Falk Symposium 187

Overcoming Challenges in IBD Management

April 19 – 20, 2013
Palau de Congressos de Catalunya
Barcelona, Spain

Innovative Drugs
for bowel and liver diseases
Modern formulations and specially designed delivery systems ensure targeted release of the active drug

Scientific Dialogue
in the interest of therapeutic progress
Falk Symposia and Workshops over 250 with almost 130,000 international participants since 1967
Continuing medical education seminars over 15,500, attended by more than 1.2 million physicians and patients in Germany alone
Comprehensive literature service for healthcare professionals and patients with more than 200 publications

www.falkfoundation.org www.drfalkpharma.com
Leinenweberstr. 5 79108 Freiburg Germany Tel +49 (0)761/1514-0 Fax +49 (0)761/1514-321 Mail zentrale@drfalkpharma.de

Abstracts
Poster Abstracts
Falk Symposium 187

OVERCOMING CHALLENGES IN IBD MANAGEMENT

Scientific Organization:
J. Panés, Barcelona (Spain)
S. Ghosh, Calgary (Canada)
F. Gomollón, Zaragoza (Spain)
E. Louis, Liège (Belgium)
CONTENTS

Session I

Understanding the mechanisms of disease

Chair:
M. Allez, Paris
S. Danese, Rozzano

Exploiting eQTL information to identify causative genes in risk loci for inflammatory bowel disease

13

The role of memory cells in inflammation perpetuation
(No abstract)
M. Allez, Paris

Mechanisms of tissue remodeling in IBD
C. Fiocchi, Cleveland

14 – 15

Challenging question: Is it possible to stratify IBD on a molecular and microbiologic basis?
S. Schreiber, Kiel

16

Session II

Advanced techniques for diagnosis of IBD

Chair:
M. Georges, Liège
S. Ghosh, Calgary

High-resolution endoscopy, chromoendoscopy and confocal endomicroscopy
R. Kiesslich, Frankfurt

19

Endoscopic assessment of the small bowel
A.R. Eliakim, Tel Hashomer

20

Cross-sectional imaging in IBD
S. Danese, Rozzano

21
Challenging question: Can we diagnose Crohn’s disease without histology?
A.M. Griffiths, Toronto

Session III

Optimal use of available drugs in IBD

Chair:
L. Beaugerie, Paris
S. Schreiber, Kiel

Should we still be using steroids for treating IBD?
A. Bitton, Montreal

Strategic use of immunosuppressants and anti-TNF in IBD
E. Louis, Liège

Expert use of drugs: Criteria for failure
I. Dotan, Tel Aviv

Challenging question: Is treating IBD an art or a strictly evidence-based matter?
B.G. Feagan, London, ON

Session IV

Emerging new therapies

Chair:
B.G. Feagan, London, ON
E. Louis, Liège

Cell therapies in IBD
E. Ricart, Barcelona

Anti-adhesion therapy
J. Panés, Barcelona

Modulation of cell signalling
S. Ghosh, Calgary

Challenging question: How do new therapies contribute to personalized medicine in IBD?
R. Panaccione, Calgary
Session V

Best surgical approaches for IBD

Chair:
A. Bitton, Montreal
A. Dignass, Frankfurt

Stricturing disease: Dilation, strictureplasty, and resection
(No abstract)
A. D’Hoore, Leuven

Perforating Crohn’s disease: Conservative and surgical treatment
G.M. Sampietro, Milan

Best prevention of postoperative recurrence in Crohn’s disease
G. D’Haens, Amsterdam

Challenging question: Surgery or anti-TNF in steroid-refractory
terminal ileal disease?
W.A. Bemelman, Amsterdam

Session VI

Managing IBD outside the gut

Chair:
S. Ardizzone, Milan
I. Dotan, Tel Aviv

Dermatologic diseases and treatment-related complications
of IBD: Prevention and treatment
S. Ghosh, Calgary

Ocular manifestations
L. Pablo, Zaragoza

IBD and liver diseases
H. Tilg, Innsbruck

Challenging question: Osteoarticular manifestations:
Specific treatments and/or treating the intestinal disease?
M. de Vos, Gent
Session VII

Cancer in IBD

Chair:
Y. Bouhnik, Clichy
J. Panés, Barcelona

Management of colonic dysplastic lesions
M. Pellisé, Barcelona 53

Small bowel dysplasia and cancer in Crohn’s disease
F. Carbonnel, Le Kremlin-Bicêtre 54

5-ASA and chemoprevention: Does it work?
L. Peyrin-Biroulet, Vandœuvre-lès-Nancy 55

Challenging question: Use of immunosuppressants and biologicals in patients with previous cancer
L. Beaugerie, Paris 56

Session VIII

Closing lecture

Chair:
E. Ricart, Barcelona

Towards personalized medicine in IBD
S. Vermeire, Leuven 59

List of Chairpersons, Speakers and Scientific Organizers 61 – 63
Poster Abstracts

1. A systematic review and meta-analysis of pancreatic autoantibody's (PAB) diagnostic accuracy vs standard diagnosis in patients with inflammatory bowel disease

2. CMV infection in IBD: Preliminary results of a prospective study

3. High prevalence of low bone mineral density in new onset of inflammatory bowel disease
   N. Ben Mustapha, M. Cheikh, M. Fekih, M. Serghini, L. Kallel, J. Boubaker, A. Filali (Tunis, TN)

4. Inflammatory bowel disease in Turkish children: An analysis of 127 children

5. Clostridium difficile infection – A permanent challenge in inflammatory bowel disease patients
   R. Cerban, L.S. Gheorghe, R. Vadan, M. Manuc, B. Cotruta, C. Gheorghe (Bucharest, RO)

6. Endoscopic efficacy of two regimens of maintenance therapy in patients with Crohn's disease aged 7–17 years – Multicenter randomized study

7. Vegetative dysregulation in patients with Crohn's disease and anemia syndrome
   L.V. Demeshkina, E.V. Zigalo, A.V. Kovaleva (Dnipropetrovsk, Zaporozhye, UA)

8. IL28Rα deficiency enforces T cell-dependent experimental colitis via suppression of regulatory T-cells
   H. Dornhoff, S. Doyle, M.F. Neurath, J. Siebler (Erlangen, DE; Seattle, US)

9. Long following of total proctocolectomy with ileoanal anastomosis:
   A monocentric experience study
   M. Fekih, A. Laabidi, H. Debbabi, L. Kallel, N. Ben Mustapha, M. Serghini, J. Boubaker, A. Filali (Tunis, TN)
10. Alexithymia and Crohn's disease: A case-control study in 70 patients  
M. Fekih, H. Zalila, H. Ben Ammar, N. Ben Mustapha, M. Serghini, J. Boubaker,  
S. Matri, A. Boussetta, L. Kallel, A. Filali (Tunis, Manouba, TN)

11. Management of perianal fistulas in Crohn's disease  
M. Fekih, M. Cheikh, N. Ben Mustapha, L. Kallel, M. Serghini, J. Boubaker,  
A. Filali (Tunis, TN)

12. Mucosal healing in ulcerative colitis (UC) after infliximab treatment –  
Ultrastructural study  
O.C. Fratila, C. Craciun (Oradea, Cluj Napoca, RO)

13. Risks and benefits of the combined therapy in the treatment of severe steroid-refractory Crohn's disease  
A. Genunche-Dumitrescu, D. Badea, M. Badea, P. Mitrut, A. Badea  
(Craiova, RO)

A. Genunche-Dumitrescu, D. Badea, M. Badea, P. Mitrut, A. Badea  
(Craiova, RO)

15. Central modulatory role of IL-9 in inflammatory bowel disease  
K. Gerlach, H.-A. Lehr, A. McKenzie, M.F. Neurath, B. Weigmann  
(Erlangen, DE; Lausanne, CH; Cambridge, GB)

16. Anti-TNF-alpha therapy in patients receiving tuberculosis chemoprophylaxis  
I. Girleanu, A. Trifan, O. Stoica, S. Chiriac, A.-M. Singeap, C. Stanciu (Iasi, RO)

17. Risk factors and incidence for low urinary tract infections in patients with inflammatory bowel disease  
I. Girleanu, A.-M. Singeap, C. Cojocariu, C. Sfarti, A. Trifan (Iasi, RO)

18. Clinical course and treatment options of Crohn's disease patients in Serbia  
V. Gligorijevic, D. Bojic, M. Krstic, D. Tarabar, A. Nagorni, L. Hadnadjev,  
P. Dugalic, G. Nikolic, B. Maksimovic, T. Brocic, Z. Milenkovic, N. Jojic  
(Belgrade, Nis, Novi Sad, RS)

19. The utility and cost-effectiveness of testing for latent TB infection in UK inflammatory bowel disease patients initiating anti-TNFα agents  
K. Greveson, S. Capocci, S. Murthy, C. Smith, S. Morris, C. Murray, I. Cropley,  
M. Hamilton, M. Lipman (London, GB)

20. The immunohistochemical assessment of MMP-2, MMP-7 and MMP-9 in IBD  
K. Guzinska-Ustymowicz, K. Niewiarowska, A. Pryczynicz, W. Famulski,  
A. Kemona, D. Cepowicz, M. Gryko (Bialystok, PL)

21. Cytomegalovirus infection reactivation and IBD: What was the primary?  
K. Hospodarska, I. Hospodarskyy (Ternopil, UA)
22. Is occult hepatitis B infection really a serious problem in patients with inflammatory bowel disease

23. Retrospective study of endoscopic polypectomy in ulcerative colitis-associated polyps
T. Ilias, O.C. Fratila, D. Puscasiu (Oradea, RO)

24. Clinical efficacy of two regimens of maintenance therapy in patients with Crohn's disease aged 7–17 years – Multicenter randomized study

25. Cell therapy in patients with acute attack of ulcerative colitis
O. Knyazev, A.I. Parfenov, P. Shcherbakov, A. Konoplaynnikov (Moscow, Obninsk, RU)

26. Cell therapy and quality of life of patients with inflammatory bowel disease
O. Knyazev, I. Ruchkina, L. Efremov, A.I. Parfenov (Moscow, RU)

27. Mesenchymal stem cells increases the effectiveness of anti-inflammatory therapy with newly diagnosed Crohn's disease – 4 years of observation
O. Knyazev, A. Konoplaynnikov, I. Ruchkina, A.I. Parfenov, P. Shcherbakov (Moscow, Obninsk, RU)

28. The safety of biological treatment of IBD
M. Konecny, V. Prochazka (Olomouc, CZ)

29. Pseudotumoral colonic form of Crohn's disease: A series of 16 cases
S. Matri, M. Fekih, B. Ben Slimene, A. Laabidi, N. Ben Mustapha, M. Serghini, J. Boubaker, L. Kallel, A. Filali (Tunis, TN)

30. Crohn's disease of the upper gastrointestinal tract: Is this location more severe?

31. Colon polyps distribution analyse in patients with inflammatory bowel disease
V. Mokricka, I. Ozola-Zalite (Riga, LV)

32. Age distribution analyses in adult patients with onset Crohn's disease
I. Ozola-Zalite, V. Mokricka (Riga, LV)

33. Is anxiety and depression responsible for some symptoms in patients with inflammatory bowel disease (IBD)?
A. Pacurari, C. Banciu, A. Munteanu, C. Serban, I. Romosan (Timisoara, RO)
34. Inflammatory bowel disease – A risk factor for low bone mineral density
   A. Pacurari, A. Munteanu, C. Banciu, C. Serban, I. Romosan (Timisoara, RO)

35. Osteo-articular affecting in IBD – Importance and treatment
   O. Petrascu, V. Birlutiu (Sibiu, RO)

36. Efficacy of infliximab in the treatment of inflammatory bowel disease (IBD) in children
   A. Potapov, M. Venediktova, E. Tsimbalova, A. Anushenko, M. Varichkina (Moscow, RU)

37. Switching patients with ulcerative colitis to once daily mesalazine improves outcome and reduces cost in primary and secondary care
   H. Prasher, P. Savania, R. Jazrawi (Leicester, Bucks, GB)

38. The expression of various apoptotic proteins in inflammatory bowel diseases
   A. Pryczynicz, K. Niewiarowska, K. Guzinska-Ustymowicz, W. Famulski, A. Kemona, D. Cepowicz, M. Gryko (Bialystok, PL)

39. Long-term outcome of eradication of complex perianal fistula by mucosal advancement flap in IBD patients
   O. Ryska, Z. Serclova, J. Marvan, J. Kalvach (Prague, CZ)

40. The levels of long and short pentraxins in inflammatory bowel disease
   I. Silosi, M. Cojocaru, V. Biciusca, C.A. Silosi, S. Rogoz, I.M. Cojocaru, V.M. Boldeanu (Craiova, Bucharest, RO)

41. The role of the Tec-family kinase Itk in the development of inflammatory bowel disease
   S. Steiner, R. Atreya, M.F. Neurath, B. Weigmann (Erlangen, DE)

42. Mannan-binding lectin (MBL) in inflammatory bowel disease
   A. Szala, L. Bak-Romaniszyn, A. Sokolowska, A. Swierzko, L. Durko, E. Malecka-Panas, M. Cedzynski (Lodz, PL)

43. Infliximab therapy in children with moderate-to-severe ulcerative colitis
   M. Szychta, M. Dadalski, P. Landowski, B. Klincewicz, M. Sladek, K. Karolewska-Bochenek, G. Czaja-Bulska, E. Jarocka-Cyrta, B. Korczowski, J. Kierkus (Warsaw, Gdansk, Poznan, Cracow, Szczecin, Bialystok, Rzeszow, PL)

44. Inducing role of mucosal mast cells during colitis-associated colorectal cancer
   B. Weigmann, M. Stassen, M.F. Neurath (Erlangen, Mainz, DE)

45. The adaptive potential of organism in patients with ulcerative colitis and anemia
   E.V. Zigalo, L.V. Demeshkina, V.M. Zigalo (Dnipropetrovsk, UA)
Session I

Understanding the mechanisms of disease
Exploiting eQTL information to identify causative genes in risk loci for inflammatory bowel disease

Y. Momozawa, E. Théâtre, V. Deffontaine, W. Coppieters, M. Mni, F. Crins, L. Karim, M. De Vos, D. Franchimont, S. Vermeire, E. Louis, M. Georges
Unit of Animal Genomics, GIGA-R & Faculty of Veterinary Medicine, University of Liège (B34), 1 Avenue de l'Hôpital, 4000 Liège (Sart Tilman), Belgium

GWAS have identified more than 150 risk loci for inflammatory bowel disease (IBD). Risk loci typically span ~ 200 Kb encompassing ~ 4 genes on average (range: 0 to > 35). Formal identification of the causative genes has only been achieved for a handful of loci, yet achieving this is essential to gain better understanding of pathogenesis and to reap the full benefits of GWAS.

