follow up 3–10 years). This difference in relapse rates between the two groups approaches statistical significance where disease recurrence is defined by evidence of inflammation at either/both postoperative MRE and colonoscopy.

Validation by larger studies is required but may allow the identification of a new cohort of Crohn’s patients with a higher risk of postoperative disease relapse in whom targeted immunomodulatory therapy might be justified.
Early diagnosis of malignancy of colon polyps

S.M. Mamatkulov, B.S. Navruzov, S.T. Rakhmanov
Research Center of Coloproctology, Tashkent, Uzbekistan

Introduction: Despite significant medical advances, with high frequency occurs diffuse polyposis of the colon (DPTK). In this paper I would like to emphasize not only the urgency of the polypoid process, but also affect one of the possible complications of the disease – desmoid fibroma (DF).

Material and methods: A retrospective analysis of 120 patients treated with at DPTK showed that 6 (5%) patients had DF. Of these, two (1.7%) patients Fs were detect before the operation. These patients have been taken drastic intervention. Biopsy showed in all cases the presence of DF. Dynamic observation for 1 (0.8%) patients after the first operation in 10 months were found dense painless formation of the anterior abdominal wall in the line the area of postoperative scar and around. In 2 (1.7%) patients after a multi-stage surgery for recurrence of the cancer process, and histologically found no evidence of cellular atypia and polymorphism, mitotic activity in the DF. 5 (4.2%) patients with DF in 4 (3.3%), they were located in the mesentery card rectosigmoid colon. In 1 (0.8%) patient DF is localized on the terminal part of the mesentery of the small intestine. Despite the huge size of the tumor, 1 (0.8%) patients refused surgery.

Conclusion: Thus, desmoid fibroma of the abdominal wall in patients with diffuse polyposis of the colon is a serious postoperative complications. In most cases, they appear after surgery for malignancy polyposis or cancer on the background of familial adenomatous polyposis. This proves once again the need for radical intervention to malignancy polypous formations colon.
Determination serum lactoferrin concentration as a way assess treatment of ulcerative colitis

L. Mamedova, G.N. Tarasova, A. Galushkin
Department of Propaedeutics of Internal Medicine, Rostov Medical State University, Rostov-on-Don, Russia

Introduction: An important component of innate immunity is lactoferrin (LF). LF is endogenous antimicrobial peptide, which is considered as a highly sensitive and specific diagnostic marker of inflammatory activity and treatment efficacy of inflammatory bowel disease (IBD) and tumors of the colon.

Methods: 86 patients with UC (49 – women 37 – men) were investigated. The mean age was 39.0 ± 1.4 years. The control group consisted of 20 healthy volunteers (15 – women 5 – men) aged 26.2 ± 8.3 years. 39 patients achieved clinical and endoscopic remission at the end of the study. Serum LF was determined by ELISA. Statistical analysis of the data was performed using the computer program “STATISTICA 8.0” (StatSoft, USA).

Results: We identified an increase in the concentration of serum LF in patients with UC. Concentration of LF in patients with relapse of UC was more in the 7 times (p < 0.05) compared with the control group (2748.6 ± 194.7 ng /ml). Concentration of LF in patients with remission of UC was 686 ± 211.5 ng/ml and was more in the 1.7 times (p > 0.05) compared with the control group (382.9 ± 29.5 ng/ml). Statistical analysis revealed correlation dependence between concentration of LF and the severity, extent, duration of the inflammatory process.

Discussion/Conclusion: Dynamic estimation of the concentration of serum LF in the can present as an additional indication for assessing the severity of ulcerative colitis and evaluate the effectiveness of therapy, and is a composite marker of disease remission.
Decreased fibrogenesis in CH25H⁻/⁻ mice in a newly developed mouse model of intestinal fibrosis

Tina Raselli, Annika Wyss, Céline Mamie, Gerhard Rogler, Martin Hausmann, Benjamin Misselwitz
University Hospital Zurich, Zurich, Switzerland

Introduction: Crohn's disease (CD) is a chronic immune-mediated inflammatory condition of the gastrointestinal tract. Intestinal stenosis and fibrosis are common complications of CD. Oxysterols are oxidized derivatives of cholesterol and have recently been recognized as immune-modulators and chemoattractants. Cholesterol 25-hydroxylase (CH25H) mediates enzymatic conversion of cholesterol to 25-hydroxycholesterol (25-HC), which was shown to modulate immune responses and oxidative stress. In vitro analysis of human fetal lung fibroblasts demonstrated 25-HC to be able to promote alpha-smooth muscle antigen expression and collagen production, augment the release of matrix metallopeptidase 2 and 9 and stimulate transforming growth factor-beta release. We are aiming to characterize the role of CH25H in the development of intestinal fibrosis.

Methods: Small bowel resections from donor mice, either wildtype or CH25H knockout littermate mice, were transplanted subcutaneously into the neck of a recipient mouse of the same genotype. 7 days after surgery the intestinal grafts were isolated and examined for collagen layer thickness and mRNA expression of fibrosis mediators.

Results: In our in vivo fibrosis model, mice deficient for the CH25H enzyme developed a significantly thinner collagen layer compared to wildtype littermates (10.73 ± 1.37 vs. 14.22 ± 1.26 μm, respectively, p < 0.001). Reduced collagen deposition in CH25H⁻/⁻ animals was confirmed by automated microscopy quantification of total collagen content. mRNA expression of fibrosis mediators including lysyl oxidase-like 2, collagen type 1 and type 3 was decreased in CH25H⁻/⁻ mice compared to wildtype littermates as confirmed by qPCR.

Discussion/Conclusion: Our findings suggest an involvement of CH25H in the development of intestinal fibrosis. CH25H deficiency partially prevented development of fibrosis, pointing to oxysterols as a potential new treatment option for CD associated fibrosis. Further mechanistic and therapeutic studies will be necessary to develop this option.
Ulcerative colitis patient with complicated interstitial cystitis

Viktorija Mokricka\(^1,3\), Polina Zalizko\(^1,2\), Juris Pokrotnieks\(^1,4\), Kaspars Snippe\(^5\), Janis Vilmanis\(^6\), Aldis Pukitis\(^1,3\)

\(^1\)Gastroenterology, Hepatology and Nutrition Center, Pauls Stradins Clinical University Hospital, Riga, Latvia
\(^2\)Internal Medicine Residency, University of Latvia
\(^3\)Department of Internal Medicine, University of Latvia
\(^4\)Department of Internal Medicine, Riga Stradiņš University, Riga, Latvia
\(^5\)First City Hospital, Surgeon, Riga, Latvia
\(^6\)Department of Surgery, Pauls Stradins Clinical University Hospital, Riga, Latvia

Introduction: Interstitial cystitis (IC) is a rare disease with an autoimmune nature. Association of IC with other autoimmune diseases prevalence in general population is around 0.07%, where 2.3% of the patients with classic IC had either ulcerative colitis (UC) or Crohn's disease. Our aim was to demonstrate a rare clinical case of a patient with UC and complicate IC, application of combined treatment and outcome.

Methods: This is a prospective observational review of a 36 years old female with UC who had been diagnosed IC.

Results: A 36-year-old female, who had UC since age 21. For regular treatment she had sulfasalazine 3 g/daily. Last relapse (Mayo 4) she had in the January 2015. She went to hospital for i/v iron administration due to chronic iron deficiency anemia. She had complaints of lower abdominal pain, dysuria and hematuria. Abdominal ultrasound revealed signs of cystitis. Ciprofloxacin 0.4 g daily (4 days) had no effect; complains worsen, CT urography established signs of cystitis with bladder wall thickness up to 2 cm, bilateral urotrastis. Piperacillin/tazobactam 4.5 g/daily was initiated. Concomitant skin infection of the anterior abdominal wall (hyperemia, tightness and edema) was diagnosed. 5 days treatment was not effective and changed to vancomycin 2 g and meropenem 3 g/daily. Blood microflora was negative, urine Enterococcus was present. Skin symptoms improved, UC activity – Mayo 2. Control CT showed edema and circularly thickened bladder. Transurethral resection (TUR) revealed bladder wall necrosis with destruction. Objective clinical status of the patient did not improved (dominated abdominal pain symptoms). Abdominal exploratory surgery was performed. Multiple abscess drainage, excision of necrotic tissue, and V.A.C. system were placed. One month after surgery the patient was discharged from the hospital (UC activity Mayo 2), continued sulfasalazine 3 g/daily, Hb was normal, the abdominal MR showed positive healing dynamics and revascularization features.

Conclusions: Association of UC and interstitial cystitis is uncommon combination of autoimmune diseases. Our case report showed infectious complications and efficacy of combined treatment; antimicrobials and surgical intervention.
The choice of treatment the patients with ulcerative colitis

B.S. Navruzov, S.T. Rahmanov
Research Center of Coloproctology, Tashkent, Uzbekistan

**Introduction:** The choice of tactics of treatment is one of the problems in patients with ulcerative colitis. Actual rational ulcerative colitis patient’s treatment tasks the following problems: to mix the sharp attack of illness, to avert recurrence, to determine indications to surgical treatment.

**Methods:** Conservative treatment was received by 156 patients. Among patients received conservative treatment remittent current was marked in 41.7% cases, intermittent – in 58.3%. It’s necessary to note that we used sulfanilamide and aminosalicylic medicines as basis therapy. As drug containing mesalazine used Salofalk®.

**Results:** Efficiency marks of conservative treatment carried out by various parameters. Analysis shows, that by intermittent current the effectiveness of conservative therapy marked in 93.6% patients against 64.8% by remittent current of inflammatory ulcerative process.

Patients were divided into 2 groups by the type of used medicine. I-group were 74 (43.9%) patients, who used Salofalk®. II-group were 82 (56.1%) patients, who used only sulfanilamide preparations.

Comparative analysis of the results of treatment of this patients show, that on application of Salofalk® good results are marked at 92.2% of patients. As opposed to I-group, II-group get the best results in 78.0% of cases, but in 22.0% of cases therapy based on this preparations was unsuccessful.

**Conclusion:** Thereby, Salofalk® completely correspond to actual scientific representations about adequate medicamentous therapy of chronic inflammatory diseases of thick gut, which allow us to avoid of glucocorticosteroids application in the treatment of distal form ulcerative colitis.
The problem of the treatment of severe ulcerative colitis

B.S. Navruzov, S.T. Rakhmanov
Republican Scientific Center of Coloproctology, Tashkent, Uzbekistan

Introduction: Severe ulcerative colitis is more common than others form.

Materials and methods: Material research were 187 patients, of whom 146 (78.1%) patients with severe forms of ulcerative colitis. In our opinion the choice of treatment for severe ulcerative colitis is surgery, as active-progressive course of inflammatory and ulcerative process in the colon rather quickly leads to the development of intestinal and extraintestinal complications. And the use of anti-ulcer conservative therapy in such cases does not give the desired result, and increases the risk of perforation and peritonitis. We have the following types of operations: total colproctectomy with the formation of an end ileostomy – in 86 (58.9%), total colproctectomy with the formation of the pouch-anal anastomosis – in 45 (30.8%) patients, the formation of preventive ileostomy – in 15 (10.3%).

Results: In most cases, the results assessed as good and satisfactory (87.6%) and 12.4% of the cases the results were unsatisfactory, since these patients had post-operative complications – anastomosis failure, purulent complications sepsis. Mortality was not observed.

Conclusion: In most cases, the choice of treatment of severe ulcerative colitis is surgery. The surgical procedure depends on study data and condition of the patient.
Mucosal healing in ulcerative colitis

Department of Gastroenterology, Habib Thameur Hospital, Tunis, Tunisia

Introduction: In recent years, after the emergence of biologic therapies for ulcerative colitis (UC), the old concept of endoscopic activity of disease has been translated into the new concept of mucosal healing (MH) as the therapeutic goal to achieve. This is partially the consequence of growing evidence of a positive prognostic role of MH on the disease course. However, an excessive adherence to the MH could lead to the over-prescription of unnecessary endoscopic examinations and/or the overtreatment of patients.

We aimed to determine the prevalence of mucosal healing in UC and to analyze its impact on the outcome of the disease.

Methods: A total of 116 patients with UC, evaluated between 2002 and 2014, were enrolled. The diagnosis of UC was based on standard clinical, endoscopic and histological criteria. Mucosa healing was defined as the complete resolution of the visible alterations or lesions, irrespective of their severity and/or type at baseline colonoscopy. Patient characteristics, disease extent according to Montreal classification, clinical, endoscopic and histological activity, as well as severity of the disease were recorded.

Results: According to Montreal classification, a majority of patients had extensive colitis (48 cases), 27 had left-sided colitis and 41 had only proctitis. Moreover, 75 patients (64.6%) had mild to moderate UC and 41 (35.4%) had severe UC. Clinical remission was obtained in 91 patients (78.4%). Endoscopic remission was observed in 36 patients (31%) within 3 months in 75%. Histological remission was noted in only 9 patients (25%). A relapse was observed in 39.6% within an average follow-up of 50 months. The flare was moderate in all cases. Patients with a histological remission didn’t have a relapse whereas 50% of patients with only endoscopic remission relapsed. No patient resorted to surgical treatment, likewise no case of colorectal cancer was observed.

Discussion/Conclusion: Due to the important risk of relapse in this study, endoscopic remission is mandatory before considering any maintenance treatment. Moreover, only histological remission was associated with a change in the natural history of UC raising the prominent role of the concept of histological MH.
New therapeutic approach in ulcerative colitis: Fecal microbiota transplantation

K. Ozturk, A. Uygun, H. Demirci, C. Oger, I. Avci
Gulhane School of Medicine, Ankara, Turkey

Aim: In recent years, several clinical studies suggested that dysbiosis can play an important role in development and progression of inflammatory bowel disease. To date, researchers showed in case reports and clinical studies that fecal microbiota transplantation (FMT) is improved the clinical, laboratory, and histologic findings of inflammatory bowel disease. We aimed to investigate the efficiency of FMT in patients with refractory ulcerative colitis (UC) in this study.

Method: Sixteen patients with UC were enrolled in this prospective, uncontrolled single-center study. Inclusion criteria for FMT were follow as: age > 18 years, currently active disease (Mayo score ≥ 4), and failure of all therapeutic options such as mesalamine, steroid, azathioprine, and anti-TNF. Patients who have malignancy, infection, pregnancy, and immunosuppression were excluded. All patients underwent a baseline screening colonoscopy to confirm their diagnosis of UC prior to undergoing FMT. All donors were chosen from apparently healthy volunteers and screened for viral markers and pathogen stool microorganisms. Donor stool was diluted with 0.9% saline and administered to 30–40 cm proximal from ileocecal junction. Immunomodulator therapies was stopped in all patients with UC after FMT.

Results: FMT was administered two times in two patients with UC and one time in remaining patients. Clinical remission was observed throughout three months in 3 patients with UC. Clinical response rates for remaining patients with UC as analyzed stool frequency, the number of rectal bleeding, endoscopic improvement of mucosal lesions was 60% at 3 months. We did not see clinical worsening in the study population. No patients experienced any adverse events throughout 3 months after FMT.

Conclusion: FMT is an effective and safe treatment options for UC patients who did not respond to either thiopurines or tumor necrosis factor inhibitors. This findings are preliminary results of an ongoing study investigating the effect of FMT on UC. ClinicalTrials.gov Number: NCT02575040.
Factors associated with anxiety and depression in Korean IBD patients

Dong Il Park
Department of Internal Medicine, Kangbuk Samsung Hospital Sungkyunkwan University, Seoul, Korea

Introduction: Psychological distress is highly prevalent in patients with inflammatory bowel disease (IBD). However, most studies on this topic have been conducted exclusively in Western countries. The aim of this study was to evaluate the disease characteristics and socioeconomic factors associated with anxiety and depression in Korean patients with IBD in the remission state.

Methods: From July 2013 to December 2013, 142 patients with IBD who were regularly evaluated at a single tertiary academic medical center completed self-report questionnaires, including the Hospital Anxiety and Depression Scores, Modified Morisky Adherence Scale-8, socioeconomic deprivation score, and the Crohn’s and Colitis Knowledge Score questionnaires.

Results: A total of 142 IBD patients [67 with Crohn’s disease (CD), 75 with ulcerative colitis (UC)] were enrolled. In the CD group, 30 patients (44%) were anxious and 10 patients (15%) were depressed and in the UC group, 31 patients (41%) were anxious and 18 patients (24%) were depressed. Using multivariate analysis on data from the CD patients, the factor found to be associated with anxiety was socioeconomic deprivation [odds ratio (OR) = 3.95, 95% CI: 1.14–13.67, p = 0.030] and the factors associated with depression were disease duration (OR = 1.24, 95% CI: 1.01–1.53, p = 0.040) and socioeconomic deprivation (OR = 8.22, 95% CI: 1.57–43.03, p = 0.013). In the UC group, there was no significant independent predictor of anxiety and/or depression, however, low income tended to be associated with depression (OR = 2.78, 95% CI: 0.83–9.32, p = 0.096).

Discussion/Conclusion: Despite clinical remission, a significant number of IBD patients present with anxiety and/or depressive symptoms. IBD patients in remission, particularly those that are especially deprived, should be provided with appropriate psychological support.
Comparing the clinical outcomes between young-onset and adult-onset ulcerative colitis: A multicenter KASID study

Dong Il Park
Department of Internal Medicine, Kangbuk Samsung Hospital Sungkyunkwan University, Seoul, Korea

Introduction: The aim of this study was to compare the clinical features and outcomes of ulcerative colitis (UC) according to the age of onset in Korea.

Methods: A total of 1,141 patients who were diagnosed with UC between July 1987 and November 2013 at 11 tertiary hospitals were enrolled. The baseline disease characteristics and treatment regimens were retrospectively reviewed among patients with young-onset (YO < 20 years) and adult-onset (AO ≥ 20 years) UC. Patients were characterized as having severe outcomes based on the use of IV steroids, infliximab, immunosuppressants or having undergone UC-related surgeries.

Results: There were 55 YO (mean age 17.8 ± 2.4; male 52.7%) patients and 1086 AO patients (mean age 43.0 ± 13.6; male 56.7%). Smoking and BMI ≥ 23 kg/m2 were less frequent in the YO group than they were in the AO group (5.6% vs. 25.3%, p = 0.000; 12.7% vs. 41.1%, p = 0.000, respectively). The Mayo scores (7.7 ± 3.0 vs. 5.6 ± 2.7, p = 0.000) and prevalence of extensive UC (52.7% vs. 25.8%, p = 0.000) were more frequent in the YO group than they were in the AO group. There were no significant differences between the two groups with regard to the frequency of UC-related admissions, surgeries or oral steroid use. However, there was more IV steroid (41.8% vs. 18.0%, p = 0.000), immunosuppressant (47.3% vs. 26.9%, p = 0.002) and infliximab (20.0% vs. 7.2%, p = 0.001) use in the YO than there was in the AO group. According to multivariate analysis, severe outcomes were related to YO disease (HR = 2.18, 95% CI: 1.27–3.71, p = 0.040), lower BMI (HR = 1.46, 95% CI: 1.07–2.00, p = 0.018), severe (HR = 2.29, 95% CI: 1.36–3.38, p = 0.002) and moderate (HR = 2.48, 95% CI: 1.67–3.67, p = 0.000) disease status, extensive UC (HR = 2.90, 95% CI: 1.79–4.69, p = 0.000), UC-related admissions (HR = 63.89, 95% CI: 20.41–200.02, p = 0.000), and oral steroid use (HR = 0.51, 95% CI: 0.39–0.67, p = 0.000).

Discussion/Conclusion: Young-onset ulcerative colitis produces more advanced clinical features at diagnosis and more severe outcomes than does adult-onset disease. Therefore, YO cases require careful and strategic management.
Early change in faecal calprotectin predicts primary non-response to anti-TNFα therapy in Crohn’s disease

Polychronis Pavlidis¹, Shraddha Gulati¹, Patrick Dubois¹, Guy Chung-Faye¹, Roy Sherwood², Ingvar Bjarnason¹, Bu’Hussain Hayee¹
¹Department of Gastroenterology, ²Department of Biochemistry, Viapath Laboratory, King’s College Hospital, Denmark Hill, SE5 9RS, London, UK

Introduction: The early identification of primary non-response to anti-TNFα therapy facilitates the timely management of patients with Crohn’s disease (CD). A recent, pilot study to detect prognostic markers of early response to anti-TNFα therapy identified the two genes coding for the calprotectin subunits (S100A8, S100A9) to be among the most highly expressed gene transcripts in non-responders. This study tests the hypothesis that measurements of faecal calprotectin (FCAL) pre- and post- anti-TNFα induction can predict primary non-response.