To streamline the identification of causative genes within risk loci we have collected samples from nine IBD-relevant cell types (CD4, CD8, CD19, CD14, CD15, platelets, ileum, colon, rectum) from 350 healthy Caucasians. We have performed transcriptome analysis on all ~3,150 samples using Illumina HT12 arrays. All individuals were genotyped with the Illumina OmniExpress array and additional genotypes imputed from the 1,000 Genomes project. eQTL analyses revealed > 5,500 cis-eQTL (FDR < 0.05), and > 200 trans-eQTL (experiment-wide p < 0.05). eQTL sharing between tissue ranged from 86% (CD8-CD4) to 13% (CD8-PLA). IBD risk loci were enriched in eQTL for all tissue types except platelets, and was most pronounced for CD8 and CD15 cells.

The majority of risk loci are thought to reflect the effect of regulatory variants on the expression of the causative gene(s) in a target tissue. The ensuing prediction is that for such risk loci the “disease association pattern” (DAP) should be very similar to the corresponding “eQTL association pattern” (EAP). We have developed a metric that quantifies the resemblance between DAP and EAP, accounts for known coding variants, and provides an empirical estimate of its statistical significance. We have applied it to all known IBD risk loci and have developed a website (CEDAR) to make the information available to the community.

We observed highly significant correlations between DAP and the EAP of specific positional candidate genes in specific tissues. For some of these (type 1), increased risk is associated with increased transcript levels, while the opposite is observed for others (type 2). We have selected the 25 genes with most significant correlation between DAP (CD) vs EAP correlation and have re-sequenced their exons in 3,000 cases and 3,000 controls using the Truseq Custom Amplicon approach. Our aim is to prove the causality of some of them by demonstrating an increase in the burden of disruptive coding variants in either cases (type 1) or controls (type 2). Latest results will be presented.
Mechanisms of tissue remodeling in IBD

Claudio Fiocchi
Department of Gastroenterology and Hepatology, Digestive Disease Institute, Department of Pathobiology, Lerner Research Institute, The Cleveland Clinic Foundation, Cleveland, OH, USA

All chronic inflammatory diseases are invariably accompanied by tissue remodeling caused by the response of resident tissue cells to multiple signals derived from molecules produced by cells in the inflammatory milieu. Both forms of inflammatory bowel disease (IBD), Crohn’s disease (CD) and ulcerative colitis (UC), are prime examples of the powerful forces mediating tissue remodeling in a transmural or mucosal fashion, respectively. In IBD remodeling can involve all layers of the gut, but the degree, type and location of this process is dictated primarily by the site, intensity and duration of the inflammatory infiltrates. This does not mean that inflammatory cells are the exclusive controllers of remodeling while all other cells are passive responders. In reality all cells are actively involved in remodeling, although diverse cell types exert distinct functions and mediate various effects at different stages of the process. Epithelial cells probably have a limited input in the remodeling except when ulcers develop, while immune, mesenchymal, endothelial and lymphatic cells are more directly involved. Very little is known about the input of nerve cells in remodeling.

Stromal mesenchymal cells, primarily fibroblasts and myofibroblasts, have attracted the most attention as mediators of intestinal remodeling because they are responsible for transmural fibrosis that typically develops in CD and the subepithelial fibrosis in UC. Both responses are the result of mesenchymal cell activation and proliferation leading to an excessive production of extracellular matrix (ECM) proteins, typically exemplified by collagens and fibronectins. A number of factors are involved in this response, including cytokines, chemokines, growth factors (TGF-β isoforms in particular), prostaglandins, and surface molecules like receptors, integrins and cadherins.

In addition to activation induced by immune cell-derived soluble factors, it is becoming increasingly evident that microbial factors also play a major role in the fibrogenic and remodeling response. Through the binding to Toll-like and NOD-like receptors (TLRs and NLRs, respectively) a large number of microbial ligands, called Pathogen- or Microbial-Associated Molecular Patterns (PAMPs and MAMPs, respectively), can activate not only epithelial and immune cells, but also mesenchymal and endothelial cells. In fact, there is emerging evidence that the type and composition of the local microbiota has important modulatory effect on the fibrotic response, both in a positive and negative fashion. In addition to PAMPs and MAMPs, Damage-Associated Molecular Patterns (DAMPs), represented by a large number of intracellular molecules (such as DNAs, RNAs, nuclear proteins, ECM degradation products, etc.) that are normally not recognized by the innate immune response, also appear to be involved in fibrosis and tissue remodeling.

Once the resident mesenchymal cells are activated they proliferate and start producing massive amounts of ECM proteins which are deposited locally and begin
modifying tissue composition and function. This event is accompanied by the concomitant release of multiple proteolytic enzymes (such as matrix metalloproteinases – MMPs) from intestinal resident and luminal microbiota cells, demonstrating that tissue remodeling is in reality the outcome of multiple positive and negative forces acting together. The imbalance among these forces will ultimately result in ulcerations, fibrosis, angiogenesis and functional abnormalities, while in the normal intestine the remodeling forces are balanced and maintain the normal tissue architecture.

The stimulation of fibroblasts causes their transformation in myofibroblasts, a process mediated by numerous signaling pathways, such as those of TGF-β1 or Wnt, and a downstream activation of the transcriptional machinery follows leading to secretion of ECM proteins as well as other factors. New information suggests that the inflammasome, autophagy, and telomerase are also involved in fibroblast activation, fibrosis and remodeling. A clear genetic input in IBD-induced fibrosis has not been identified yet, but the most recent GWAS show some associations with loci containing tissue-remodeling genes, such as collagens and MMPs.

As it has been the case for many other biological responses, tissue remodeling in IBD is far more intricate that previously anticipated, and comprehensive genomic, transcriptomic and proteomic analyses may be needed to grasp its complexity and devise preventive or curative therapeutic approaches.
Challenging question: Is it possible to stratify IBD on a molecular and microbiologic basis?

Stefan Schreiber  
Internal Medicine I, University Clinic of Schleswig-Holstein, Campus Kiel, Christian-Albrechts-University, Kiel, Germany

Heritable components have been suggested long before confirming molecular discoveries were made by the observations of clustering of inflammatory bowel disease in large families and an increased concordance between monozygotic twins. Analysis of heritability suggested that IBD represents a “complex disease” and may involve a large number of interacting disease genes.

Crohn’s disease has since become a paradigm example for the successful molecular exploration of a polygenic etiology. In 2001 three coding variations in the NOD2 gene were identified that are highly associated with development of the disease. All variants affect a part of the gene that codes for the leucin rich part of the protein, that appears to be involved in bacteria induced activation of NFkB in macrophages and epithelial cells. A particular subphenotype with localization of the disease in the ileocecal region is highly associated with the variants in the NOD2 gene.

Variants in the NOD2 gene by far not explain the genetic risk for Crohn’s disease. With the advent of high-density, genome wide association studies enormous progress has been made to discover the remaining disease genes. More than 100 disease genes have been identified until today, which however still do not fully explain the total genetic risk. In addition to innate immune barrier genes, cytokine response genes (e.g. IL-23R, IL12B, STAT3) and autophagy related genes (e.g. ATG16L1, IRGM) have been identified.

In ulcerative colitis GWAS studies are lagging behind the progress in Crohn’s disease. The first GWAS studies pointed among several cytokine and macrophage function related genes point to a locus in the 3’ end of the IL10 gene. Now more than 50 disease genes are known through large meta-analyses similar to the ones conducted in Crohn’s disease.

The further genetic exploration of Crohn’s disease and ulcerative colitis will result in molecular risk maps that are presently completed with amazing speed. Most interestingly, parallel GWAS in psoriasis, atopic dermatitis and other inflammatory diseases shows an unexpected overlap in identified disease genes and regions between the different types of inflammatory barrier diseases. While these insights are challenging news for a novel understanding of disease there is no black-and-white differentiation between healthy and diseased individuals in polygenic diseases. Prediction by individual genetic variants is not possible and even individuals with disease vary only slightly from the normal population. This is different in early and extreme phenotypes where oligogenic or monogenic causations have been identified and where this has guided therapeutic interventions.
Session II

Advanced techniques for diagnosis of IBD
High-resolution endoscopy, chromoendoscopy and confocal endomicroscopy

R. Kiesslich
Medical Clinic, St. Mary’s Hospital, Frankfurt, Germany; E-Mail: info@ralf-kiesslich.de

Colorectal cancer (CRC) is a serious potential complication of inflammatory bowel disease (IBD). Regular surveillance colonoscopy to diagnose early neoplasia is the mainstay of CRC prevention in IBD.

Traditional surveillance recommendations advocate for obtaining random biopsies at regular intervals throughout the colon, as IBD patients have a propensity towards developing early flat and subtle neoplasms that may evade detection and rapidly progress to CRC. Total proctocolectomy (TPC) is further recommended for the treatment of advanced pre-cancerous lesions in IBD, including dysplasia-associated lesion or mass (DALM) and high-grade intraepithelial neoplasia.

However, newer endoscopic technologies, including high-definition endoscopy, chromoendoscopy, and confocal endomicroscopy, have significantly improved the neoplasia detection and characterization capabilities of endoscopic imaging and have the potential to alter the surveillance paradigm in IBD in favor of targeted neoplasia detection with endoscopic resection of even advanced pre-cancerous lesions.

In my talk, I will present evidence supporting the adoption of such a strategy in the routine surveillance and staging of IBD patients.

References:


Endoscopic assessment of the small bowel

Abraham Rami Eliakim, M.D.
Chaim Sheba Medical Center, Ramat-Gan, Israel

Small bowel imaging and endoscopy in IBD underwent a lot of change and advancement in the recent years. Modalities have shifted from gastroscopy, colonoscopy and small bowel follow through, to ileo-colonoscopy, CT or MR enteroscopy, wireless video capsule endoscopy and balloon assisted enteroscopy.

Nowadays endoscopy has a major role in the diagnosis of IBD, assessing its extent, treating some of its complications (stricture, bleeding), assessing the success of various treatments (mucosal healing), and possibly as a predictor of disease course.

Wireless Capsule Endoscopy (WCE) is a relatively new "toy" allowing direct, patient friendly visualization of the entire small bowel mucosa. It has gained a substantial role in the evaluation of patients with suspected Crohn's Disease (CD) and indeterminate colitis. WCE has a high positive predictive value in patients with suspected CD, when one uses more than two of the International Conference on Capsule Endoscopy (ICCE) criteria, and not less important – a very high negative predictive value in patients with suspected CD. Its role in patients with known CD, assessing their disease activity and extent, its role in assessing post-surgical small bowel recurrence and its role in the evaluation of mucosal healing are still unclear.

Balloon assisted enteroscopy has established its role as a complementary tool in cases where there is need of biopsies or treatment (dilatation of strictures).

My lecture will concentrate on these two modalities.
Cross-sectional imaging in IBD

S. Danese
Istituto Clinico Humanitas IRCCS, IRCCS in Gastroenterology, Rozzano, Italy

Appropriate imaging in Crohn’s disease is essential in many steps of disease management, including diagnosis, disease staging, and monitoring of complications and response to therapies. Indeed, the use of several cross sectional imaging techniques has evolved over time and is fully available for gastroenterologists.

Since Crohn’s disease is a transmural disease, imaging is also required to look beyond the mucosa and to assess bowel damage, including perianal lesions. In this regard, the concept of transmural healing is emerging in Crohn’s disease.

Several imaging methods have been used to assess disease activity and severity in Crohn’s disease, including small bowel follow-through, ultrasonography, computer-tomography and magnetic resonance imaging. As chronic progressive and destructive diseases, monitoring of Crohn’s disease requires repeated gastrointestinal imaging studies. For this reason, exposure to radiation over time should be minimized. Ultrasonography is a non irradiating, chip, accurate and easy accessible technique, but has some limitations. The use of ultrasonography is limited by the fact that it is highly operator-dependent and therefore difficult to standardize between centers or to archive for serial comparisons over time.

A better assessment of fibrotic and inflammatory components of intestinal strictures by imaging methods may be helpful in developing appropriate disease therapeutic strategies. Finally, proper assessment of bowel damage with the newly developed Lemann score will help monitoring disease Crohn’s digestive damage over time.
Challenging question: Can we diagnose Crohn’s disease without histology?

Anne M. Griffiths, M.D.
University of Toronto, The Hospital for Sick Children, Department of Gastroenterology, Toronto, Canada

Crohn’s disease (CD) denotes a heterogeneous group of disorders, for which no single test is diagnostic. In the presence of a compatible clinical presentation, diagnosis is confirmed by a combination of imaging, serologic, endoscopic and histologic investigations (ECCO guidelines, J Crohns Colitis 2010). “A diagnosis should neither be based nor excluded on any one variable or result” (Baumgart and Sandborn, Lancet 2012). In addressing the question, “can CD be diagnosed without histology?” several distinct scenarios must be considered.