Methods: This is a retrospective cohort study of 32 CD patients treated in one centre. FCAL was tested before anti-TNFα commencement and at 6–8 weeks post induction for adalimumab or 8–10 weeks for infliximab, as per departmental clinical protocol. Outcomes were assessed at 6 months based on clinical activity scores and the use of corticosteroids: (a) Remission: Harvey Bradshaw Index (HBI) < 5, off corticosteroids > 2 months; (b) Response: drop in HBI > 3, off corticosteroids; (c) non-response. ∆FCAL (and ∆CRP respectively) was calculated as (FCALpost induction – FCALpre induction)*100/FCAL pre induction.

Results: At 6 months, 23 (72%) patients had responded [median (range) HBI: 4 (1–10), FCAL: 55 (10–1696)], 17 (73%) of whom were in remission [HBI: 3 (1–4) and FCAL: 42 (10–171)]. There was a significant difference in the ∆FCAL from baseline to post-induction in the three groups (p < 0.0001). Comparing non-responders to combined response and remission groups, the AUC of ∆FCAL to predict outcome at 6 months was 0.97. Using ROC analysis, a ∆70% returned a sensitivity and specificity of 99% and 96%, respectively (likelihood ratio, LR = 23). ∆CRP did not predict 6 month outcomes.

Discussion/Conclusion: A drop in FCAL < 70% after induction predicts primary non-response to anti-TNFα in CD.
The efficacy and tolerability of azathioprine therapy in inflammatory bowel disease patients

Kristina Pavloska¹, Maja Slaninka Miceska¹, Igor Kikerkov¹, Emilija Atanasovska¹, Vladimir Avramovski³, Ljudmila Efremovska², Petranka Mishevska³
¹Department of Preclinical and Clinical Pharmacology and Toxicology, Medical Faculty, Skopje, Macedonia
²Institute of Physiology, Medical Faculty, Skopje, Macedonia
³Gastroenterohepatology Clinic, Medical Faculty, Skopje, Macedonia

Introduction: Azathioprine (AZA) as an immunomodulator drug is very often used as a treatment option in patients with inflammatory bowel disease (IBD).

Methods: The aim of this study was to observe the efficacy and tolerability of azathioprine in patients with IBD. 63 patients with IBD were observed in the study, 45 with Crohn’s disease and 18 with ulcerative colitis from the Gastroenterohepatology clinic at the Medical faculty in Skopje, Macedonia. The patients were followed in a period of one year.

Results: Adverse effects occurred in 17% of the patients. The main side effects were: increased α-amylase in serum, bone marrow suppression, aphthous ulcer, pancreatitis and hepatic impairment. In 14 patients (22%) azathioprine was premature precluded during the time duration of this study as a result of gastrointestinal intolerance, hepatic impairment, pancreatitis, α-amylase increased and “NO” effect.

Using the Crohn’s disease activity Index (CDAI) and the ulcerative colitis activity Index (UCAI) for assessing the acute and remission phase in the patients receiving AZA, the results have shown that 39 patients (61%) had achieved remission and 24 of the patients (38%) were still in the active phase of the disease during the duration of this study. None of the patient that had received AZA less than 3 months had achieved remission.

Discussion/Conclusion: AZA is effective in the treatment of inflammatory bowel disease patients. AZA seems to be safe, but blood monitoring schedule is suggested. More studies are needed to evaluate the efficacy and safety of AZA in the treatment of inflammatory bowel disease patients.
Extensive pustular pyoderma gangraenosum: The rare skin extraintestinal manifestation of ulcerative colitis. A case report

Cvetka Pernat Drobež¹, Grujica Vujnović², Pij Bogomir Marko³
¹,²Clinical Department for Gastroenterology, University Clinical Center, Maribor, Slovenia
³Department for Dermatology, University Clinical Center, Maribor, Slovenia

Introduction: Pyoderma gangraenosum (PG) is a rare skin manifestation of inflammatory bowel disease (IBD). In IBD patients PG is associated with inflammation of the large bowel, the form and disease activity play a minor role.

Case report: A 23-year-old woman was diagnosed by ulcerative colitis (UC) in 2012. Last relapse was on February 2015 with abdominal pain and bloody diarrhea 10 times daily. Rectosigmoidoscopy confirmed the severe inflammation (UCEIS SCORE 8). CMV colitis and infective colitis were excluded. Methylprednisolone in dose 0.5 mg/kg was started. On the day 8 she developed ulcerative blepharitis and painful pustules on the pubic and axillary area, on the face, scalp, arms and legs, which in few days deteriorated into painful ulcerations. Patient deteriorated with general debilitation, abdominal pains, 20 bloody diarrhea daily and severe pain around skin alterations. Biopsy of the skin revealed intensive inflammatory with numerous neutrophil granulocytes. Methylprednisolone was intensified to the dose 2.5 mg/kg. After three days the skin picture improved. The reduction of methylprednisolone resulted in relapse of UC. After four weeks infliximab was introduced. The skin inflammation showed a marked improvement. Infliximab also was effective in the UC.

Discussion: Our case presents a patient with an UC and extensive pustular form of PG. PG is usually presented as single skin alterations. Extensive skin changes occur only in 10% of patients. Upon the outbreak of pustules our patient suffered a relapse of UC. Sudden appearance of painful pustules and skin ulcers with associated symptoms and signs of systemic inflammation in a patient with an IBD requires rapid diagnostic procedures. If infection is excluded the possibility of PG should be taken into consideration soon enough to start treatment. According to our experience systemic glucocorticoids remains the first choice of treatment. Infliximab can be the choice in IBD patients.
Targeting personalized therapies in IBD: Polymorphisms of IL-4 (C-590T) and GJB2 (35delG) genes associate with pro- and anti-inflammatory cytokines

O. Plehutsa, R. Sydorchuk, L. Sydorchuk, I. Sydorchuk, A. Sydorchuk
Bukovinian State Medical University, Chernivtsi, Ukraine

Introduction: Genetic predisposition to IBD is extensively discussed. Although the complex interaction among genetics have been long recognized among researchers, the understanding of its contribution to IBD pathogenesis continues to evolve. Genetic factors not only determine personal predisposition to particular pathogenetic mechanism, but also may potentially predict therapeutic response and treatment efficacy. About 30 genes are known to play role in IBD etiology and their number is expanding. We hypothesized that С-590Т polymorphism of IL-4 gene and 35delG polymorphism of Gap junction β-2 protein/connexin (GJB2) gene (suspected to be responsible for L. van Beethoven's IBD and deafness) may have pathogenetic role in IBD.

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

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

Discussion/Conclusion: IL-4 gene’s C-allele (CC/CT) associates with lower TNF-α; high or normal IL-4, IL-10, IL-13 in 35delG-genotype of CJB2 gene. IL-4 hyperproduction in TT-genotype of IL-4 gene, form conditions for chronic inflammatory process. 35delG mutation of GJB2 gene is characterized by increased production of TNF-α, without significant growth of IL-1β and hyperproduction of IL-4 backed by activity of IL-10, IL-13.
Regulatory role of the transcription factor GATA-3 in ulcerative colitis and blocking of experimental colitis by GATA-3-specific DNAzyme

V. Popp¹, K. Gerlach¹, S. Mott¹, A. Turowska², H. Garn², R. Atreya¹, I.C. Ho³, H. Renz², M.F. Neurath¹, B. Weigmann¹
¹Department of I. Medical Clinic, University Clinic, Erlangen, Germany
²Sterna Biologicals, Marburg, Germany
³Harvard Medical School, Brigham and Women’s Hospital, Boston, USA

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 study the function of GATA-3 in the ulcerative colitis and with GATA-3 DNAzyme technique for 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 KO mice were used in the oxazolone-medat ed colitis model. Inflammation level was documented with miniendoscopic analysis. The colon was isolated for histological sections for immunofluorescent staining as well as LPMCs 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 DNAzyme hgd40 as a therapeutic treatment for oxazolone treated 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.
Arterial stiffness as a marker of vascular aging in IBD patients – A pilot study

R. Prijic1, V. Premuzic2, M. Jelakovic1, A. Kunovic4, D. Grgic1, M. Brinar1,3, N. Turk1, Z. Krznaric3,4, B. Vucelic1,3, S. Cukovic-Cavka1,3

1Division of Gastroenterology and Hepatology, University Hospital Center Zagreb, Croatia
2Division of Nephrology, Arterial Hypertension, Dialysis and Transplantation, University Hospital Center Zagreb, Croatia
3School of Medicine, University of Zagreb, Croatia
4Center for Clinical Nutrition, University Hospital Centre Zagreb, Croatia

Introduction: Recent research has demonstrated higher risk of developing atherosclerosis in inflammatory bowel disease (IBD). Chronic systemic inflammation can contribute to development of arterial stiffness increase and accelerated vascular aging. Non-invasive measurement of aortic pulse wave velocity (PWV) has predictive value for future fatal cardiovascular events and total cardiovascular mortality in general population. The aim of our pilot study was to assess the level of arterial stiffness by measuring aortic pulse wave velocity as an index of arterial stiffness in IBD patients.

Methods: We conducted a pilot observational study in our cohort of IBD patients during the period from October 2015 to December 2015. We measured PWV in the hospital patients, using validated, non-invasive oscillometric device (Tensiomed Arteriograph device (Medexpert Ltd., Budapest, Hungary). Analysis on the patient population, PWV values and laboratory values was done.

Results: A total of 20 patients (median age 31, range 18–66, 50% male, 14 Crohn’s disease (CD) patients – median age 28.5, range 18–46, 50% male, 6 ulcerative colitis (UC) patients – median age 42.5, range 18–66, 50% male) were included in our study. Mean PWV value was 8.1 ± 1.8 m/s, in CD group PWV was 7.8 ± 1.4 m/s, in UC group 8.7 ± 2.6 m/s.

Comparing subgroups of patients with CD and UC we found no statistically significant difference in PWV values and age between the groups. Higher PWV values were observed in female group of patients, although these result did not reach level of statistical significance (p = 0.078).

Discussion/Conclusion: By measuring aortic PWV we showed no statistical differences in level of arterial stiffness between CD and UC patients, although UC group had higher PWV by almost 1 m/s. Next steps in our prospective study will be to assess the level of arterial stiffness by measuring aortic PWV in a larger cohort of IBD patients compared to healthy controls. In addition, to determine differences within IBD patient groups, according to disease phenotype, disease length and treatment regimens.
Diagnosis and treatment of Crohn's disease

S.T. Rakhmonov, B.S. Navruzov
Research Center of Coloproctology, Tashkent, Uzbekistan

Introduction: Diagnosis and treatment of Crohn's disease is a difficult problem for the physician. Early diagnosis of the disease warns about the possible complications of the disease.

Materials and methods: The study included 96 patients with Crohn's disease. The men were 56, women – 40, age of patients 17 to 76 years. A colonoscopy or radiological methods of investigation were not always effective. In such cases, we helped computed tomography or laparoscopy. Conservative treatment was performed in 38 patients (39.6%). Surgical treatment was performed in 58 patients (60.4%). Perform the following operations: 16 patients underwent total colectomy with ileostomy formation end ohms, 22 patients resection of the ileocecal region with the formation ileoascendo anastomosis, 20 patients underwent total colectomy with formation ileorectal anastomosis.

Results: The study revealed the following localization of the pathological process: in the colon – in 72 patients (75.0%), terminal ileitis – in 24 patients (25.0%). After surgery, 3 patients died. A good result was observed at 70.7%, 19.5% satisfactory, unsatisfactory in 9.8% of patients.

Conclusion: Thus, when complex shapes Crohn conservative treatment nor always effective, and it is necessary to conduct surgery. The amount and method of operation depends on the localization of the pathological process.
Can the inflammatory bowel disease biologics registry lead to improved quality of care?

Ibtihal Rikaby, M.Pharm.2, Laith Alrubaiy, MRCP1, Hayley Anne Hutchings, Ph.D.1, John Gordon Williams, FRCP, CBE1
1Patient and Population Health and Informatics Research, College of Medicine, Swansea University, Swansea SA2 8PP, UK
2Cardiff and Vale University Health Board, Heath Park, Cardiff CF14 4XW, UK

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

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

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

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

Ibtihal Rikaby, M.Pharm.², Laith Alrubaiy, M.D., MRCP¹, Mohamed Sageer, M.D.³, Hayley Anne Hutchings, Ph.D.¹, John Gordon Williams, CBE, FRCP¹
¹Patient and Population Health and Informatics Research, College of Medicine, Swansea University, Swansea SA2 8PP, UK
²Cardiff and Vale University Health Board, Heath Park, Cardiff CF14 4XW, UK
³Lahey Hospital and Medical Center, Burlington, Massachusetts, USA

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.
LYC-53976, a ROCK2-selective inhibitor, attenuates the fibrogenic response of intestinal myofibroblasts to TGF-beta and substrate stiffness

Eva S. Rodansky¹, Xikui Liu², Laura A. Johnson¹, Kellie Demock², Anthony J. Celeste², Laura L. Carter², Peter D.R. Higgins¹
¹Division of Gastroenterology, Internal Medicine, University of Michigan, Ann Arbor, MI, USA
²Lycera Corp., Ann Arbor, MI, USA

Introduction: Intestinal fibrosis is the critical final pathway of intestinal failure in Crohn’s disease (CD). No medical therapies exist to treat intestinal fibrosis. Blocking fibrogenic signals at the convergence point of Rho kinase (ROCK) offers an attractive anti-fibrotic target. However, previous inhibitors of these kinases are limited by known off-target effects and are not clinically used for anti-fibrotic indications. We aimed to develop and test selective ROCK inhibitors with potent anti-fibrotic effects in two in vitro models of Crohn’s disease.

Methods: Enzymatic and cell-based assays were used to determine ROCK1/2 selectivity, then candidates were screened for drug-like properties. Promising compounds were tested for reversal of TGF-beta-driven profibrotic induction in CCD18co human intestinal myofibroblasts. Successful compounds were screened for efficacy in the CCD18Co matrix stiffness model. Efficacy in each in vitro model was evaluated by qPCR for expression of the profibrotic genes COL1A1, ACTA2, FN1, and MYLK. Promising compounds were also evaluated on an extended human fibrotic gene PCR array.

Results: A representative compound, LYC-53976, was found to be ROCK2 selective, with potency against ROCK2 at 385 nM and no activity against ROCK1 at the highest concentration tested (10 micromolar) in the cell-based assay. In the TGF-beta-driven profibrotic model, 3 micromolar LYC-53976 abrogated induction of COL1A1, FN1, and ACTA2 gene expression, as well as aSMA protein expression. In the pathological stiffness-driven model, 3 micromolar LYC-53976 also abrogated induction of COL1A1 and MYLK genes. LYC-53976 was effective in modulating multiple fibrotic genes in TGF-beta-stimulated LL-29 human fibroblast superarray by 2- to 4-fold.

Discussion/Conclusion: Our data suggests the utility of ROCK inhibition as an anti-fibrotic therapy for Crohn’s disease strictures.
Factors associated with non-adherence to medication for inflammatory bowel disease: A monocentric Tunisian study

Department of Gastroenterology, Mongi Slim Universitary Hospital, Tunis, Tunisia

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

Methods: Retrospective study including patients with IBD receiving maintenance medication and followed in our department between 2011 and 2015. We assessed a range of adherence behaviors. Demographic, clinical, and psycho-social characteristics were also assessed by chi 2 test. Adherence was considered as a continuous variable and then categorized as high or low adherence for logistic regression analysis to determine predictors of adherence behavior.

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

Conclusion: Approximately half of the IBD patients were low adherers. Predictors of low adherence were aged younger than 30 years, low socioeconomic condition, active smoking and male gender.
Risk factors for decreased bone mineral density in inflammatory bowel disease in a Tunisian cohort

Department of Gastroenterology, Mongi Slim Universitary Hospital, Tunis, Tunisia

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

Methods: Retrospective study including patients with IBD admitted in our department between January 2011 and December 2015. Demographic and clinical characteristics of patients were analyzed. Bone mineral density of the femoral neck, total femur and lumbar spine was quantified by dual-energy X-ray absorptiometry.

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

Conclusion: In our Tunisian cohort of IBD patients, Crohn’s disease, high steroid dose and extraintestinal manifestations were associated with increased risk for metabolic bone disease. High risk patients should be identified and appropriate therapies should be started early to improve long term quality of life.
Clinical features of the patients with IBD in Croatia

Bruna Rošić Despalatović, Andre Bratanić, Miroslav Šimunić, Ante Tonkić
1“J&J MEDICI” Policlinic of Internal Medicine, Split, Croatia
2Department of Gastroenterology, University Hospital Center, Split, Croatia

Introduction: The aim of this study is to determine change of clinical features of IBD in Split-Dalmatian County, Croatia from 2006–2014.

Methods: The research is a prospective study that included patients from the Register of IBD. All the patients were over 18 years old with diagnosis of Crohn's disease and ulcerative colitis according to criteria of ECCO.

Results: During the nine-year long period there were 414 new patients with IBD. 284 (68.5%) of those patients with ulcerative colitis and 130 (33.5%) patients with Crohn's disease. Onset of the ulcerative colitis is between the age of 18 and 30, with a new increase of incidence from the age of 51 to 60. With the patients with Crohn's disease onset of the disease is from the age of 18 to 30. In ulcerative colitis all three localized diseases are equally represented. At the time of diagnosis most od patient was with severe disease. The proportion of patients with severe disease activity declines with years of research. In patients with Crohn's disease as initial localization of the disease most patients have ileocolon and most of patients have an initial severe form. According to the phenotype of Crohn's disease patients with inflammatory and structuring form of the disease are equally represented.

Discussion/Conclusion: This is the first population-based epidemiological study of clinical characteristics of patients with IBD in Split-Dalmatian County, Croatia. Clinical characteristics of the disease are similar to other countries in the Mediterranean region and the countries of Western Europe, where the incidence of these diseases is high.
Incidence and severity of pre-pouch ileitis: A distinct disease entity or a manifestation of refractory pouchitis? A retrospective cohort study of patients from Amsterdam, Leuven and London

M.A. Samaan¹,²,³, MBBS, D. de Jong³, S. Sahami⁴, M.D., Ph.D., S. Morgan¹, MBBS, K. Fragkos², MBBS, M.Sc., M.Phil., S. Subramaniam¹, MBBS, K. Kok¹, M.D., Ph.D., J. Makanyanga¹, MBBS, I. Barnova¹, M.D., H. Saravanapavan¹, MBBS, I. Parisi¹, M.D., S. Di Caro¹, M.D., Ph.D., R. Vega¹, M.D., Ph.D., F. Rahman¹, Ph.D., FRCP, S. McCartney¹, Ph.D., FRCP, S.L. Bloom¹, DM, FRCP, G.R. van den Brink³, M.D., Ph.D., M. Löwenberg³, M.D., Ph.D., C.Y. Ponsioen³, M.D., Ph.D., C.J. Buskens⁴, M.D., Ph.D., P.J. Tanis⁴, M.D., Ph.D., A. de Buck van Overstraeten⁵, M.D., A. D’Hoore⁵, M.D., Ph.D., W.A. Bemelman⁵, M.D., Ph.D., G.R. D’Haens²,³, M.D., Ph.D.

¹Department of Gastroenterology, University College London Hospital, London, UK
²Robarts Clinical Trials Inc., Amsterdam, The Netherlands
³Department of Gastroenterology, Academic Medical Center, Amsterdam, The Netherlands
⁴Department of Surgery, Academic Medical Center, Amsterdam, The Netherlands
⁵Department of Surgery, University Hospitals, Leuven, Belgium

Introduction: Restorative proctocolectomy with ileal pouch-anal anastomosis is the operation of choice for patients with treatment-refractory ulcerative colitis. However, after this intervention, up to 50% of patients develop pouchitis. Moreover, a subgroup will also develop inflammation in the afferent ileum proximal to the pouch, a condition named prepouch ileitis (PI).