Classic phenotypic expressions of terminal ileal or ileocolonic CD
In patients presenting with typical clinical symptomatology, supportive laboratory testing, and classic endoscopic findings in the ileocolon, mucosal biopsies are routinely taken for histopathologic examination. For the most part, however, the diagnosis has been made and treatment often initiated prior to their review, and most histologic findings are “compatible with” rather than “diagnostic of” CD. Although histologic features useful for the diagnosis of CD have been reviewed, there are no data available as to how many of these must be present to allow a firm diagnosis of CD. Granulomas (collections of monocytes/macrophages) in the lamina propria not associated with crypt injury are a corroborating feature of suspected CD after exclusion of identifiable infectious etiology, but reported prevalence in mucosal biopsies at time of first diagnosis varies between 25 and 60%. Moreover, data indicating clinical significance or prognostic value of presence or absence of granulomata have unfortunately not been convincing.

Inflammatory small intestinal disease not easily accessible to endoscopic biopsy
Isolated CD in the proximal or mid-small intestine is rare, but does occur. These cases test the convention of the requirement for histologic corroboration. Decisions must be made on a case-by-case basis whether the diagnosis is clearly CD based on other clinical features (e.g. associated perianal disease and family history of CD in first-degree relative) so that treatment could be initiated without direct biopsy e.g. of the jejunal or mid-ileal lesion(s), or whether alternate diagnoses must first be absolutely excluded.

Predominantly colonic inflammation
When suspected chronic inflammatory bowel disease (IBD) involves the colon predominantly, differentiation of CD from ulcerative colitis is often challenging. This may be particularly true in young children. pANCA and CD-associated anti-microbial antibodies, moreover, are least likely to be helpful in differentiating UC from CD in the setting of isolated colonic involvement, where most needed. Inter-rater reproducibility in diagnosis of type of IBD by different paediatric clinical investigators based on clinical, endoscopic and histologic findings, continues to be problematic (Sherlock, Inflamm Bowel Dis 2011). A review by paediatric IBD experts and pathologists of
published evidence addressing controversial questions such as gastric inflammation, rectal sparing, cecal patch, and backwash ileitis in the labeling of predominantly colonic IBD as CD-colon or UC or IBD-unclassified (IBD-U) attempted to raise awareness of diagnostic difficulties and bring consistency to interpretation of endoscopic and histologic data (Bousvaros, J Pediatr Gastroenterol Nutr 2009). The overlap of genes conferring susceptibility to UC and colonic CD is increasingly recognized, and points to the importance of identifying pathways involved in chronic inflammation and anticipated treatment responsiveness rather than diagnostic “labels”.
Session III

Optimal use of available drugs in IBD
Should we still be using steroids for treating IBD?

Alain Bitton, M.D., FRCP
Department of Gastroenterology, McGill University – Health Centre Royal Victoria Hospital, Montreal, QC, Canada

Corticosteroids (CS) have been the mainstay of medical therapy in moderate to severe inflammatory bowel disease (IBD) for over 50 years. These agents have proven to consistently induce remission in active IBD. However, their use particularly in long-term has been subject to great debate due to the multitude of associated adverse affects. As well, the available anti-TNF agents can effectively replace CS and provide significant advantages beyond induction of remission.

In 1955, a landmark placebo-controlled study established oral CS as effective therapy for acute UC exacerbations. The National Cooperative and European Cooperative Crohn’s disease placebo-controlled trials demonstrated CS efficacy in active CD but not as maintenance agents. In the severe hospitalized IBD patients parenteral CS were shown to induce remission. The consistent efficacy of CS in acute flares, their rapid onset of action, their wide availability to clinicians and low cost make them an attractive short-term choice for active IBD.

So why question the use of CS in IBD? Factors relating to adverse effects and overall efficacy temper their use. Significant CS adverse effects include avascular necrosis, bone loss, myopathy and serious infections. In addition, CS fail to achieve important therapeutic goals including mucosal healing in CD and maintenance of long-term clinical remission. Population-based studies also report poor 1 year outcomes including steroid dependency/resistance or surgery in about 50% of patients who received a first CS prescription. In light of these factors, and with the advent of biologics that are effective as induction and maintenance agents and the shift in the therapeutic paradigm toward use of biologic agents early in the disease, the role of CS in IBD has been challenged.

Nevertheless, the complete removal of CS from the IBD therapeutic arena is unlikely given their proven efficacy in acute flares. The aim therefore is their optimal use while minimizing their toxicity. Prolonged or repeated CS use should be avoided. Corticosteroids should be used judiciously and restricted to the acute setting most often as a bridge to maintenance immunosuppressive and/or biologic therapy. When indicated and the clinical condition permits biologics should be favored over CS. Synthetic CS such as budesonide can be used to attenuate CS side effects. With the push toward personalized medicine, optimization of CS use by predicting and targeting those individuals who would best respond to CS remains a major therapeutic goal.
Strategic use of immunosuppressants and anti-TNF in IBD

E. Louis
Department of Gastroenterology, University Hospital CHU of Liège, Belgium

Controlled trials and meta-analyses have showed that immunosuppressants (IS) are effective in steroid-dependent Crohn's disease (CD) and, although less well demonstrated, ulcerative colitis (UC). It has also been demonstrated that anti-TNF are effective in steroid-dependent and steroid refractory CD and UC. Anti-TNF can also decrease hospitalization rate and the need for surgery. This has not been clearly demonstrated for IS. The early use of anti-TNF seems more effective than later use and early mucosal healing is associated with decreased rate of surgery. On the contrary, early use of purine analogues does not seem to improve outcome in CD. Anti-TNF have been showed superior to IS and combo therapy superior to anti-TNF to induce steroid-free remission and mucosal healing. The main strategic questions which remain at this stage are: Is there still a place for IS monotherapy? When to start an anti-TNF? How to optimize anti-TNF? Is it possible to stop anti-TNF? The main justification of IS monotherapy is the low cost of this treatment and the possibility of achieving a very stable and longstanding remission in a subset of patients. According to this and provided there is no rapid need for more effective therapy, this treatment could be tried in any IBD patient not correctly maintained after a course of steroids and 5-ASA. However the failure to respond to this treatment should be recognized early and a step up to anti-TNF considered. An anti-TNF treatment should be considered early in patients at risk of rapid evolution towards tissue damage and complications. Combo therapy with anti-TNF and IS is superior to anti-TNF monotherapy but the benefit of this strategy should be put in the balance on a case by case basis with the increased risk of intolerance and complications. Anti-TNF treatment should always be fully optimized by adapting dosage and potentially adding an immunosuppressant before considering treatment failure. A treatment deescalation should only be considered when a longstanding stable remission has been achieved both clinically and at the tissue level. The cost sparing and theoretical decrease in complication risk should be put in perspective with the risk of relapse and disease progression.
Expert use of drugs: Criteria for failure

Iris Dotan, M.D.
Head, IBD Center, Department of Gastroenterology and Liver Diseases, Tel Aviv Sourasky Medical Center, 6 Weizmann Street, Tel Aviv 64239, Israel,
Tel: +972-3-6947305, Fax: +972-3-6974184, E-Mail: irisd@tasmc.health.gov.il

Therapy in inflammatory bowel diseases (IBD), both Crohn's disease (CD) and ulcerative colitis (UC) is generally administered for two main reasons: control of active inflammatory disease – whether luminal in CD and UC, or perianal in CD, and maintenance of remission. As the armamentarium of existing drugs is limited, drugs should be given at their maximal effective doses. However, the effort to overcome disease symptoms and signs should be limited, as continued therapy of an ineffective medicine will not only delay the search for an effective alternative, but may also unnecessarily expose patients to side effects. The criteria for a failing drug should be applied at different time points for each of the drug groups used in IBD, i.e. up to a couple of weeks for oral steroids (1 mg/kg), 2–4 weeks for 5-ASA, ~10–12 weeks for parenteral methotrexate (15–25 mg), ~12–16 weeks for thiopurines at doses of 1.5 g/kg for 6-mercaptopurine, and 2.5 mg/kg azathioprine. Noticeably, all drugs should be used at maximal doses for induction of remission. Moreover, pharmacological-based approach for drug optimization should be applied, rather than traditional mg/weight based approach. This is specifically relevant for the thiopurine anti metabolits. Most authors would evaluate biologic therapy effects after a few weeks, however, drug optimization considerations may be relevant here as well, and may require later evaluation, depending on the strategy assessed.

Criteria for a failing drug take into account clinical disease activity, laboratory findings, serum and fecal biomarkers of inflammation. However, more recent criteria such as mucosal healing in CD and UC, and imaging findings were suggested as well. Drug specific considerations and side effects are additional criteria.

The discussion will address suggested criteria for a failing drug, time points for decision making and specific drug-related issues. Thus, improved use of current drugs could be applied, to achieve maximal efficacy, as well as prevent unnecessary exposure to failing, ineffective drugs.
Challenging question: Is treating IBD an art or a strictly evidence-based matter?

Brian G. Feagan, M.D.
University of Western Ontario, Robarts Research Institute, London, ON, Canada

Although most gastroenterologists are aware of evidence-based medicine (EBM), some misconceptions about the subject still exist. In this lecture I will provide some insight into how clinicians should use EBM in their daily practice.

Evidence-based medicine is simply the application of the most valid scientific information to patient care. Physicians who treat patients with inflammatory bowel disease should practice medicine using the best available evidence, and this requires the ability to access and evaluate scientific information. Although it has been argued that physicians have always practiced according to the doctrine, considerable evidence exists that this is not the case; for example, large variances have been documented in practice patterns despite the presence of strong scientific evidence for a particular standard of care.

Several misconceptions exist about the EBM movement. The first is the notion that practitioners of EBM rely exclusively or even slavishly on the results of RCTs to make clinical decisions. Perhaps some clarification is necessary. There is no doubt that the RCT is the scientific gold standard for the evaluation of new therapies. Nevertheless, in some situations data from RCTs is either difficult or impossible to obtain and other kinds of evidence must be used. For example, in studies of causation it is often problematic to perform randomized experiments. Nevertheless, high quality observational evidence including clinical experience is needed to guide clinical decision-making.

Another common misconception is that data generated from RCTs have only limited relevance to the “real world” of clinical medicine because of the unique features of each clinical encounter. The nidus for this argument is that RCTs are experiments performed on unique populations of patients who are intrinsically different than those encountered in your own practice. The question then becomes whether the results of an internally valid trial is also equally valid in the context of a specific practice setting. This issue, known as generalizability in EBM-speak, is dear to the hearts of critics of EBM. It is certainly true that the volunteers who participate in RCTs are healthier and have a better prognosis than unselected patients. Furthermore, participants also are selected on the basis of inclusion and exclusion criteria that tends both to increase the likelihood of successful treatment and to minimize the possibility of adverse events. Therefore, it is reasonable to speculate that some treatments found to be effective by RCTs might not translate well in the setting of usual practice. Unfortunately, this supposition has led to underutilization of many highly effective therapies.

For example, many gastroenterologists have been reluctant to prescribe combination therapy for patient with Crohn’s disease despite the presence of favorable efficacy and safety data derived from RCTs (SONIC, Top Down). My perspective on this issue is that the results of an RCT are generalizable to my patient unless strong
evidence exists that this is not the case. Too often, clinicians deny patients access to effective therapies based on an incorrect clinical instinct.

Finally, one of the most troubling misconceptions about EBM is that it is a separate entity from traditional clinical skills. Use of the principles of EBM in the management of patients is only complementary to the qualities possessed by expert clinicians and will never supersede careful observation, sound judgment, and compassion for the patient. It is important to recognize that good clinicians intrinsically have used some of the fundamental concepts of EBM by espousing principles such as ‘do the last test first’ and ‘go where the money is’.

Most of us would like to believe that we practice EBM; however, my perception is that there are several areas, particularly with respect to the treatment of IBD, where this is not the case. Some illustrated examples will be provided.

In conclusion, although medicine requires artistry, if you believe that patient care should be based on the best data available, it is difficult not to buy into the concept of EBM.
Session IV

Emerging new therapies
Cell therapies in IBD

Elena Ricart, M.D., Ph.D.
Department of Gastroenterology, Hospital Clinic, Barcelona, Spain

Present therapy of inflammatory bowel diseases (IBD) is aimed to control inflammation and to treat signs and symptoms of the disease. Therapy consists of non-specific anti-inflammatory agents such as 5-aminosalicylic acid, steroids, immunomodulators, and anti-tumour necrosis factor (TNF) therapy. The goals of therapy include the induction and maintenance of remission and an attempt to heal the mucosa with the ultimate goal of reconstituting the normal intestinal function and preventing irreversible intestinal damage. Primary and secondary failure to respond to approved therapies, and in some cases inability to provide a surgical solution to a particular patient due to extension and/or location of lesions, are unmet needs in the treatment of IBD, mainly Crohn's disease. Two streams of research, experimental and clinical, are the origin of the increasing utilization of cell therapies for severe immune-mediated diseases (IMIDs) including IBD. The types of cell therapies for these diseases can be divided into two different areas: hematopoietic stem cell therapies, and selected/conditioned immune cell therapy, the latter including mesenchymal stem cells (MSC) based cell therapies and more recently the use of ovalbumin-specific T-reg cells. The considerable enthusiasm surrounding the stem cell field was initially based on the unique biological properties of these cells and their capacity to self-renew and regenerate tissue and organ systems; later, the immunomodulatory power of stem cell therapy has become also evident.
**Anti-adhesion therapy**

Julian Panés  
Department of Gastroenterology, Hospital Clinic, Barcelona, Spain

Recruitment of circulating leukocytes to areas of inflammation is a key process in the pathophysiology of inflammatory bowel diseases. Interaction between circulating leukocytes and venular endothelium comprises a multistep process in which specialized adhesion and signaling molecules participate to mediate each of a series of sequential steps. In the first step, leukocytes marginated from central venular blood flow contact the endothelium and initiate rolling along the vascular lumen. Rolling delays the transit of leukocytes, allowing “sampling” of the local microenvironment for activating factors that act primarily through serpentine receptors. In this second step, these activating factors (chemokines) trigger rapid intracellular signaling in the leukocyte, leading to functional activation of cell surface adhesion molecules through conformational changes (integrins), which then mediate firm arrest of the cell on the vessel wall. Finally, transendothelial leukocyte migration can occur if a chemotactic signal is generated in the perivascular compartment.