Methods: Data on 546 patients who underwent ileal pouch-anal anastomosis for ulcerative colitis were retrospectively collected from 3 tertiary inflammatory bowel disease referral centers in the Netherlands (Academic Medical Center, Amsterdam), Belgium (University Hospital Leuven) and England (University College London Hospital). PI was considered present if there was endoscopic and histological inflammation in the afferent limb proximal to the pouch. Crohn’s disease was excluded by reviewing the histology of colectomy resection specimens.

Results: PI was present in 33/546 (6%) patients and all of these had concurrent pouchitis. One hundred forty-four (26%) patients had pouchitis without PI and 369 (68%) patients did not have inflammatory pouch disease. Of the 33 patients with PI, 6 (18%) received no specific treatment, 9 (27%) responded to antibiotics, and 18 (54%) required escalation in therapy to steroids/immunomodulators or anti-tumor necrosis factor agents. Potent immunosuppressive treatment was required more frequently in patients with PI than those with pouchitis alone.

Discussion/Conclusion: PI is less common and more treatment refractory than pouchitis alone. Once PI is diagnosed, clinicians should be aware that response to antibiotic therapy is less likely than in pouchitis alone. Immunomodulatory therapy and escalation to anti-tumor necrosis factor agents should be considered early in cases of non-response. The suggestion that PI represents misdiagnosed Crohn’s disease could not be substantiated in our cohort.
IL-36R signalling in intestinal epithelial cells and fibroblasts promotes mucosal healing in vivo

Kristina Scheibe, Markus F. Neurath, Clemens Neufert
First Department of Medicine, Universitätsklinik Erlangen, Erlangen, Germany

Introduction: IL-36R signaling promotes inflammation in multiple organs including the skin, but the role of IL-36R ligands in inflammatory diseases of the intestine is still unknown.

Methods: We analyzed the IL-36R ligand expression in human inflammatory bowel diseases (IBD) and murine experimental colitis. The functional role of IL-36R signaling in the intestine was addressed in acute colitis models and wound healing models in vivo by using mice with defective IL-36R signaling (IL-36R−/−) or Myd88 (Myd88−/−), neutralizing anti-IL-36R antibodies, recombinant IL-36R ligands and RNA-seq genome expression analysis.

Results: Expression of IL-36α and IL-36γ was significantly increased in active human IBD and experimental colitis. While IL-36γ was mainly detected in nuclei of intestinal epithelial cells, IL-36α was predominantly found in the cytoplasm of CD14+ inflammatory macrophages. Functional studies showed that absent IL-36R signaling causes high susceptibility to acute DSS colitis and impairs wound healing. Mechanistically, IL-36R ligands released upon mucosal damage activated IL-36R+ colonic fibroblasts via Myd88 thereby inducing expression of chemokines, GM-CSF and IL-6. Moreover, they induced proliferation of intestinal epithelial cells and expression of the antimicrobial protein lipocalin 2. Finally, treatment of experimental intestinal wounds with IL-36R ligands significantly accelerated mucosal healing in vivo.

Discussion/Conclusion: IL-36R signaling is activated upon intestinal damage, stimulates intestinal epithelial cells and fibroblasts and drives mucosal healing. Modulation of the IL-36R pathway emerges as a potential therapeutic strategy for enhanced recovery of mucosal inflammation in IBD.
5-HT7 receptor mechanism for stress-induced analgesia: A new therapeutic target for inflammatory pain

Melik Seyrek¹, Yusuf Serdar Sakin², Ozgur Yesilyurt¹, Marcello Leopoldo³, Ahmet Dogrul¹

¹Department of Pharmacology, Gulhane Military Medical Academy, Ankara, Turkey
²Department of Gastroenterology, Gulhane Military Medical Academy, Ankara, Turkey
³Department of Pharmacology, Universita Degli Studi ‘a Moro’, Bari, Italy

Introduction: Despite the availability of several pharmacologic agents, the management of visceral pain is problematic and its economic and social burden may surpass that of the pain from somatic sources due to work day loss, reduced productivity and long term use of the medication with their associated side effect. It’s well known that serotonin has been implicated as a key neurotransmitter in the control of acute and chronic pain responses with the sites of action located in both the peripheral and central nervous systems.

Serotonin affects pain modulation by acting via seven families of 5-HT receptors (5-HT1–7). The role of the 5-HT7 receptors in somatic and neuropathic pain has been broadly examined. In this study, we aimed to examine the role of the 5-HT7 receptors in visceral pain using acetic acid writhing test as an inflammatory pain model in mice. We tested the effects of systemic and intrathecal administration of selective 5-HT7 receptor agonist and antagonist on visceral pain.

Methods: Adult male Balb-C mice weighting 25–30 g were used. The potent and selective 5-HT7 receptor agonists, LP 44 and AS 19; 5-HT7 receptor antagonist, SB 269970 were injected via intraperitoneally or intrathecal route. The writhing syndrome was elicited by i.p. injection of 0.6% acetic acid in a volume 10 ml/kg and the total number of writhes made each mouse was recorded between 10 and 20 min after acetic acid injection.

Mice were assigned randomly to the groups. LP 44 and AS 19 were administered i.p. (5, 10, 20 mg/kg) or i.th. (5, 10 and 20 µg) 30 min before 0.9% acetic acid administration. In other groups of mice, SB 269970 was given i.p. (20 mg/kg) or i.th. (20 µg) 20 min before i.p. and i.th. administration of LP 44 and AS 19 to assess reversal effects of selective 5-HT7 antagonist, respectively.

Results: The vehicle treated group exhibited writhing responses of 20.63 ± 1.97. The systemic (5, 10 and 20 mg/kg, i.p.) or i.th. (5, 10 and 20 µg) administration of LP 44 and AS 19 exhibited dose dependent and significant (p < 0.001) inhibition of writhing responses (Figure 1). After systemic administration of LP 44 and AS19 at the dose of 20 mg/kg, writhing responses were profoundly diminished and found to be 0.8 ± 0.7 and 0.5 ± 0.17, respectively. Systemic administration of 5-HT7 receptor antagonist, SB 269970 (20 mg/kg, i.p.) significantly blocked LP 44 and AS 19 (20 mg/kg)-induced antinoiceptive effect. Similar to systemic administration, intrathecal injection of the LP 44 and AS 19 produced dose dependent analgesic effect (Figure 2). injection of SB 269970 (20 µg) significantly reversed LP 44 and AS 19 (20 µg)-induced antinoiceptive effect in writhing test (Figure 2).
Discussion/Conclusion: In the present study, we found that the systemic or spinal administration of 5-HT7 receptor agonists AS 19 and LP 44 elicit analgesic activity in chemically induced visceral pain model in mice. The pretreatment with selective 5-HT7 receptor antagonist SB269970 blocked the analgesic activity of 5-HT7 receptor agonists. Taken together, our study provides evidence that 5-HT7 receptors play a crucial role in the processing of the visceral pain.

**Figure 1:** The selective 5-HT7 receptor agonist LP 44 and AS 19 were given i.p. 30 minute prior to 0.9% acetic acid. The number of writhing responses was counted from 10 to 20 minute after i.p. acetic acid injection. The selective 5-HT7 receptor antagonist SB 269970 was given i.p. 30 minute before AS 19 and LP 44, p < 0.05, significantly different from vehicle groups for LP 44 and AS 19, p < 0.05, significantly different compared with corresponding LP 44 and AS 19 alone groups.

**Figure 2:** The selective 5-HT7 receptor agonist LP 44 and AS 19 were given i.th. 30 minute prior to 0.9% acetic acid. The number of writhing responses was counted from 10 to 20 minute after i.p. acetic acid injection. The selective 5-HT7 receptor antagonist SB 269970 was given i.th. 15 minute before AS 19 and LP 44, p < 0.05, significantly different from vehicle groups for LP 44 and AS 19, p < 0.05, significantly different compared with corresponding LP 44 and AS 19 alone groups.
Extraintestinal manifestations in inflammatory bowel diseases (IBD) among Egyptian patients: A tertiary center experience

M. Sharaf-Eldin, M. Enaba, S. Abousaif
Tanta University Hospital, Tanta, Egypt

Introduction: The increasing incidence of IBD in Egypt may be explained by changing dietary habits and the availability of diagnosis especially in the era of endoscopy and wireless capsule endoscopy. IBD (mainly ulcerative colitis and Crohn's disease) are associated with extraintestinal manifestations. The aim was to evaluate these extraintestinal manifestations in IBD among Egyptian patients.

Methods: This prospective study was done in Tanta University Hospital from January, 2014 to June, 2015. A total 224 patients were diagnosed as IBD. 168 diagnosed as ulcerative colitis and 56 diagnosed as Crohn's disease by endoscopic examination. After clinical, laboratory investigations, imaging and histological examination, extraintestinal manifestations were reported and analyzed.

Results: Males were 142 patients (63.4%) and females were 82 (36.6%). Extraintestinal manifestations were detected in 111 (49.55%) in ulcerative colitis and 45 (20.09%) in Crohn's disease patients. The most common extraintestinal manifestations were: arthritis in ulcerative colitis 67 (30%) and 31 (13.84%) in Crohn's disease, anemia in 59 (26.34%) in ulcerative colitis and 51 in Crohn's disease (22.77%), ankylosing spondylitis 34 (15.18% ) in ulcerative colitis and 18 in Crohn's disease, erythema nodosum 17 (7.59%) in ulcerative colitis and 17 ( ) in Crohn's disease, sclerosing cholangitis 7 (7.59%) in ulcerative colitis and 2 ( .89%) in Crohn's disease and eye manifestations 10 (4.46%) in ulcerative colitis and 8 (3.57%) in Crohn's disease.

Discussion/Conclusion: Extraintestinal manifestations of IBD were frequent, mainly in Crohn's disease more than ulcerative colitis. The most common were arthritis, anemia, ankylosing spondylitis and erythema nodosum. Some reflects the disease activity, others has no relations. Treatment of IBD helps in the resolutions of these extraintestinal manifestations of the IBD.
Thalidomide therapy for vascular malformations of the gastrointestinal tract

Sue Surgenor¹, Jonathon Snook²
¹Gastroenterology Nurse Consultant, ²Consultant Gastroenterologist, Poole Hospital NHS Foundation Trust, Poole Dorset, UK

Introduction: An otherwise fit Caucasian male presented in the spring of 2013 at the age of 70 with mild iron deficiency anaemia. There were no clinical clues as to the cause, and no significant abnormalities on bidirectional endoscopy or duodenal biopsy histology. He made a good haematological response to oral iron replacement therapy. He re-presented in early 2014 with a symptomatic recurrence of more severe iron deficiency anaemia. His haemoglobin concentration ([Hb]) was 69 g/l, and he reported passing dark stool at times. MR enterography was normal, but capsule endoscopy revealed numerous vascular malformations of varying morphology scattered through the small bowel.

Methods: Single patient study.

Results: Despite serial total dose iron infusions every 6–8 weeks over the following 12 months he had persisting anaemia. His average [Hb] during this period was 86 g/l, with significant associated symptoms of breathlessness and fatigue.

After discussion of his limited management options and appropriate counselling, he commenced therapy with oral thalidomide 100 mg od, which he tolerated well. For three months there was no appreciable change in his mean blood count or iron infusion requirement. After that point however his blood count progressively rose – 8 months after starting treatment his Hb had reached 151 g/l, having required no further iron infusions for over 3 months.

Discussion/Conclusion: There is increasing published evidence of the benefit of thalidomide in the treatment of vascular malformations of the GI tract, including a recent randomized, controlled trial. The mechanism of action is uncertain, but it is thought that inhibition of the expression of Vascular Endothelial Growth Factor (VEGF) may be important – VEGF is strongly expressed in GI vascular malformations, and may be involved in pathological angiogenesis.
Approaching personalized therapy for IBD: ACE gene's polymorphisms participate in IBD pathogenesis through changes of colonic microbiota and mesenteric vascularization

Bukovinian State Medical University, Chernivtsi, Ukraine, *National State Medical University, Kyiv, Ukraine

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

Methods: Totally 104 individuals participated in the study. Among them 34 had proven IBD (UC/CD in remission), others with at least three risk factors for IBD (family history, smoking, antibiotics, travel history, immune, etc.). Diagnosis and management provided according to ECCO Guidelines. Standard microbiology techniques and PCR for insertion/deletion (I/D) ACE polymorphisms were used. Mesenteric vascular changes determined by plasma NO, ultrasonography and in pathomorphologically.

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

Discussion/Conclusion: Presence of D allele (ID, DD genotypes) increases chances for clinically significant dysbiosis 4.75 i 3.38 fold (OR = 12.7 and OR = 5.6, 95% CI OR = 1.06–62.6, p ≤ 0.031–0.0004). DD genotype carriers have highest risk of decompensated microbiota violations. While the exact role of microbiota changes in IBD remains unclear, it is defined that these changes play role in IBD pathogenesis. Traditional understanding of genetic factors’ role in IBD is limited immune and cytokines’ response. This study uncovers possible genetically determined mechanism of microbiota changes emphasizing personalized therapy in IBD.
Targeting colonic microbiota in IBD: Oral probiotic therapy

L. Sydorchuk, T. Boychuk, R. Sydorchuk, I. Sydorchuk, O. Plehutsa, A. Sydorchuk
Bukovinian State Medical University, Chernivtsi, Ukraine

Introduction: The mechanisms explaining complex relationship between the commensal colonic microbiota and inflammatory bowel disease (IBD) have a common outcome, a violation of bacterial antigens exposure to effector T-cells and innate immune cells residing in the intestinal mucosa and/or alteration of the host immune response to bacteria. While the role of gut microbiota and respective immune changes has become more evident in recent years there is no sufficient database explaining the character of microbiota changes in IBD. Probiotics are thought to work by altering the composition of the intestinal microbiota, the epithelial barrier function of the intestine, and have important immunoregulatory activity. Expanding this idea, probiotics have been subject for intensive research, mainly focusing on bifidobacteria and lactobacteria. However, existing reports of probiotic use in IBD are contradictory.

Methods: Totally 104 individuals participate in the study. Colonic resistance studied in mucosal bioplates. Standard aerobic and anaerobic microbiology techniques with nosology identification and quantity composition of microbiota were used. Specially designed (T73) strain of P. Shermani with high antagonistic/immunoregulatory potential was orally given twice on a daily basis during 150–180 days in a form of suspension containing 10^{12}–10^{14} bacteria. Patients without probiotic treatment formed control. Both groups' patients received mesalazine 1500–3000 mg daily as a basis therapy. Treatment efficacy evaluated according to WGO Global Guidelines and included CDAI, SF-36 and IBDQ scores.

Results: Major autochthonic species (14 in total) were present in all samples: among them Lactobacteria, Bifidobacteria, E. coli, several other anaerobic species were dominating. However, Lacto- and Bifidobacteria were found in significantly lower levels compared to healthy subjects (p = 0.02–0.0031). The general tendency for colonic resistance in IBD was decrease of autochthonic anaerobes (Bifido-, Lactobacteria, Bacteroides spp., Clostridia spp., Bacillae spp.) and significant growth of allochtonic aerobes and facultative anaerobes (E. coli Hly+, Pseudomonas, Serratia, Hafniae, P. mirrabilis and other conditionally pathogenic Enterobacteriaceae). Enterococci were present in 60.0% of healthy and 7.14–20.69% of IBD patients. Staphylococci were present only in IBD group (17.24–31.58%). There were 16.67% and 22.22% recurrences requiring hospitalization during the study period. CDAI score at the end of study was 49.37 ± 3.14 points lower in study group (p < 0.05). SF-36 score difference between groups became 11.8 ± 0.84%. Abdominal pain, stool, and drug use for symptomatic therapies improved in study group, too. However, probiotic treatment did not influence anemia and other extra abdominal symptoms. Endoscopic picture and biopsies presented no specific differences between groups after treatment.
Discussion/Conclusion: Our data suggest that morbid changes of colonic mucosal microbiota, e.g. abnormal ratio of autochthonic and allochthonic species, may be considered as a strong characteristic feature of IBD. We hypothesized that results of existing studies of probiotic use in IBD are confusing due to improper selection of probiotic agent. P. Shermani T73 is comparatively rare and understudied probiotic, showing its usefulness for use in IBD. Furthermore, it may be interesting to compare obtained results with fecal transplant therapy.
Mesalazine vs. probiotic use in maintaining remissions in IBD

R. Sydorchuk, T. Boychuk, L. Sydorchuk, I. Sydorchuk, O. Plehutsa, A. Sydorchuk
Bukovinian State Medical University, Chernivtsi, Ukraine

Introduction: The role of gut microbiota has become more appreciated in recent years emphasizing the IBD etiology. Probiotics are thought to work by altering the composition of the intestinal microbiota, the epithelial barrier function of the intestine, and have important immunoregulatory activity. Expanding this idea, probiotics have been subject for intensive research, mainly focusing on bifidobacteria and lactobacteria. However, existing reports of probiotic use in IBD are contradictory.

Methods: Ninety-eight patients (34 CD, 64 UC) participate in the study. Colonic resistance studied in mucosal bioptates. Specially designed (T73) strain of P. Shermani with high antagonistic/immunoregulatory potential was orally given triple daily in a form of suspension containing \(10^{12}-10^{14}\) bacteria/day. Patients without probiotic treatment formed second group (57.14%), they received mesalazine 1500 mg (3 x 500 mg) daily as a basis therapy. Study duration was 50 weeks, treatment efficacy evaluated according to WGO, ECCO Guidelines and patients were assessed by clinical and endoscopic activity indices as well as by biopsies. The primary endpoint of the study was to compare efficacy in prevention of relapses.

Results: Systemic probiotic use significantly improved colonic resistance. There were relapses in 16 of 56 (28.57%) patients in second group (with mesalazine) and in 19 of 42 (45.24%) in probiotic group (\(p = 0.007\)). No statistically significant variations between UC and CD patients inside groups were found. CDAI score at the end of study was 12.37 ± 5.14 points lower in mesalazine group (\(p > 0.05\)). Abdominal pain, stool, and drug use for symptomatic therapies improved in both groups, too. Endoscopic picture and biopsies presented no specific differences between groups after study. Safety profiles and tolerability were satisfactory for both groups and without significant differences.

Discussion/Conclusion: Probiotics are living microorganisms that exert health effects on the host; their use in IBD is promising. Our study shows that probiotic treatment of IBD patients with P. Shermani is safe but lacks efficacy in maintaining remission equivalent to the gold standard in IBD treatment – mesalazine. However, this study has limitations in both volume and control. Further controlled trials are needed to clarify whether probiotics alone are sufficient enough to prevent IBD relapses.
Is it Crohn's disease (CD) or intestinal TB (iTB), dilemma that can lead to a catastrophe: Case report

Yousry Taher, Mohamed Sharaf-Eldin
Alexandria and Tanta Hospitals, Faculties of Medicine, Tanta, Egypt

Introduction: Literature summary and analysis of the case:
Crohn's disease (CD) and intestinal tuberculosis (iTB) are granulomatous bowel diseases that are difficult to differentiate due to similarity in clinical, radiological, endoscopic and histological aspects.

iTB is a curable diseases as compared to life-long CD. Inappropriate use of immunosuppressive treatment in misdiagnosed cases of CD may have catastrophic outcome. In iTB diagnosis depend mainly upon high clinical suspicion and isolation of mycobacterium tuberculosis (MT). The diagnosis of CD is based on clinical, laboratory, endoscopic, and pathological findings. Screening for latent TB infection (LTBI) and prophylactic treatment has become mandatory before starting infliximab.

The aim was to report the case of a female patient 35 years presented with chronic diarrhea, loss of body weight (she lost 10 kg during last year) and severe anemia (Hb was 6 gm).

Methods: On clinical evaluation patient had a palpable mass at the right iliac fossa ON CT scan raised the possibility of CD. Colonoscopy confirm SD diagnosis. Histopathological examination of biopsies revealed picture of CD.