Integrin function abrogation by means of neutralizing monoclonal antibodies has proven to be a very effective strategy in limiting both acute and chronic forms of inflammation in animal models and in human IBD. However, selective blockade of the β2-integrin receptor ICAM-1 by means of an anti-sense molecule was not effective for treatment of Crohn’s disease.

The anti-α4 antibody natalizumab has shown efficacy for induction and for maintenance of response and remission in patients with moderate and severe Crohn’s disease, but a major safety setback such as the appearance of progressive multifocal leucoencephalopathy in 1/1000 treated cases, led to impose limitations to its clinical use, and search for more specific blocking mechanisms.

The more selective anti-α4β7 antibody vedolizumab has proved efficacious for induction of clinical and endoscopic remission in ulcerative colitis, and initial results also suggest efficacy for induction of response in Crohn’s disease. Selective blockade of the α4β7 receptor MAdCAM-1 expressed predominantly in the intestine, may avoid the risk of central nervous system infectious complications associated with the nonselective blockade of all α4-integrins, and treatment with an anti-MAdCAM-1 antibody showed promising results for induction of remission in UC. New anti-α4β7 and anti-β7 antibodies are now under development. Selective blockade of these molecules has not been associated with progressive multifocal leucoencephalopathy in the cases treated so far.

In conclusion, the development of safe and effective drugs that target these molecular components of the inflammatory response may yield novel, improved therapies for IBD that cover unmet needs.
Modulation of cell signalling

Subrata Ghosh, FRCP, FRCPC, FRCPE, FCAHS,
Professor of Medicine, Chairman of the Department of Medicine, University of
Calgary, Calgary, AB, Canada

Cytokines orchestrate immune and inflammatory responses involved in the pathogenesis of inflammatory bowel disease (IBD). Protein kinases mediate most of the signal transduction in eukaryotic cells. Janus kinases (JAKs) are a family of protein tyrosine kinases that play a pivotal role in cytokine receptor signaling. Indeed, a major subgroup of cytokines use Type I and II cytokine receptors which signal via the activation of JAKs. CP-690,550 (tofacitinib) is an oral JAK inhibitor that has been studied in autoimmune pathologies, including IBD and rheumatoid arthritis with good overall efficacy and acceptable safety profile. Other oral JAK inhibitors have also been developed and are evaluated in different phases of clinical trials. Mitogen-activated protein kinases (MAPKs) are also part of a family of protein kinases that have a role in intestinal inflammation, cytokine production, and T cell activation. However, MAPK inhibitors have been disappointing in the treatment of IBD, either due to toxicity or lack of efficacy. Modulation of cell signalling may also affect mononuclear cell trafficking and intestinal restitution.
Challenging question: How do new therapies contribute to personalized medicine in IBD?

Professor Remo Panaccione
Inflammatory Bowel Disease Clinic, University of Calgary, Calgary, AB, Canada

The mapping of the human genome was a major scientific milestone that has opened the door to new approaches to understand and treat disease. Cancer and cardiovascular disease are two areas in which genomics are showing promise for treatment advances, although challenges remain. From a genetics perspective inflammatory bowel disease (IBD) serves as guiding light for complex genetic disorders and there has been a significant advance in genes that put individuals at risk for developing IBD in the last 5 years which also provides insights into potential therapeutic targets for drug development.

Personalized medicine refers to the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not. We’re moving from the age of one size fits all medicine to personalized medicine based on the genetic profile of individual patients.

Personalized medicine has made tremendous strides in other areas such as oncology due to the discovery of biomarkers and their corresponding targeted therapies. Biomarkers are defined a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. Biomarkers may be used to see how well the body responds to a treatment for a disease or condition. One of the first examples of personalized medicine is the drug Herceptin. About 30% of patients with breast cancer have a form that over-expresses a protein called HER2, which is not responsive to standard therapy. Herceptin was approved for patients with HER2 positive tumors in 1998 and further research in 2005 showed that it reduced recurrence by 52% in combination with chemotherapy.

Despite, the advances in our understanding of the genetics in IBD and the search for novel biomarkers we are still a long way from a true personalized medicine approach. A review of our current understanding as it relates to IBD therapy will be presented.
Session V

Best surgical approaches for IBD
Perforating Crohn’s disease: Conservative and surgical treatment

Gianluca M. Sampietro, M.D.
Head of IBD Surgical Unit, Department of Surgery, Gastroenterology and Oncology, “Luigi Sacco” University Hospital, Milan, Italy

Surgery is a part of the clinical history of patients with Crohn’s disease (CD), since nearly all the patients receive at least one surgical procedure. The main indication for surgery is obstruction, but 50–60% of patients present a concomitant perforating disease at surgery, and 10% of patients have a primary indication for abscess or fistula. Generally, fistulas are classified on an anatomical basis, indicating the site of origin followed by the target (i.e. ileo-colic, ileo-vescical, etc). Entero-enteric fistulas are frequently asymptomatic and are not always considered an indication for surgery. However, in case of by-pass with severe malnutrition or bacterial overgrowth (i.e. duodenal involvement) surgery is the only option. Entero-vescical, -ureter, -biliary, fistulas, due to their potential for septic complications are a definite indication for surgery. Entero-genital fistulas have an indication mainly for their impact on the quality of life. Entero-cutaneous fistulas are, in most cases, a late surgical complication, and the indication and timing for treatment are due to their output volume. Abscesses may be present alone or in association with enteric fistulas. The initial approach is conservative, and a percutaneous drainage should be a good treatment or a bridge to elective surgery. Since a modern surgical approach to CD has to be minimally invasive and highly conservative whenever possible, the presence of perforating disease should be well characterized in order to plan a laparoscopic approach and to reduce the amount of resected bowel, in case combining resection and strictureplasty. Perforating CD necessitate of a multi-disciplinary approach involving, behind the gastroenterologist and the surgeon, the radiologist, the urologist, the gynaecologist and the nutritionist in order to obtain the best tailored treatment.
Best prevention of postoperative recurrence in Crohn’s disease

Geert D’Haens, M.D., Ph.D.
Academic Medical Center, Amsterdam, The Netherlands

Introduction: Postoperative recurrence of Crohn’s disease is virtually inevitable, with more than 80% of patients having endoscopic recurrence 1 year after surgery and approximately 10% of patients suffering from clinical recurrence per year following surgery. Since the vast majority (> 75%) of CD patients require surgery during their disease course, it is of paramount importance to develop therapeutic interventions that alter the ‘natural history’ of CD recurrence in order to avoid further bowel loss and eventually intestinal failure.

Available preventive therapies have, so far, been disappointing. While corticosteroids have been totally ineffective, aminosalicylates and thiopurines have had only marginal effects on the severity and incidence of postoperative CD recurrence. Recently, however, the effects of the anti-TNF antibody infliximab were studied in pilot trial at a single academic center. The results were extremely encouraging in favor of anti-TNF treatment and this finding led to a larger placebo-controlled trial (Prevent) to investigate the benefits of infliximab in the postoperative setting. Simultaneously, the effect of adalimumab on progressive recurrence is being tested in the POCER trial in Australia and New Zealand.

Over the years, several risk factors for recurrence of postoperative Crohn’s disease have been identified. These include smoking (particularly in female patients), young age, short disease history, multiple surgeries and perforation as the indication for surgical resection. Using these factors, it has become possible to use more proactive preventive strategies in a subset of patients at high risk.

We propose a therapeutic algorithm based on which all patients undergo an ileocolonoscopy 6–12 months following surgery. The endoscopic image at that point is predictive of the further course of the disease including symptomatic recurrence. Patients with severe lesions need treatment intensification in order to establish mucosal healing. Patients with no or mild lesions can be followed even without treatment with repeat endoscopic assessment 1–3 years later. This individualized tailored approach may lead to significant reductions in recurrence rates and hence alter the natural course of the disease.
Challenging question: Surgery or anti-TNF in steroid-refractory terminal ileal disease?

W.A. Bemelman
Academic Medical Center, Amsterdam, The Netherlands

Ileocecal Crohn's disease (CD) can be treated medically as well as surgically. Both treatment modalities have been improved markedly in the last two decades, making CD more manageable. However, multidisciplinary research, addressing issues such as timing of surgery or medical treatment versus surgery, is scarce. Particularly in limited ileoceleal CD, ileocolic resection might be a good alternative to long-term medical therapy. This lecture discusses the evidence on medical and surgical treatment options for ileoceleal CD. It provides an aid in decision-making by discussing a treatment algorithm that can be used until further evidence on treatment is available.
Session VI

Managing IBD outside the gut
Dermatologic diseases and treatment-related complications of IBD: Prevention and treatment

Subrata Ghosh, FRCP, FRCPC, FRCPE, FCAHS
Professor of Medicine, Chairman of the Department of Medicine, University of Calgary, Calgary, AB, Canada

With the ever-growing list of pharmacotherapy available to treat patients with inflammatory bowel disease (IBD), more complex adverse events are coming to the fore. Dermatological adverse events may be confused with extra-intestinal manifestations of IBD. Present thiopurine exposure was associated with a 5.9-fold risk (95% confidence interval [CI]: 2.1–16.4) increased risk of developing non-melanomatous skin cancer (NMSC). The incidence peak was highest in Caucasians over the age of 65 with crude incidence ratios of 4.04 and 5.7/1000 patient-years for present and previous use described. In anti-TNFα-exposed subjects drug-induced lupus was witnessed in 1% of the cases and a psoriatic rash in up to 3% of the cases. Recent and persistent anti-TNFα therapy use was associated with a development of NMSC (adjusted OR 2.07, 95% CI: 1.28–3.33 and adjusted OR 2.18, 95% CI: 1.07–4.46 respectively). Cutaneous lymphomas have been rarely witnessed in subjects on thiopurine or anti-TNFα drug monotherapy. Combination therapy seemed to have an additive effect on the risk of developing NMSC and lymphoma. In addition, a wide range of cutaneous manifestations, such as psoriasis, cutaneous lupus, interstitial granulomatous dermatitis, vasculitis, acneiform reactions, vitiligo, alopecia are noted to occur with immunosuppressive drugs especially anti-TNF therapy. Newer agents such as ustekinumab has been paradoxically associated with worsening of plaque psoriasis. Many of these reactions are self limited or are treatable, not requiring discontinuation of therapy. Physicians need to be aware of the wide spectrum of dermatological complications of IBD therapy. Drug withdrawal is not always necessary, but multidisciplinary discussions should be undertaken to decide each individual case.
Ocular manifestations

L. Pablo
Head of Department, Professor of Ophthalmology and Optics, Miguel Servet University Hospital, Zaragoza, Spain

Extra-intestinal manifestations are common in inflammatory bowel disease (IBD), being reported in over 25% of patients. Ocular complications of IBD occur in around 10% of cases, but may precede systemic symptoms and are usually very nonspecific. Complications of therapy, such as cataracts or glaucoma from steroid use or keratoconjunctivitis sicca related to 5-ASA medications may also involve the eyes.

Pathogenesis remains unclear but factors as the extent of intestinal disease, disease activity, and the presence of associated arthritis have been associated with ocular involvement.

Conjunctivitis, episcleritis, scleritis and uveitis are by far the most common ophthalmic complications of IBD. However, posterior uveitis, intraretinal hemorrhages, vasculitis, choroiditis, optic neuropathy, and vasoocclusive phenomena may also occur.

The most frequent ocular manifestation is anterior uveitis (more common in women). It usually presents as a mild anterior nongranulomatous uveitis (60% of the cases). The inflammation in the eye and the inflammation in the gut rarely are correlated.

Patients with uveitis, scleritis, and other anterior segment inflammation usually respond to steroids (topical, periocular or systemic). If the inflammation is resilient to steroids, or if appreciable steroid adverse effects are encountered, systemic immunosuppressive treatment should be considered, this is more likely in HLA-B27 positive patients with uveitis.

Evaluation of the eye should be a routine component in the care of patients with IBD.
IBD and liver diseases

Herbert Tilg, M.D.
Department of Medicine, Division of Gastroenterology, Endocrinology & Metabolism, Medical University Innsbruck, Anichstr. 35, 6020 Innsbruck, Austria

Diseases of the liver and the biliary tract are commonly observed extraintestinal manifestations of inflammatory bowel diseases (IBD). Besides the most common associated liver disease i.e. PSC, drug-induced hepatotoxicity, non-alcoholic fatty liver disease (NAFLD), cholelithiasis, pericholangitis, granulomatous hepatitis and amyloidosis are well known “liver complications” associated with IBD.

PSC is a chronic inflammatory and commonly progressive disorder of unknown etiology associated with fibrosis and stricture development in the intrahepatic and extrahepatic biliary tree. Interestingly, this form of liver disease is mainly associated with ulcerative colitis (UC) but less with Crohn’s disease, although this fact is not understood. Development of PSC is highly relevant for IBD patients as cholestasis-associated problems increase over time resulting in biliary strictures, cholangitis and concurrent infection, cholangiocarcinoma and importantly UC patients with concomitant PSC have a higher chance to develop colon cancer. Diagnosis is driven by increased liver biochemical tests (mainly alkaline phosphatase), hypergamma-globulinemia with increased serum IgM levels and commonly with the detection of atypical perinuclear antineutrophil cytoplasmic antibodies (P-ANCA). Furthermore, MRCP plays today a major role in establishing its diagnosis besides ERCP. Accompanied PSC dramatically affects survival of UC patients as median survival without liver transplantation after diagnosis of a PSC is approximately 12 years. Effective treatments are unfortunately still not available and it is important to enroll these patients in early colonoscopic surveillance trials.

The other major aspect regarding IBD and liver disease refers to drug-induced hepatotoxicity. Clinically most relevant is the liver toxicity of immunosuppressants as they are used so commonly nowadays in the management of IBD. Azathioprine and mercaptopurine can cause a spectrum of liver injury from asymptomatic elevated liver enzymes (seen in 5% of patients) to cholestasis and veno-occlusive disease. 6-thioguanine, a metabolite of azathioprine, probably is the most hepatotoxic drug leading to nodular regenerative hyperplasia, which can only be recognized by liver biopsy. Concerns regarding hepatotoxicity of methotrexate have decreased in the last years. Anti-TNF agents also rarely lead to increased aminotransferase levels. Cholestatic hepatitis has been described in a few cases of anti-TNF treated patients. Sulfasalazine, which is currently mainly used in UC patients with extraintestinal symptoms, can cause both hepatocellular and cholestatic enzyme abnormalities.

NAFLD seems to be more common in IBD patients compared to healthy controls. Cholecystolithiasis, pericholangitis, liver abscesses, primary biliary cirrhosis and pericholangitis are less frequently observed in IBD patients. Overall, IBD physicians have to be familiar with these liver complications to improve and to optimize management of their patients.
Challenging question: Osteoarticular manifestations: Specific treatments and/or treating the intestinal disease?

M. De Vos
Department of Gastroenterology, University Hospital Gent, Gent, Belgium

The association between spondyloarthropathy and microscopic gut inflammation has been recognised for a long time.

Over the past years, much emphasis has been made to identify patients at an earlier stage of disease, prior to the presence of structural changes. To this end, new classification criteria have been developed which allow the classification of patients to the spondyloarthritis (SpA) cluster based on their predominant symptoms: axial SpA with inflammation in axial skeleton (sacroilitis, spondylitis) and peripheral SpA with inflammation in peripheral joints (arthritis) and/or entheses (enthesitis). Axial SpA is subdivided in ankylosing spondylitis (AS) associated with radiographic evidence of structural damage and non-radiographic axial SpA (nr-axial SpA) characterised by the absence of structural changes on conventional X-rays but the presence of inflammatory changes on MRI (erosion on 1 sacroiliac joint quadrant and/or bone marrow edema on 2 sacroiliac joint quadrants) (Weber et al. 2012). To evaluate axial involvement on MRI T1 weighted sequences are necessary for structural damage and short T inversion recovery sequence (STIR) or T2-weighted fat-suppressed fast spin echo (FSE) sequence or T1w fat suppressed FSE after administration of gadolinium (Hermann et al. 2012).

Using these new classification criteria, an ileocolonoscopy was done in 65 patients with SpA including 49 patients with axial SpA and 16 peripheral SpA. Gut inflammation was found in 46.2% of patients (16.9% acute inflammation – 29.2% chronic inflammation). Sites of involvement were ileum in 50% – colon in 23.3% and ileocolon in 26.7% of patients). Macroscopic lesions were identified in 50% of inflamed area varying from oedema and erythema to erosions and ulcerations. Gut inflammation was independently associated with male sex, high articular disease activity, restricted spinal motility and younger age. As previously reported, we confirmed that these findings are independent of HL-B27 carriage. Prevalence of gut inflammation was similar in AS and nr-axial SpA and independent of HLA-B27 carriage (Van Praet et al. 2012). Anti-TNF has been proved to be clinical effective in this new subgroup of patients with early inflammatory non-structural involvement of axial skeleton (Sieper et al. 2012). Effect on long term evolution is today unknown.

The introduction of this newly redefined concept of spondyloarthritis is essential in the identification of IBD-phenotypes and their link to genetic analysis. Similarly, the presence of gut inflammation in these early inflammatory axial SpA together with animal data (TNFΔARE mice) support the thight link between gut and articular inflammation in the global concept of immune mediated diseases. At the present time anti-TNF seems to be the most effective drugs for both pathologies.
Session VII

Cancer in IBD
Management of colonic dysplastic lesions

Maria Pellisé
Department of Gastroenterology, Hospital Clinic, Barcelona, Spain

The aim of any screening or surveillance program must be to identify early lesions to enable treatment and prevention before the development of invasive cancer. A surveillance program must be acceptable to patients and practically possible to implement. There is a move away from using random colonic biopsies towards targeted biopsies aimed at abnormal areas identified by newer colonoscopic techniques (narrow band imaging, chromoendoscopy, confocal microendoscopy). However, the attitude towards a patient with a dysplastic lesion is not well established. Bowel cancer screening in the general population relies on identification of adenomatous lesions which can be resected before they transform into carcinoma. The therapeutic approach to such lesions, the patients groups at risk and the intervals of surveillance are reasonably established. Contrarily, IBD-CRC poses different challenges: dysplastic lesions do not follow the adenoma-carcinoma sequence, they can be difficult to see (flat lesions), difficult to resect completely, and multifocal. Prophylactic proctocolectomy eliminates the risk of CRC but this strategy is not acceptable to most patients or physicians. Moreover, IBD patients can harbor dysplastic lesions related to the sporadic colorectal cancer pathway which clinical significance differs clearly from colitis associated dysplastic lesions. Nowadays, therapeutic recommendations for management of dysplasia in IBD are based on macroscopic pattern and microscopic characteristics. As an example, consensus guidelines state that adenoma-like lesions can be adequately treated by polypectomy unlike non-adenoma-like raised lesions or flat high-grade dysplasia that should undergo colectomy. The present article is aimed to summarize the existing evidence on this thorny matter.
Small bowel dysplasia and cancer in Crohn's disease

Franck Carbonnel, M.D., Ph.D.
Service de Gastroentérologie, Hôpitaux Universitaires Paris-Sud, Site de Bicêtre, Assistance Publique-Hôpitaux de Paris (AP-HP), Université Paris Sud, Le Kremlin-Bicêtre, France

Small bowel adenocarcinoma (SBA) is an important concern in Crohn’s disease (CD) patients. Patients affected with CD of the small bowel are at higher risk of developing SBA. The standardized incidence ratio (SIR) of SBA in patients with CD varies from 18.75 to 33.2 in population-based studies. Although rare in absolute number, SBA in CD accounts for approximately 30% of the risk of colorectal cancer in patients with CD of the colon (Elriz et al. Inflamm Bowel Dis. 2013; in press). Carcinogenesis of SBA associated with CD share some similarities with colorectal carcinogenesis associated with UC and CD. An inflammation-dysplasia-carcinoma sequence exists in SBA associated with CD. Carcinomatous and dysplastic lesions occur in inflammatory areas. Dysplasia is found in half of the SBA specimens, either adjacent or distant and can either be raised or flat. The accumulation of genetic alterations during the inflammation-dysplasia-carcinoma sequence in SBA associated with CD is similar with those observed in colitis-associated CRC. MSI occurs in a minority of patients, overexpression of the p53 protein occurs in approximately 60% of SBA and small bowel dysplasia. Mutation in KRAS occurs in approximately 20% of SBA and 10% of dysplastic lesions and. Several protective factors for SBA in CD have been proposed, among which long term use of mesalamine and previous small bowel resection (Piton et al. Am J Gastroenterol. 2008;103:1730). SBA in patients with small bowel CD occurs at an earlier age than SBA de novo (43 vs 68 years; Palacsak-Juif et al. Inflamm Bowel Dis. 2005;11:828). Diagnosis of SBA is difficult in CD patients. Symptoms of SBA are nonspecific and are hard to distinguish from relapse of CD. Current morphological investigations fail to differentiate benign and malignant stricture in small bowel CD. Most SBA in CD are diagnosed intraoperatively or by microscopic examination of resected specimens. SBA in patients with CD carries a poor prognosis as shown by its median survival of only 35% at 5 years (Palacsak-Juif et al. Inflamm Bowel Dis. 2005;11:828). Until now, SBA in patients with small bowel CD has long been viewed as a rare and ominous disease for which any screening or early detection strategy is unlikely to be useful. However this view can be challenged. We suggest that screening of small bowel cancer and dysplasia similar with that of colorectal cancer screening in patients with longstanding extensive UC or colonic CD may reduce SBA incidence and improve its prognosis. The feasibility and yield of endoscopic screening of SBA and dysplasia in patients with longstanding small bowel CD remain to be established. It is the purpose of an ongoing prospective study by the GETAID.
5-ASA and chemoprevention: Does it work?

Prof. Laurent Peyrin-Biroulet, M.D., Ph.D.
Inserm U954 and Department of Hepato-Gastroenterology, University Hospital of Nancy-Brabois, Université Henri Poincaré 1, Allée du Morvan, 54511 Vandœuvre-lès-Nancy, France
Tel.: +33-3-83153631, Fax: +33-3-83153633, E-Mail: peyrinbiroulet@gmail.com

5-Aminosalicylic acid (5-ASA)-containing drugs are the mainstay of therapy in inflammatory bowel disease (IBD). Intestinal inflammation is known to the main risk factor for colorectal cancer (CRC) in IBD. Hence, all drugs that are able to induce and maintain mucosal (MH) may prevent CRC risk in IBD. In patients with mild to moderate ulcerative colitis (UC), a recent systematic review of 5-ASA trials demonstrated that mucosal healing (MH) was achieved in nearly 50% of patients. This meta-analysis clearly underscored the potential of 5-ASA therapy for reducing CRC risk in IBD patients. Furthermore, a systematic review including 48 studies linked 5-ASA chemopreventive properties to 5 distinct pathways. These include interference with cell cycle progression (12 references), scavenging of reactive oxygen- or nitrogen-derived metabolites (16 references), TNF-alpha/TGF-ss signalling (11 references), WNT/beta-catenin signalling (5 references) and antibacterial properties (4 references). Therefore, in addition to their overall anti-inflammatory activity on the intestinal mucosa, 5-ASA compounds have specific effects on colorectal carcinogenesis at the molecular level. In 2005, a landmark meta-analysis of observational studies found a protective association between 5-ASA and CRC or a combined endpoint of CRC/dysplasia in UC patients. More recently, a meta-analysis failed to identify a protective effect of 5-ASA on CRC risk in non-referral populations, but in a separate analysis of 9 clinic-based studies, the pooled OR was 0.58 (95% CI: 0.45–0.75), further highlighting the chemopreventive effect of 5-ASA on CRC risk.

In conclusion, 5-ASA therapy may reduce CRC risk by healing the mucosa of UC patients and via specific mechanisms of action at the molecular level. Conducting a clinical trial providing the best level of evidence by comparing UC patients receiving 5-ASA treatment versus those included in a placebo arm would be unethical. According to international guidelines, long-term maintenance 5-ASA therapy is thus recommended in all UC patients who are primary responders to this drug class, with the exception of some patients with proctitis.
Challenging question: Use of immunosuppressants and biologicals in patients with previous cancer

Professor Laurent Beaugerie, M.D., Ph.D.
Department of Gastroenterology, AP-HP, Hôpital Saint-Antoine F-75012 and
Université Pierre et Marie Curie Univ Paris 06, F-75005 Paris, France

Thiopurines promote EBV-related lymphomas, non-melanoma skin cancers and acute myeloid leukemias. Tumor necrosis factor alpha (TNFα) may inhibit or activate carcinogenesis according to the cellular pathways that are activated. It is why it is difficult to predict the impact of anti-TNFα drugs on cancer risk in clinical practice. Recent data from rheumatology suggest no or slight increase in the risk of cancer in general, and at worst a slight increase in the risk of lymphoma and non-melanoma skin cancers, in patients receiving anti-TNFα therapy. However, the risk of melanoma seems to be increased by these drugs. Whether corticosteroid-induced immunosuppression is associated with an increased risk of cancer is controversial.

Transplanted patients with previous history of cancer are at high risk of cancer recurrence when receiving post-transplant immunosuppressive therapy, particularly within the first two years of treatment. The interval between the treatment of previous cancer and the initiation of immunosuppressive therapy impacts on the risk of cancer recurrence. A 5-year interval between cancer and immunosuppression is associated with the most acceptable risk, and desirable for transplantation candidates for cancers at highest risk of recurrence, such as aggressive breast, colon, prostate, and renal cancers. Few data exist for patients with chronic inflammatory disease. In two registers of patients with rheumatoid arthritis, no excess risk of cancer recurrence was evidenced in patients exposed to anti-TNFα. In the CESAME cohort that included essentially patients receiving thiopurines, there was no excess incidence of recurrent or new cancer associated with exposure to immunosuppressants in the 405 patients with previous cancer at cohort entry.

In clinical practice, the decision of starting or resuming immunosuppressants in IBD patients with recent cancer should be discussed case by case with cancer specialists. However, taken into account the experience of transplant specialists, it could be suggested not to consider a waiting period for women with uterine cervical cervix high-grade dysplasia adequately treated. For other cancers, a waiting period of two years should be considered if possible. During this period, treatment of IBD should be restricted to 5-ASA, steroids, nutritional therapy, or surgery, except in case of aggressive IBD that cannot be controlled by these methods. A longer waiting period of 5 years could be recommended for the most aggressive forms of cancers, such as melanomas, severe breast cancers, sarcomas, urinary tract cancers, and myelomas. Regarding the choice of immunosuppressive therapy, monotherapies, if efficient, should be preferred to combo-therapies, and among monotherapies, anti-TNF could be preferred to thiopurines, except for melanomas and breast cancers.
Session VIII

Closing lecture
Towards personalized medicine in IBD

Séverine Vermeire, M.D., Ph.D.
Division of Gastroenterology, University Hospitals Leuven, Belgium

Treatment options for long-term control of disease activity in patients with IBD include primarily 5-aminosalicylates, immunomodulators and biological agents targeting TNF-alpha. For UC, 5-ASA should be the initial therapeutic choice for most patients, and when this fails, combination of azathioprine with infliximab has shown to be most efficacious. For CD, also the combination of azathioprine with infliximab is superior over either drug alone, but here, an additional choice between adalimumab and infliximab is also available. With the advent of new classes of biological therapies, choosing who is a candidate for anti-TNF or for an anti-adhesion strategy (vedolizumab being the most advanced in development), will become important as 15–20% of patients are primary non-responder or respond very minimally to anti-TNF. Also, SONIC showed that 30% of patients enter complete clinical remission and 16% have complete healing after 6 months of monotherapy with only azathioprine. Identification of these patients will allow to avoid expensive biologicals.