Results: She was given conventional treatment and mild improvement occurred. She remained complaining of frequent abdominal pain and distension with infrequent attacks of diarrhea after two months. Patient with her surgeon preferred a trial of infliximab. She started taking 0, 2 and 6 weeks dosages. After initial improvement she suffered from chest infection and on doing X-ray chest examination, her treating physician was rash to diagnose the case as open TB and advised her isolation and starting immediate anti-tuberculous treatment. Patient received anti-tuberculous treatment (isoniazid 6 mg/kg, ethionamide 25 mg/kg and rifampicin 12 mg/kg) wrongly for 6 weeks during that period she started to suffer from manifestations of liver failure with marked elevation of liver enzymes and serum bilirubin (total serum bilirubin was 20 mg) direct fraction 12 mg, ALT 300, AST 400, prothrombin time 30% of normal). Patient was admitted to ICU. Two weeks later she died from hepatorenal failure.

Discussion/Conclusion: Every effort should be done to differentiate iTB from CD before giving treatment for the diagnosed one.
Correlation of MR enterography parameters with clinical and endoscopic disease activity indices

Oyku Tayfur Yurekli¹, Aylin Demirezer Bolat², Naciye Semnur Buyukasik², Oktay Algin³, Huseyin Koseoglu², Mustafa Tahtaci¹, Osman Ersoy¹
¹Yildirim Beyazit University, Faculty of Medicine, Gastroenterology Department
²Ankara Ataturk Research and Teaching Hospital, Gastroenterology Department
³Ankara Ataturk Research and Teaching Hospital, Radiology Department, Ankara, Turkey

MR enterography recently has been proved to be an excellent imaging modality in experienced hands for CD follow up. Increased mural thickness, abnormal enhancement in bowel wall, increased T2 signal, mesenteric engorgement, lymphadenopathy and comb sign have been defined as indicators of active disease. Data about the correlation of MRE findings with clinical activity indices are scarce so we aimed to define correlation of patients’ clinical and lab parameters with MR findings. 51 Patients who had been followed in Ankara Ataturk Education and Research Hospital IBD clinic between 2011 and 2015 and had MR enterography obtained were included in this study. 29 of these patients had ileal, 3 had colonic and 19 had ileocolonic CD. There was no correlation between CDAI and SES-CD scores. There were significant correlations between MR parameters and categorized CDAI scores. Ileal CD patients comprised a significant portion of our patients so we further analyzed ileal CD patients considering the fact that ileal SES-CD scores would be lower than ileocolonic CD patients. After this separation we were able to find significant correlations between T2 hyperintensity, max mural thickness and CM enhancement parameters with ileal SES scores. CDAI scores correlated significantly with most of the MRE findings while SES scores did not. After further analysis of ileal CD patients we found significant correlations between most of the MRE parameters with ileal SES scores. This implies using multiple scores like endoscopic, radiologic and clinical scores together will provide valuable information in diagnosis and follow-up of these patients.

Introduction: Crohn’s disease is progressive disease causing cumulative bowel damage. Early aggressive treatment in suitable patients is expected to prevent bowel damage. Close follow up of these patients is of upmost importance but the optimal follow up strategy has not been defined yet. Colonoscopy is gold standard but it is invasive and cannot visualize small bowel except for the 20–30 cm of the terminal ileum. Due to progressive nature of the disease multiple imaging techniques will be employed during the course of the treatment. Safety of these imaging techniques becomes important in young patients. An ideal imaging technique must be safe and provide optimal information about activity of the luminal disease as well as extraintestinal complications like abscess or fistula formation. MR enterography recently has been proved to be an excellent imaging modality in experienced hands for CD follow up. Increased mural thickness, abnormal enhancement in bowel wall, increased T2 signal, mesenteric engorgement, lymphadenopathy and comb sign have been defined as indicators of active disease. Due to good contrast resolution it performs better than CT for identification of fistulas or abscesses. But MR enterography is a time consuming examination, needs an experienced radiologist and cannot be employed in certain situations like claustrophobia or in the presence of
prosthetic implants or pacemakers. Data about the correlation of MRE findings with clinical activity indices are scarce so we aimed to define correlation of patients’ clinical and lab parameters with MR findings.

**Methods:** 51 Patients who had been followed in Ankara Atatürk Education and Research Hospital IBD clinic between 2011 and 2015 and had MR enterography obtained were included in this study. Patients’ hemoglobin, erythrocyte sedimentation rate (ESR), CRP levels, CDAI scores at the time of MRE were extracted from patient files. Colonoscopies were re-evaluated according to SES-CD score retrospectively. Colonoscopies obtained up to 3 months before or after MRE were included for analyses. CDAI scores and SES-CD scores were categorized for analyses. CDAI < 150: asymptomatic remission, 150–220: mild-moderate CD, 220–450: moderate CD, > 450: severe fulminant CD. SES-CD: 0–3: inactive disease, 4–10: mild activity, 11–19: moderate activity, ≥ 20: severe CD.

**Results:** Female/Male ratio was 22/29. Mean age was 38.55 ± 13.59. 29 of these patients had ileal, 3 had colonic and 19 had ileocolonic CD. There was no correlation between CDAI and SES-CD scores (r = 0.053, p = 0.34). There were significant correlations between MR parameters and categorized CDAI scores (table 1). We were unable to find any significant correlation between any MR parameters and SES-CD scores. Ileal CD patients comprised a significant portion of our patients so we further analyzed ileal CD patients considering the fact that ileal SES-CD scores would be lower than ileocolonic CD patients. After this separation we were able to find significant correlations between T2 hyperintensity, max mural thickness and CM enhancement parameters with ileal SES scores (table 2).

**Discussion/Conclusion:** Main limitation of our study was its being retrospective in nature. MRE findings and SES scores were recorded retrospectively. CDAI scores correlated significantly with most of the MRE findings while SES scores did not. After further analysis of ileal CD patients we found significant correlations between most of the MRE parameters with ileal SES scores. This implies using multiple scores like endoscopic, radiologic and clinical scores together will provide valuable information in diagnosis and follow-up of these patients. Further large-scale prospective studies are needed for validation of an MRE scoring system.
The influence of the modified symbiotic bacteria metabolites on immune cells

G. Tereshchuk¹, D. Vatlitsov²
¹National Technical University of Ukraine “Kyiv Polytechnic Institute”, Kiev, Ukraine
²Shupyk National Medical Academy of Postgraduate Education, Kiev, Ukraine

Introduction: Tannins have a certain variety of biological properties in mammalian organisms, i.e. anti-oncogenic effect, reduce blood pressure, modulate an immune response and promotes the restoration of the gastrointestinal tract.

The aim of the study was to develop the most effective combination of cultivation medium and investigate the influence of modified Lactobacillus plantarum metabolites on native and malignant immune cells.

Methods: For the study of tannase activity the strain was grown on the modified medium of L. plantarum – liquid MRS with 0.2% gallic acid.

Research was carried out on WBCs and Namalwa cells were investigated the index of distribution of MAM, the levels of lipid peroxidation, protein concentrations, glucose, changes of mitochondrial membrane potential, DNA concentration and cells concentration.

Results: There was observed an exponential growth to \(20.60 \pm 2.04 \times 10^7\) CFU/ml after 24 h and to \(25.41 \pm 0.78 \times 10^7\) CFU/ml after 48 h in MRS. However, there was observed much slower proliferation of L. plantarum in modified MRS: almost no changes after 24 h and a slight increase to \(15.70 \pm 5.58 \times 10^7\) CFU/ml after 48 h. Also was observed an accumulation of endotoxin in cultural medium. It was shown the decrease of Index of distribution of MAM from \(0.79 \pm 0.04\) c.u. to \(0.62 \pm 0.09\) c.u. But the modification of the medium decreases after 24 h with the subsequent increasing after 48 h, from \(0.75 \pm 0.17\) c.u. to \(0.80 \pm 0.06\) c.u. and to \(0.72 \pm 0.07\) c.u. respectively.

Discussion/Conclusion: Thus, gallic acid affects on lactobacilli metabolism and changed the cultural products, this fact was approved by results of apoptosis level of normal and malignant immune cells.
7-alpha-cholestenone and faecal calprotectin in patients with collagenous colitis

Rebecca C. Trimble*, Diana E. Yung, Anastasios Koulaouzidis
Centre for Liver and Digestive Disorders, Royal Infirmary of Edinburgh, UK

Introduction: Collagenous colitis (CC) causes chronic, watery diarrhoea [1]. Bile acid malabsorption (BAM) often accompanies CC [2,3] and CC can respond to treatment with bile acid sequestrants [4]. The European Microscopic Colitis Group advises that BAM should be sought in investigation for CC [1]. The selenium-labelled homocholic acid-taurine (SeHCAT) test is considered the gold standard for BAM diagnosis; however, serum 7-alpha-hydroxy-4-cholesten-3-one (7aC) is simpler and less expensive, with comparable sensitivity [5]. Faecal calprotectin (FC) is well-established as a biomarker of bowel inflammation, but data in CC is scant [6]. We present data from a tertiary referral centre on 7aC and FC in patients with CC.

Methods: Pathology records were interrogated for patients diagnosed with CC (2000–2015), extracting results on 7aC and FC. Results are presented as mean (± SD) or median (range).

Results: Over 15 years, 399 patients were diagnosed with CC (280 F/119 M). Of these, 164 were excluded from further analysis due to lack of appropriate data. 7aC was available in 83 (20.8%) patients, mean levels of 11.5 ± 9.70 ng/ml. 11/83 (13.3%) patients had elevated 7aC. FC levels were measured in 101 (25.3%) patients, mean levels 251.89 ± 282.62 µg/g. Of these, 76/101 (75.2%) had elevated FC ≥ 50 µg/g (FC ≥ 100 µg/g: 63/101; FC ≥ 200 µg/g: 30/101). Of the 101 patients with FC measurement, 76 had FC results ± 30 days from the point of histological diagnosis. In this group, median FC was 165 µg/g, range 20–1375 µg/g.

Discussion/Conclusion: This is the first cohort data on 7aC in CC. Our findings confirm that a significant proportion of CC patients have co-existing BAM; however, the incidence is lower than that reported in other studies using SeHCAT. The high incidence of raised FC in our cohort supports the position that FC is a useful marker of histologic inflammation in CC.