For those patients responding to anti-TNF, monitoring response rates and loss of response has been made much easier since drug and antibody levels can be determined in the blood. Low drug trough levels without antibodies should urge to decrease the interval and/or increase the dose. Likewise, high trough levels in the presence of symptoms, CRP and/or mucosal lesions, should drive the physician to stop therapy and seek alternative therapeutic options. Ongoing studies will give the answer if this individually-tailored therapy based on anti-TNF drug levels is superior to our current management which is based on clinical symptoms and biological signs of inflammation such as CRP or faecal calprotectin.

Although a lot of progress has been made in the past years, there is still much to be done to introduce the concept of individualized therapy in every day’s practice. Nevertheless, one should not think the available biomarkers are research tools only and we should start using what we have available already!
List of Chairpersons, Speakers and Scientific Organizers

Dr. Matthieu Allez
Service de Gastroentérologie
Hôpital Saint-Louis
1, avenue C. Vellefaux
75010 Paris
France

Dr. Sandro Ardizzone
Gastrointestinal Unit
Ospedale “Luigi Sacco”
Via G.B. Grassi 74
20157 Milan
Italy

Prof. Dr. Laurent Beaugerie
Department of Gastroenterology
Hôpital Saint-Antoine
184, rue du Faubourg St.-Antoine
75571 Paris
France

Prof. Dr. Willem A. Bemelman
Academic Medical Center
Meibergdreef 9
1105 AZ Amsterdam
The Netherlands

Dr. Alain Bitton
Department of Gastroenterology
McGill University - Health Centre
Royal Victoria Hospital
687 Pins avenue
Montreal, QC H3A 1A1
Canada

Prof. Dr. Yoram Bouhnik
Department of Gastroenterology
Hôpital Beaujon
100, Bd. Général Leclerc
92118 Clichy
France

Dr. Franck Carbonnel
Service d’Gastroentérologie
CHU de Bicêtre
Université Paris-Sud
78, rue du Général Leclerc
94275 Le Kremlin-Bicêtre
France

Dr. Silvio Danese
Istituto Clinico Humanitas IRCCS
IRCCS in Gastroenterology
Via Manzoni, 56
20089 Rozzano
Italy

Prof. Dr. Martine De Vos
Department of Gastroenterology
University Hospital Gent
De Pintelaan 185
9000 Gent
Belgium

Prof. Dr. Geert D’Haens
Afdeling MDL C2-112
Academic Medical Center
Meibergdreef 9
1105 AZ Amsterdam
The Netherlands

Prof. Dr. André D’Hoore
Department of Abdominal Surgery
University Ziekenhuis
Gasthuisberg
Herestraat 49
3000 Leuven
Belgium

Prof. Dr. Axel Dignass
Innere Medizin I
AGAPLESION
Markus Krankenhaus
Wilhelm-Epstein-Str. 4
60431 Frankfurt
Germany
Prof. Dr. Julián Panés
Department of Gastroenterology
Hospital Clínico y Provincial
Universidad de Barcelona
c/ Villarroel no. 170
08036 Barcelona
Spain

Dr. Maria Pellisé
Department of Gastroenterology
Hospital Clínico y Provincial
Universidad de Barcelona
c/ Villarroel no. 170
08036 Barcelona
Spain

Prof. Dr. Laurent Peyrin-Biroulet
Department of Hepato-Gastroenterology
Hôpitaux de Brabois
CHU de Nancy
Allée du Morvan
54511 Vandœuvre-lès-Nancy
France

Dr. Elena Ricart
Department of Gastroenterology
Hospital Clínico y Provincial
Universidad de Barcelona
c/ Villarroel no. 170
08036 Barcelona
Spain

Dr. Gianluca M. Sampietro
Department of Surgery, Gastroenterology and Oncology
Ospedale “Luigi Sacco”
Via G.B. Grassi 74
20157 Milan
Italy

Prof. Dr. Stefan Schreiber
Innere Medizin I
Universitätsklinikum
Schleswig-Holstein, Campus Kiel
Arnold-Heller-Straße 3 (Haus 6)
24105 Kiel
Germany

Prof. Dr. Herbert Tilg
Innere Medizin I
Universitätsklinik Innsbruck
Anichstr. 35
6020 Innsbruck
Austria

Prof. Dr. Séverine Vermeire
Gastro-entérologie
University Ziekenhuis
Gasthuisberg
Herestraat 49
3000 Leuven
Belgium
POSTER ABSTRACTS

Poster Numbers 1 – 45

Author Index to Poster Abstracts
A systematic review and meta-analysis of pancreatic auto-antibody’s (PAB) diagnostic accuracy vs. standard diagnosis in patients with inflammatory bowel disease

F.M. Al-Sulttan1,2, K.C. Fragkos1,2, D.P. Bogdanos3, A. Forbes1,2
1Centre for Gastroenterology and Nutrition, University College London; 2GI Services, University College London Hospitals; 3Division of Transplantation Immunology and Mucosal Biology, King’s College London School of Medicine at King’s College Hospital, London, UK; E-Mail: farisaboush@yahoo.com

Introduction:
• The diagnosis of IBD is currently based on the combination of clinical, endoscopic, laboratory, histological and radiological criteria. Despite the conventional methods of assessment, a small proportion of IBD patients remain unclassified, with a change of diagnosis in the first year from ulcerative colitis (UC) to Crohn's disease (CD) or vice versa in up to about 14% of patients.
• Serology is becoming an important and emerging diagnostic tool in IBD. Pancreatic auto-antibody (PAB), among others has been described as an immunological marker of IBD. As it stands, serology is not part of the "standard" diagnosis of IBD mainly because of its low diagnostic accuracy.
• The main advantage of PAB in the diagnosis of IBD is high specificity. On the other hand, the main limitation is very low sensitivity making it a poor screening test. More than one study suggested that PAB is specific for Crohn’s disease but stressed on the fact that patients with UC and healthy controls may test positive as well [1].
• The purpose of the present study is to synthesize available data from the literature on the diagnostic accuracy of PAB against standard diagnosis of IBD (with clinical, radiological and histological criteria).

Methods:
• We searched articles and abstracts indexed in Medline/PubMed, Scopus, EMBASE and Google Scholar using the following search terms: pancreatic autoantibody and inflammatory bowel disease. There was no language or time limit in our literature search.
• Papers included had to mention diagnostic accuracy measures (e.g. sensitivity, specificity) of PAB against standard diagnosis of IBD. The standards for reporting of diagnostic accuracy initiative and the review of methodological standards were used to assess study quality.
• Pooled sensitivities and specificities were calculated for PAB with use of the DerSimonian-Laird random effects model; an assessment of heterogeneity was performed with use of Cochran’s Q statistic. A pooled diagnostic OR was calculated for each of the diagnostic tests evaluated. All statistical analyses were performed with use of MetaDisc software.
Results:
1. Seventeen studies were included in the meta-analysis.
2. The pooled sensitivity was 27.6% (95% CI: 26.1–29.1%; range 11–38.2%), specificity 97.3% (95% CI: 96.6–97.9%; range 92–100%), and the diagnostic odds ratio was 13.33 (95% CI: 7.93–22.41; range 4.10–137.54), revealing moderately good discriminating characteristics.
3. This was also supported by the area under the curve (AUC) (Symmetric Curve AUC: 0.4050) in the Summary Receiver Operating Characteristic (SROC) curve (Figure 1).
4. The results were heterogeneous, as all I-square values were high and statistically significantly different from zero (p < 0.001).

Conclusion: This is the first meta-analysis of PAB’s diagnostic accuracy for the detection of IBD. Due to its low sensitivity, PAB appears to be a weak screening test for IBD; however, its high specificity indicates moderate power to diagnose IBD but it would be particularly valuable in difficult IBD cases, in conjunction with standard diagnostic criteria.

<table>
<thead>
<tr>
<th>Study</th>
<th>Clinical features &amp; settings</th>
<th>Participants</th>
<th>Study design</th>
<th>Target condition &amp; reference standard(s)</th>
<th>Index and comparator tests</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beltrao, 2010</td>
<td>Cronies diseases, healthy controls</td>
<td>81 IBD + 33 healthy controls</td>
<td>Retrospective</td>
<td>IBD, CD, UC, healthy controls</td>
<td>ASCA (IgA, IgG), PANCA, anti pancreatic</td>
<td>No follow-up</td>
</tr>
<tr>
<td>Conrad, 2002</td>
<td>CD, UC, indeterminate colitis, healthy controls, other diseases</td>
<td>112 CD, 65 UC, 13 IC, 212 others, 250 healthy GI dis. (CD, malign.)</td>
<td>Retrospective</td>
<td>IBD, healthy controls, other diseases (celiac, malig.)</td>
<td>ASCA, PAB, TTG (tissue transglutamase), anti Goblet and ANCA</td>
<td>-</td>
</tr>
<tr>
<td>Demirsoy, 2010</td>
<td>CD, UC, other GI diseases, 1º degree relatives to CD and UC</td>
<td>CD 64, UC 63, relatives to UD 25, relatives to UC 28, control 34</td>
<td>Retrospective</td>
<td>CD, UC and their first degree relatives</td>
<td>Standard + ASCA + PAB</td>
<td>No</td>
</tr>
<tr>
<td>Desplat-Jego, 2007</td>
<td>CD, UC, coeliac diseases, healthy controls</td>
<td>109 CD, 78 UC, 45 coeliac diseases, 50 healthy controls</td>
<td>Retrospective</td>
<td>CD, UC</td>
<td>Standard, PAB, ANCA, ASCA</td>
<td>No</td>
</tr>
<tr>
<td>Homsak, 2010</td>
<td>UC, CD and healthy controls</td>
<td>CD 43, UC 28, 41 controls</td>
<td>Retrospective</td>
<td>CD and UC</td>
<td>Standard test, PANCA, goblet cell antibody and PAB</td>
<td>No</td>
</tr>
<tr>
<td>Joossens, 2004</td>
<td>CD, UC, healthy, relatives to CD and UC &amp; other GI conditions, healthy controls</td>
<td>CD 169, UC 120, 108 relatives to UC, 78 non-IBD, 100 healthy controls</td>
<td>Retrospective</td>
<td>CD, UC, relatives to CD and UC</td>
<td>Standard, PAB</td>
<td>No</td>
</tr>
<tr>
<td>Klebl, 2005</td>
<td>CD, UC, healthy controls</td>
<td>CD 208, UC 47, healthy controls 50</td>
<td>Retrospective</td>
<td>CD and UC</td>
<td>Standard and PAB</td>
<td>No</td>
</tr>
<tr>
<td>Study</td>
<td>Type of Study</td>
<td>Participants</td>
<td>Methods</td>
<td>Controls</td>
<td>Sensitivity (95% CI)</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------</td>
<td>--------------</td>
<td>---------</td>
<td>----------</td>
<td>----------------------</td>
<td></td>
</tr>
<tr>
<td>Koutroubakis, 2005</td>
<td>CD, UC</td>
<td>CD 77, UC 73, controls 104</td>
<td>Retrospective UC and CD</td>
<td>Standard, PAB</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Lakatos, 2009</td>
<td>CD and UC, coeliac diseases, non IBD diseases</td>
<td>CD 579, UC 110, 139 coeliac diseases, 100 healthy, 64 non-IBD disorders</td>
<td>Retrospective CD and UC</td>
<td>Standard, PAB, Goblet cell antibody, ASCA, NOD2/CARD 15 and anti Glycans</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Lawrance, 2005</td>
<td>CD, UC</td>
<td>CD 100, UC 99, control 100</td>
<td>Retrospective CD and UC</td>
<td>Standard, PAB, Goblet cell Ab, ASCA, PANCA</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Roggenbuck, 2011</td>
<td>CD and UC</td>
<td>178 CD, 100 UC, 162 healthy controls</td>
<td>Retrospective CD and UC</td>
<td>Standard, PAB, ASCA, Anti Gp2</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Seibold, 1991</td>
<td>CD, UC and relatives</td>
<td>CD 72, relatives 196, UC 16, relat. 90, control 47</td>
<td>Retrospective UC and CD</td>
<td>Standard, PAB</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Seibold, 1997</td>
<td>CD and UC</td>
<td>CD 222, UC 51, 65 healthy, 133 non IBD</td>
<td>Retrospective UC and CD</td>
<td>Standard and PAB, anti goblet antibody</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Stocker, 1984</td>
<td>CD and UC</td>
<td>CD 59, UC 46, controls 100</td>
<td>Retrospective CD and UC</td>
<td>Standard, PAB</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

Sensitivity (95% CI)

0.15 (0.06 - 0.28)
0.25 (0.19 - 0.32)
0.11 (0.06 - 0.18)
0.25 (0.19 - 0.31)
0.23 (0.16 - 0.31)
0.18 (0.10 - 0.29)
0.28 (0.23 - 0.34)
0.24 (0.18 - 0.29)
0.33 (0.26 - 0.41)
0.38 (0.35 - 0.42)
0.38 (0.31 - 0.45)
0.23 (0.18 - 0.28)
0.18 (0.14 - 0.23)
0.26 (0.21 - 0.31)
0.35 (0.25 - 0.45)
0.24 (0.16 - 0.33)
0.31 (0.16 - 0.48)

Pooled Sensitivity = 0.28 (0.26 to 0.29)
Chi-square = 105.29; df = 16 (p = 0.0000)
Inconsistency (I-square) = 84.8%
Specificity (95% CI)

<table>
<thead>
<tr>
<th>Study</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beltrao 2010</td>
<td>0.97</td>
</tr>
<tr>
<td>Conrad 2002</td>
<td>1.00</td>
</tr>
<tr>
<td>Demirsoy 2010</td>
<td>1.00</td>
</tr>
<tr>
<td>Desplat-Jego 2007</td>
<td>0.93</td>
</tr>
<tr>
<td>Folwaczny 1998</td>
<td>0.97</td>
</tr>
<tr>
<td>Homsak 2010</td>
<td>1.00</td>
</tr>
<tr>
<td>Joossens 2004</td>
<td>0.92</td>
</tr>
<tr>
<td>Klebl 2005</td>
<td>1.00</td>
</tr>
<tr>
<td>Koutroubakis 2005</td>
<td>0.99</td>
</tr>
<tr>
<td>Lakatos 2009</td>
<td>0.93</td>
</tr>
<tr>
<td>Lawrance 2005</td>
<td>0.98</td>
</tr>
<tr>
<td>Roggenbuck 2011</td>
<td>0.96</td>
</tr>
<tr>
<td>Schoepfer 2009</td>
<td>1.00</td>
</tr>
<tr>
<td>Seibold 1991</td>
<td>1.00</td>
</tr>
<tr>
<td>Seibold 1997</td>
<td>0.99</td>
</tr>
<tr>
<td>Stocker 1984</td>
<td>0.97</td>
</tr>
<tr>
<td>Sykora 2000</td>
<td>0.97</td>
</tr>
</tbody>
</table>

Pooled Specificity = 0.97 (0.97 to 0.98)
Chi-square = 90.70; df = 16 (p = 0.0000)
Inconsistency (I-square) = 82.4%
References:
CMV infection in IBD: Preliminary results of a prospective study

N. Ben Mustapha¹, B. Ben Slimane¹, A. Labidi¹, M. Fekih¹, M. Serghini¹,
J. Boubaker¹, A. Filali¹, Helifa Azzouz², Slim Haouet²
¹Gastroenterology A Department; ²Anatomical Pathology Department, La Rabta
Hospital, Tunis, Tunisia

Introduction: There is an ongoing debate regarding the significance of
cytomegalovirus (CMV) in colonic biopsies and the effect of antiviral therapy in
patients with inflammatory bowel disease (IBD). CMV infection has been described as
a cause of relapse, disease exacerbation and steroid refractory and dependency
when it is for other just a marker of the severity of the disease. Antiviral therapy in
IBD complicated by CMV infection is not consensual. Our aims were to evaluate
prospectively the prevalence of CMV disease in IBD, the influence of CMV infection
on the course of IBD and indications to antiviral treatment.

Methods: Prospective study conducted from March 2012 to August 2012, including
61 patients with IBD. An ileocolonoscopy was performed with colonic biopsy in all
consecutive patients presenting with an acute flare of their disease and in whom
endoscopy was indicated. Specimens were examined by two anatomo-pathologists
who were blinded to clinic characteristics. CMV infection was defined by the
combination of histological evidence of inflammation and presence of inclusion
bodies confirmed by immunostaining. Data collected were: demographics, disease
characteristics, treatments undertaken and course of the flare. Statistical analysis
was achieved with SPSS software version 19.

Results: We colliged 61 patients: 36 (59%) CD and 25 (41%) UC. There were 57.4%
females and 42.6% males with a mean age of 32.6 years (8–72 years). 23 patients
had been on aminosalicylates, 22 had been on oral steroids, 15 on azathioprine, 5 on
steroids and azathioprine and 5 on anti-TNF therapy. CMV was recovered from
colonic samples in 14 patients (23%); 9 out of 14 (64.3%) patients had Crohn’s
disease. CMV infection was more common in pancolotic lesions (p = 0.045). Among
patients with CMV infection, there were 8 patients who presented a severe relapse of
their disease (57.1%) and 6 patients (42.8%) with mild to moderate severity. Five of
these 14 (35.7%) patients were on steroids treatment and 4 of them were on
azathioprine, when included. Steroid refractory was seen in 7 patients (11.5%), of
whom 6 had CMV infection (85%). Nine patients with CMV colitis needed Ganciclovir
therapy for 14–21 days. The 5 others were not given Ganciclovir and did not develop
a worsening of the disease. Evolution was favourable in 67% and particularly in
patients who had been treated for a period more than 15 days (p = 0.032). There was
no favourable response in 33% among them, 4 patients had required surgical
treatment and 1 patient required an anti-TNF treatment.

Discussion/Conclusion: Our study showed that CMV infection is frequent in IBD
even in Crohn’s disease and in mild to moderate steroid-naive forms. Treatment isn’t
mandatory for all patients, but it should be given more than 15 days when indicated.
High prevalence of low bone mineral density in new onset of inflammatory bowel disease

N. Ben Mustapha, M. Cheikh, M. Fekih, M. Serghini, L. Kallel, J. Boubaker, A. Filali
Department of Gastroenterology A, La Rabta University Hospital, Tunis, Tunisia

Introduction: Osteopenia and osteoporosis are frequent in inflammatory bowel disease (IBD) with ileal involvement or treated with steroids. Our aims were to determine the prevalence of low bone mineral density (BMD) at the time of IBD diagnosis, and to identify predictive factors of reduced BMD.

Methods: A retrospective study conducted from January 2002 to December 2011 including patients diagnosed with IBD in Gastroenterology A Department at the Rabta University Hospital and in whom BMD was checked up few days after the diagnosis and before starting any treatment. Data collected were: age, gender, body mass index (BMI), disease activity, disease location. Laboratory findings included serum calcium, phosphate, albumin, hemoglobin, C-reactive protein. BMD was assessed by dual energy x-ray absorptiometry (DEXA) of the lumber spine and femoral neck. Osteopenia was defined as a T-score between -1 and -2 SD, and osteoporosis as a T-score less than -2 SD.

Results: A total of 94 patients (38 men, 56 women) were enrolled. Mean age was 32.81 ± 13.12 years (range 14–72). 73 patients (77.6%) had Crohn’s disease (CD) and 21 patients (22.4%) had ulcerative colitis (UC). Mean BMI was 20.53 ± 4.83 kg/m². Low BMD occured in 51 (54.2%) patients (38 CD, 13 UC). 32 patients (34%) exhibited osteopenia and 19 patients (20.2%) showed osteoporosis. Mean vertebral T-score was -0.982 ± 1.41 (range -4.1–1.7) and BMD in this site was 1.077 ± 0.17 g/cm² (range 0.674–1.380). Mean femoral T-score was -0.326 ± 1.2 (range -3.1–2.4) and BMD in this site was 1.001 ± 0.173 g/cm² (range 0.633–1.600). There was a positive correlation between T-score and BMI. Hypoalbuminemia (≤ 35 g/l) was found to be a predictive factor of reduced BMD at the moment of IBD diagnosis. However no correlation were found between BMD and the other variables studied (age, gender, severity of the disease, disease location, CRP).

Discussion/Conclusion: The present study showed that more than half of patients with IBD had a low BMD at the time of diagnosis. Low BMI and hypoalbuminemia were the major factors affecting BMD in these patients. Bone density measurement should be performed in all patients with IBD in an early stage of the disease and not only in patients with ileal involvement or treated with steroids.
Inflammatory bowel disease in Turkish children: An analysis of 127 children

M. Çakir1, F. Ünal2, G. Dinler3, M. Baran4, H.A. Yûksekaya5, G. Tümgör6, E. Kasirga7, A.G. Kalaycî3, S. Aydogdu8

Dept. of Pediatric Gastroenterology Hepatology and Nutrition, 1Karadeniz Technical University, Faculty of Medicine Trabzon, 2Dörtçelik Children Hospital, Bursa, 319 University, Faculty of Medicine, Samsun, 4Tepecik Education and Research Hospital, İzmir, 5Selçuk University, Faculty of Medicine, Konya, 6Çukurova University, Faculty of Medicine, Adana, 7Celal Bayar University, Faculty of Medicine, Manisa, 8Ege University, Faculty of Medicine, İzmir, Turkey

Aim: To analyze the demographic, clinical and laboratory findings and outcome of the children with inflammatory bowel disease (IBD) in Turkish children.

Patients and methods: A questionnaire form including the demographic, clinical and laboratory findings and outcome of the patients with IBD were sent to 8 pediatric gastroenterology clinics. Totally, 133 patients data were sent back and 127 (95.4%) of them included to the study.

Results: Ninety (70.9%) patients had ulcerative colitis (UC), while 29 (22.8%) had crohn’s disease (CD) and 8 (6.3%) had undetermined colitis. Mean age of the patients were 11.6 ± 4.1 years, and patients with CD were younger than the patients with UC (12.3 ± 3.5 vs. 9.6 ± 5; p = 0.01). Approximately 11% of the children were < 5 years of age (6.6% in UC vs. 24.1% in CD, p = 0.01). Female to male ratio was 1.01 (1.36 in UC vs. 0.38 in CD; p = 0.008). Six (4.7%) children had the diagnosis of FMF. The main presenting symptoms were abdominal pain (77.9%), chronic diarrhea (73.2%), weight loss (37%) and fever (20.4%). Duration of symptoms was 7.2 ± 11.2 months. Frequency of arthritis, liver involvement and uveitis were 11%, 7% and 4.7%, respectively. Anatomic location for UC was proctocolitis in 11.1%, left colon in 34.4%, diffuse in 14.4% and pancolitis in 40%. Location of CD was ileal in 13.7%, colonic in 34.4%, ileocolonic 48.2% and isolated upper GIS in 3.4%. Clinical behavior of the CD was non-penetrated and non-structural in 82.7% of the patients. Three patients (10.3%) had fistulizing diseases. Presence of anemia, leucocytosis, thrombocytosis and hypoalbuminemia was 49.6%, 37.7%, 47.2% and 29.9%, respectively. All the parameters were present in 11% of the patients and all the parameters were normal in 27.6%. 67.7% of the patients were received steroid as a first-line treatment, and 4 patients (3.1%) underwent colectomy. Overall, mortality related to IBD was 1.5% (95% CI: 0.59–3.73).

Conclusion: This is first report about the clinic and outcome of the Turkish children with IBD. Our findings support that (i) IBD is clinically increasing entity in our country, (ii) laboratory findings may be normal in 25% of the patients and (iii) colectomy rate is low in our country.
Clostridium difficile infection – A permanent challenge in inflammatory bowel disease patients

R. Cerban, L.S. Gheorghe, R. Vadan, M. Manuc, B. Cotruta, C. Gheorghe
Center of Gastroenterology and Hepatology, Fundeni, Clinical Institute, Bucharest, Romania

Background: Clostridium difficile infection (CDI) is known to be associated with disease flares in patients with inflammatory bowel disease (IBD) with an increasing prevalence in last years. Until now there are limited data the literature concerning the optimal management of CDI in this group of patients.

Aim: The aim of the study is to investigate the impact of CDI in patients with inflammatory bowel disease that were admitted in our clinic in the last two years.

Methods: In a retrospective study we indentified 12 patients with IBD, that had positive results for Clostridium difficile toxins A/B from 67 (36 ulcerative colitis/31 Crohn's disease) patients that were admitted with an acute flare of the disease in our clinic between January 2011 and November 2012.

Results: A total of 12 subjects were analyzed, 58% were males. 8 patients (66.6%) had Crohn's disease (CD) and the rest had a diagnosis of ulcerative colitis (UC). Median age was 35. There was no preceding antibiotic prescription before the first episode of CDI in 10 patients (84%). All patients presented with acute gastrointestinal symptoms which mimicked a flare-up of IBD and were tested for clostridium difficile toxins A/B in the first day of their admission. 11 patients had an endoscopic evaluation at the time of their admission with suggestive lesions of pseudomembranous colitis in 7 (58.3%) of them. All patients were treated with a combination of metronidazol and vancomycin for 14 days with frequent adverse events that required dose reductions and one case of severe neutropenia associated with metronidazol therapy. In 5 patients (41.6%) disease activity did not improve significantly after antibiotic treatment, and in these cases we considered to be a simultaneous flare of IBD and concomitant corticosteroid therapy was initiated. We had a case of severe UC non responsive to steroid therapy in which we started anti-TNF-alfa treatment along with antibiotic therapy with a good clinical response. There were no cases of toxic megacolon and no patient required a total colectomy. A recurrent infection was diagnosed in 2 patients, both patients had 1 episode in the next month after their first CDI diagnosis which was managed with tapering followed by pulsed doses of vancomycin.