References:


Hyperbaric oxygen therapy in ulcerative colitis treatment

Alma Uzunova-Genova  
Ljulin Hospital, Sofia, Bulgaria

Hyperbaric oxygen therapy is up-to date for treatment in IBD. The curative effect of hyperbaric oxygen therapy is a very important of tissue's hypoxia and compensates organ's reaction.

There were examined 64 patients with exacerbation's ulcerative colitis in our clinic. All patients were treated by Salofalk® – 4 x 500 mg, curative enemas by Salofalk® susp. and hyperbaric oxygen therapy.

The other group of patients with ulcerative colitis – 18 we treated with hyperbaric oxygen therapy only. For hyperbaric oxygen therapy we have used Dragger chambers 1000–1200 for 60–75 min – 10–12 sittings. We’ve found good effect after 5th–6th of treatment. We have made approval after endoscopical examination.

We have made clinical retrace for number of defecation, blood in feces etc.

We have found endoscopical and clinical remission after treatment with Salofalk®, curative enemas and addition hyperbaric oxygen therapy in 81% of patients. Hyperbaric oxygen therapy is useful as a part of treatment of ulcerative colitis in 81% of patients with ulcerative colitis, but hyperbaric oxygen therapy as single therapy is useful in 60% of patients.
The metabolic deregulation as response on different kind of stress load

D. Vatlitsov, N. Rusetskaya
Shupyk National Medical Academy of Postgraduate Education, Kiev, Ukraine

Introduction: The first stage of organismal response to stress is metabolic disorders. The aim of the study was to investigate the lesions of different kind of stress on rat’s metabolic homeostasis.

Methods: The study was performed on Wistar male rats (n = 60), weighing 200 ± 30 g. Every day animals pairwise was put in the dark with the immobilized partners. Additionally, immobilized rats had submerged in cold water tank and in hot water (the 1st group). The 2nd group’s animals were subjected to immobilization stress only. The 3rd group’s animals were subjected to immobilization and thermal stress only. The 4th group was control. The stress load is gradually increased throughout the study during 112 days. Were measured the levels of molecules of average mass, TBA-reactive, glucose, high-density lipoprotein, low density lipoprotein, total cholesterol, triglycerides.

Results: According to the results obtained after calculation of DI of MAM, as an indicator of endogenous intoxication, were shown a statistically significant (p < 0.05) decrease in DI in the first (1.059 ± 0.192 c.u.) and the second (1.093 ± 0.154 c.u.).

The investigation of the quantity of TBA-reactive substances demonstrated activation of antioxidant defense systems in the third group, TBA- active substances nearly doubled 0.764 ± 0.618 mmol/l in relation to the control group values (p < 0.05) 1.388 ± 0.187 mmol/l.

Studying the lipid profile and glucose after 112 days revealed that the statistically significant changes (p < 0.05) of the studied parameters were observed in the first group HDL – 1.75 ± 0.12 mmol/l TG – 0.54 ± 0.25 mmol/l TCh – 1.13 ± 0.23 mmol/l in relation to the control (the 4th group) HDL – 1.89 ± 0.03 mmol/l; TG – 0.87 ± 0.32 mmol/l; TCh – 1.38 ± 0.12 mmol/l.

Discussion/Conclusion: The results had shown the metabolic disorders caused by a different kind of stress load and the activation of the various recovery systems that depend of the type of the stress.
Acute hepatitis in a patient receiving multiple therapies for Crohn’s disease: A case report

I.K. Williams, S. Surgenor
Poole Hospital NHS Foundation Trust, Poole Dorset, UK

Introduction: A patient was admitted to hospital with an acute flare of his Crohn’s colitis and treated with infliximab (5 mg/kg). Over the following weeks, his symptoms resolved completely and inflammatory markers returned to normal. Given a previous intolerance of mercaptopurine due to flu like symptoms, at clinic review two months later, low dose mercaptopurine along with allopurinol was commenced in addition to Infliximab. Routine weekly blood test monitoring demonstrated hepatitis week 4 after the inception of thiopurine. Mercaptopurine and allopurinol were discontinued and the next infliximab infusion withheld. The patients ALT continued to rise (peak 2385 IU/l). A full autoimmune, metabolic and viral liver screen was sent.

Methods: A case report.

Results: Serology demonstrated acute Hepatitis E (HEV) infection.

Discussion/Conclusion: All immunosuppression was withheld until serum viral counts were undetectable and LFTs returned to normal (4 weeks) at which point Infliximab, mercaptopurine and allopurinol were restarted.

HEV is transmitted via the faeco-oral route. It is endemic to some developing countries where transmission is related to faecal contamination of drinking water. In Europe, there is evidence that HEV is primarily transmitted by ingestion of pork and wild boar meat. It is generally a self-limiting illness from which patients recover completely, with the exception of a few significant groups. Chronic carriage of HEV is usually only seen in solid organ transplant recipients on multiple immunosuppressants. In these individuals, chronic active HEV can lead to cirrhosis and the complications thereof.

Chronic carriage of HEV is previously only seen in individuals receiving multiple immunosuppressants for organ transplantation but with wider use of immunosuppressants for autoimmune disease including inflammatory bowel disease, it is a potential complication which needs to be considered.
Adding stewed apricot juice to senna improves the right-side and overall colon cleansing quality for colonoscopy preparation

Bulent Yasar, M.D.1, Evren Abut, M.D.2, Huseyin Kayadibi, M.D.3, Fatih Akdogan, M.D.4, Can Gonen, Assoc. Prof5
1Department of Gastroenterohepatology, Camlica Erdem Hospital, Istanbul, Turkey, E-Mail: drbyasar42@gmail.com
2Department of Gastroenterohepatology, Umruniye Erdem Hospital, Istanbul, Turkey, E-Mail: evrenabut@yahoo.com
3Department of Medical Biochemistry, Adana Military Hospital, Adana, Turkey, E-Mail: mdkayadibi@yahoo.com
4Department of Internal Medicine, Haydarpasa Numune Training and Research Hospital, Istanbul Turkey, E-Mail: mfakd2002@yahoo.com
5Department of Gastroenterohepatology, Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey, E-Mail: drcgnn@yahoo.com
Corresponding address: Bulent Yasar, M.D., Camlica Erdem Hospital, Department of Gastroenterohepatology, Alemdag Yanyol Street, 34696, Uskudar, Istanbul, Turkey, Telephone: +90 505 347 58 52, Telefax: +90 216 522 66 66

Introduction: Adequate bowel cleansing is essential for optimal colonoscopic examination. The ideal colonoscopy preparation would not only reliably empty the colon, but also not cause any patient discomfort. However, none of the preparations currently meet all of these criteria. Our aim was to determine whether adding stewed apricot juice to senna increases patient comfort and improves bowel cleansing during colonoscopy preparation.

Methods: Outpatients with either sex who were over 18 years of age and referred for elective colonoscopy were randomly allocated to drink senna with stewed apricot juice or senna alone. Quality of colon cleansing was evaluated using the validated Ottawa Bowel Preparation Quality Scale. Patients were also asked to complete a nurse-administered questionnaire to assess their tolerability and adverse events during preparation that included 18 questions.

Results: A total of 154 consecutive patients were assessed for eligibility. 26 of these patients were excluded. 128 patients were included in the randomization procedure. Stewed apricot juice plus senna had a significantly better cleansing with regard to the right and transverse colon (p = 0.038, p = 0.037, respectively). In addition, overall cleansing was superior (p < 0.001), total colonoscopy (17.6 min vs. 22.8 min, p = 0.048) and cecal entubation (7.4 min vs. 11.2 min, p = 0.042) time were shorter, and the colonoscopy procedure was more easier (79.4% vs. 49.2%, p < 0.001) in that group. Patient acceptance, compliance and adverse events did not differ between groups (p > 0.05). 91.2% of patients in stewed apricot juice plus senna group stated willingness to receive the same regimen in the future compared with 80% of the patients in senna alone (p = 0.037).

Conclusion: The addition of natural, frequently consumed stewed apricot juice to senna significantly improves cleansing outcomes without additional adverse events.
Patients with Crohn's disease: The hydrogen breath test

E. Zygalo, L. Demeshkina, O. Sorochan, V. Kudryavtseva
State Institution "Institute of Gastroenterology of National Academy of Medical Sciences of Ukraine", Dnipropetrovsk, Ukraine

Recent studies indicate that small intestinal bacterial overgrowth (SIBO) is observed frequently in patients with Inflammatory Bowel Diseases, and it may cause dys-adaptive processes with and without clinical manifestations in patients.

The study aim is to identify SIBO in patients with Crohn's disease (CD).

Materials and methods: 27 patients with CD were included in this study. Non-invasive hydrogen (H2) breath test with glucose (on an empty stomach) was used to diagnosis SIBO. Hydrogen measurements in the air, which a patient breathed out, were done every 15 minutes (8 measurings) after primary breath sampling and patient’s taking 50 ml glucose. The test was evaluated as positive, if the increase of hydrogen (on 10 ppm and more) was observed in comparison with baseline data. Positive hydrogen breath test with glucose indicated dysbiotic disorders in the proximal small intestine. Taking patient's excrement gave possibility to study microbiota of the large intestine.

Results: It was determined that 74.1% of patients with CD had SIBO in small intestinal microbiota with H2 growth in average (25.3 ± 1.2) ppm. Patients with CD and revealed SIBO (I group) had diminished amounts of Bifidobacterium, Lactobacillus and standard forms of E. coli in large intestine in comparison with patients without dysbiotic disorders of the small intestine (II group), who had the increase of atypical forms of E. coli (p < 0.01). Total these microbial pull was decrease in both groups. At the same time it was very often increase the number of opportunistic microorganisms (Clostridium, Klebsiella, and Candida) and sometimes even Staphylococcus aureus. Dysbiosis of the large intestine was revealed in all patients with CD: 1 degree of dysbiosis was in 2 patients (7.4%), 2 degree – in 10 patients (37.0%), 3 degree – 15 patients (55.6%).

Conclusions: The syndrome of SIBO was detected in 74.1% of patients with CD, which accompanied with decrease microbiota in large part of the intestine (Bifidobacterium, Lactobacillus, Escherichia coli with typical properties).
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