Conclusion: Patients with IBD that also have C. difficile infection are frequently treated with a combination of antibiotics and immunomodulators. Antibiotic treatment has been associated with an increased rate of side effects. IBD patients have an increased risk for developing recurrent CDI which represents a great challenge in treating these patients.
Endoscopic efficacy of two regimens of maintenance therapy in patients with Crohn’s disease aged 7–17 years – Multicenter randomized study

M. Dadalski¹, B. Iwanczak², M. Sladek³, A. Wegner¹, U. Grzybowska-Chlebowzyk⁴, I. Lazowska⁵, J. Maslana⁶, E. Toporowska-Kowalska⁷, G. Czaja-Bulsa⁸, G. Mierzwa⁹, B. Korczowski¹⁰, E. Czwianián⁵¹, A. Zabka¹², E. Szymanska¹, E. Krzesiek², S. Wiecek⁴, J. Kierkus¹

¹Children’s Memorial Health Institute, Warsaw; ²Department of Pediatrics, Gastroenterology and Nutrition, Medical University of Wroclaw; ³Department of Pediatrics, Gastroenterology and Nutrition Jagiellonian University School of Medicine, Krakow; ⁴The Department of Paediatrics, Medical University of Silesia, Gastroenterology Unit, Upper-Silesian Child Health Care Centre in Katowice; ⁵Medical University of Warsaw, Department of Pediatric Gastroenterology and Nutrition; ⁶Wl. Buszkowski Kielce Province Children’s Hospital, Kielce; ⁷Department of Paediatric Allergology, Gastroenterology and Nutrition, Medical University of Łódź; ⁸Paediatric Nursery Unit of Pomeranian Medical University, Division of Paediatrics, Gastroenterology and Rheumatology of Zdroje Hospital in Szczecin; ⁹Chair and Department of Pediatrics, Allergology and Gastroenterology, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun; ¹⁰Department of Pediatrics, State Hospital, Medical College, University of Rzeszów; ¹¹Gastroenterology and Pediatric Depts., Polish Mother’s Memorial Hospital, Research Institute Łódz; ¹²Department of Pediatrics, Medical University of Silesia, Zabrze, Poland

Introduction: The REACH study demonstrated the efficacy and safety of induction and maintenance therapy of infliximab with concurrent immunomodulator in children with moderate to severe Crohn’s disease (CD), whereas SONIC study revealed that combined maintenance therapy is more efficient vs. infliximab and immunomodulator alone in adults. However it is healing of mucosal lesions which seems to be most important endpoint in assessment of treatment for Crohn’s disease with biological agents. The aim of this study was to compare the endoscopic efficacy of two regimen of maintenance therapy (1. Infliximab with immunomodulator and 2. Infliximab alone) in children aged 7–17 years with moderate to severe CD.

Methods: 99 patients with PCDAI > 30 pts and endoscopic evaluation performed were involved to the study and received induction therapy with infliximab 5 mg/kg at weeks 0, 2, and 6. Clinical (PCDAI score) and endoscopic (using Simple Endoscopic Score for Crohn’s Disease (SES-CD), based on 4 endoscopic variables (ulcer size, ulcerated and affected surfaces, stenosis) in 5 ileocolonic segments and the endoscopic parameters are scored from 0–3) evaluations were performed at week 10 and patients with clinical response (decrease of PCDAI ≥ 15 and PCDAI < 30) were randomized to Group I receiving infliximab 5 mg/kg every 8 weeks with immunomodulator until week 54 (n = 45) or Group II receiving infliximab 5 mg/kg every 8 weeks with immunomodulator stopped at week 26 (n = 39). Endoscopic assessment was performed at week 54 in both groups. Primary endpoint was relapse of mucosal response defined as increase of SES CD score, and the secondary endpoint was number of patient in mucosal remission defined as SES CD = 0.
**Results:** At week 10, after induction therapy, 84 out of 99 (85%) pts had clinical response, and 78 out of 84 (93%) pts with clinical response had also mucosal response defined as decrease of SES CD score. 26 out of 84 (31%) had mucosal remission. At week 54 mucosal deterioration (increase of SES CD score) was found in 13 out of 45 pts in Group I (29%) and 11 out of 39 pts in Group II (28%) (NS). Mucosal remission was observed in 22 out of 45 pts in Group I (49%) and in 16 out of 39 pts in Group II (41%) (NS).

**Discussion/Conclusion:** Both regimens of maintenance therapy (1. Infliximab with immunomodulator and 2. Infliximab alone) are endoscopically equally efficient in children aged 7–17 years with moderate to severe CD.
Vegetative dysregulation in patients with Crohn’s disease and anemia syndrome

L.V. Demeshkina, E.V. Zigalo, A.V. Kovaleva
State Institution “Institute of Gastroenterology of AMS of Ukraine”, Dnipropetrovsk, Ukraine; Zaporozhian Medical Academy of Postgraduate Education, Zaporozhye, Ukraine

Introduction: Anemia is one of the important complications of Crohn’s disease (CD) and worsens efficiency of basic therapy because of functional reserve organism exhaustion.

The purpose of this study is to investigate vegetative regulatory systems at patients with CD with an anemia in comparison with patients with CD without anemia.

Materials and methods: 28 patients with CD were divided into two groups, those who had anemia syndrome (1 group), and those who had not (2 group). Vegetative tonus (VT), vegetative reactivity (VR), exertion index (EI), and activity of vegetative provision (AVP) by the method of varying pulsometria and loading tests (orthostatic test and Martin’s physical activities test). Statistical analysis was carried out in SPSS.

Results: Most patients with CD and anemia (80.0%) had EI 33.7 ± 7.1 symbol units (s. u.), patients of control group had normal EI 125.8 ± 14.1 (p < 0.05). These data had evidence of decreased activity of vegetative regulation in patients. Asymptomatic VR was founded more often (in 2 times) in 1 group than in 2 group that may have caused extension of humoral regulation. Results of AVP have shown that at 73.3% patients (1 group) had the increase in 4 times of protective reactions which testifies to exhaustion of compensatory adaptation reactions and the decrease in the functional reserve of these patients. This situation might contribute to treatment resistance.

Conclusions: Vagotonic VT with asympathicotonic VR and insufficient AVP were found in the most patients with UC and anemia syndrome that testified to exhaustion of compensatory adaptation reactions in these patients.
IL28Rα deficiency enforces T cell-dependent experimental colitis via suppression of regulatory T cells

H. Dornhoff1, S. Doyle2, M.F. Neurath1, J. Siebler1
1I. Department of Medicine, Friedrich-Alexander-University Nürnberg-Erlangen
Ulmenweg 18, 91054 Erlangen, Germany
2ZymoGenetics, Inc., 1201 Eastlake Avenue East, Seattle, WA 98102, USA

Type III IFNs were recently discovered and denoted as IFNλ1 and IFNλ2/3 as well as IL29 and IL28A/IL28B. Whereas IL29 occurred in human, in mice it is not functional and represents a pseudogene. IL28 signals through two different receptor complexes, the IL28Rα specific for IL29 and IL28A/B and IL10Rβ. Interaction of these cytokines with the receptors leads to the phosphorylation of the main component of the signalling STAT1, which form a trimeric complex together with IRF9, the ISGF3 complex that drives transcription of ISGs. Type III IFNs belong to the IL10 superfamily and have antiviral activity similar to the Type I IFNs. The aim of this study was to determine the functional role of IL28Rα expression on T cells in the pathogenesis of experimental colitis.

We could show that the IL28Rα is also being expressed on CD4+ T cells, which was previously described mostly for non-haematopoietic cells. Comparison between naïve and nTregs revealed a markedly downregulation of the receptor in regulatory T cells but show an upregulation by TGFβ (TiTreg)-induced peripheral Tregs in WT T cells. Interestingly, KO T cells demonstrated a significant reduction in the expression of Foxp3 in TiTregs compared to WT. There is evidence that these KO cells have an increased apoptosis rate compared to their counterparts. Analysis of these T cells in an adoptive transfer colitis model indicate a significant heightened colitis in KO reconstituted RAG mice, whereas WT reconstituted RAG mice were more protected with regard to the severity of the inflammation of the gut. Moreover, they show a massive diminishment of Foxp3 and CD25+ expressing regulatory T cells in vivo, which resulted in a higher production of proinflammatory TH1 cytokine. Furthermore, reconstitution of RAG mice with naïve WT T cells together with either in vitro generated WT TiTreg or KO TiTreg resulted in a dramatic defect in the healing of the colitis by KO TiTregs in comparison to WT TiTregs.
Long following of total proctocolectomy with ileoanal anastomosis: A monocentric experience study

M. Fekih, A. Laabidi, H. Debbabi, L. Kallel, N. Ben Mustapha, M. Serghini, J. Boubaker, A. Filali
Department of Gastroenterology A, La Rabta Hospital, Tunis, Tunisia

Background and aim: Coloproctectomy with ileoanal anastomosis (IAA) is known to be the surgical treatment of choice for most patients with intractable ulcerative colitis. The aim of this study is to report our experience with selection criteria for (IAA), functional outcomes as well as follow-up and management of complications of ileal-pouch anal anastomosis (IPAA).

Material and methods: We have conducted a retrospective chart review of patients who were admitted to hospital for inflammatory bowel disease (IBD) over thirteen years (1996–2008). Only patients who underwent IAA were included. Patient demographics, clinical indications of IAA, surgical technique, morbidity, complications and outcome following IAA were sourced from medical records. Statistical analysis was performed with SPSS software version 19.

Results: Over the thirteen-year period, twenty-two patients were included. There were 7 males and 15 females with mean age 41.45 years old (range 25–61 years old). IAA was performed after a mean time of 4 years from IBD diagnosis (range 1–13 years). Preoperative diagnoses were ulcerative colitis (UC) (n = 21) and Crohn’s disease (CD) (n = 1). Indications for coloproctectomy with IAA were severe acute colitis (SAC) resistant to intravenous corticotherapy (n = 13), SAC resistant to cyclosporine (n = 6), SAC resistant to infliximab (n = 2), dysplasia in the rectum (n = 1). Laparoscopic surgery was performed in 11.1% of patients. All patients had J-shaped ileal reservoir with a mean length of 15.67 centimetres (range 10–18). Diagnosis revision from UC to CD was noted in 4 cases after developing perianal fistula. During a mean follow-up period of 80.71 months (range 4–252 months), mortality rate was nul. Pouch-related fistula with pelvic abscesses occurred in 13.6% (n = 3) and outcome was favorable after radiological drainage and antibiotics. Pouchitis was noted in 4 patients with a mean time to IAA of 27 months (11–60 months). Episodes of pouchitis were resolved by antibiotics. Lower digestive tract bleeding occurred in 1 case and was treated with corticosteroids instillations. Mean number of stools after IAA was 5 per 24 hours during first six months. Stool and/or gaz incontinence occurred in 7 patients and sphincter anal rehabilitation was performed in 3 of them. Anastomotic stricture occurred in 4 patients and was treated by endoscopic dilatation with satisfactory functional results.

Conclusion: Restorative proctocolectomy with an IPAA is a safe procedure, with low mortality and major morbidity rates. Although total morbidity rate is appreciable, functional results generally are good and patient satisfaction is high.
Alexithymia and Crohn’s disease: A case-control study in 70 patients

M. Fekih¹, H. Zalila², H. Ben Ammar², N. Ben Mustapha¹, M. Serghini¹, J. Boubaker¹, S. Matri¹, A. Boussetta², L. Kallel¹, A. Filali¹
¹Department of Gastroenterology A, La Rabta Hospital, Tunis, Tunisia
²Department of Psychiatry D, Razi Hospital, Mannouba, Tunisia

Background: Alexithymia literally means "the inability to express emotions with words". It is a concept related to the psychosomatic medicine and included in the field of health psychology. The objectives of our study were to estimate the prevalence of alexithymia in a Tunisian population of patients with Crohn's disease and to investigate the relationship between this disease and alexithymia.

Methods: This cross-sectional study included patients treated for Crohn's disease in remission for at least six months, and controls matched for age and gender. Socio-demographic, clinical and therapeutic data were recorded for each patient. Alexithymia was assessed using the scale of Toronto (TAS-20) in the Arabic version which is validated.

Results: We included 70 patients with CD and 70 controlled matched controls. The patients with Crohn's disease were significantly more alexithymic than controls (43.3% versus 27.1% \( p = 0.036 \)). The TAS20 scores in the patients group ranged from 32 to 82 with a mean score of 54.7 ± 11.37 versus 50.13 ± 10.43 in the control group. The difference between the two groups were significant (\( p = 0.015 \)). According to a dimensional approach, patients had significantly greater difficulty describing feelings to other people (\( p = 0.007 \)), and more externally-oriented thinking (\( p = 0.03 \)). The relationship between alexithymia and Crohn's disease seems to be affected by the number of hospitalizations, the number of acute exacerbations per year, the presence of extra intestinal manifestations and the surgical treatment.

Conclusion: Psychological and affective difficulties in inflammatory bowel diseases are still underestimated. However, their existence seems to strongly influence the evolution of the illness. Our study shows that alexithymia is common in patients with Crohn's disease. A psychological intervention aiming the alexithymic dimension is essential.
Management of perianal fistulas in Crohn’s disease

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

Background and aim: Perianal fistulas are common complication of Crohn’s disease (CD), affecting up to a third of patients during their disease course. Treatment options have progressed, nevertheless, there are no guidelines as to the best management of patients with perianal CD. Through a monocentric study, we estimated the prevalence of perianal fistulas among CD patients and reported diagnostic modalities and treatment of this Crohn’s disease location.

Methods: This was a retrospective observational study over a period of 11 years from January 2000 to December 2010. All CD patients referred to our center were included. Perianal fistulas were diagnosed based on a clinical examination and/or magnetic resonance imaging (MRI). Demographic, clinical and therapeutic data was obtained. The effectiveness of treatment was evaluated.

Results: Six hundred and twenty patients were enrolled in the study. Fifty seven patients presented with perianal fistulas, 31 men and 26 women. Their mean age was 29.23 ± 8.9 years (range 14–48). The mean CD duration was 4.32 ± 2.5 years (range 0–22). In 5 patients (8.8%), perianal disease was the exclusive location of CD. Most of patients had CD with colonic involvement; either isolated (29.8%), or combined with ileal involvement (45.6%). Nine patients (15.8%) had ileal disease only. CD was inflammatory, stenosing or fistulizing respectively in 56.1%, 17.5% and 12.3% of cases. Clinical symptoms were purulent perianal discharge in 71.9% and egress of gas or feces through the vagina in 8.8%. Anal fissures and stricturing were associated respectively in 31.6% and 3.5%. MRI was performed in 2/3 of cases. Among the fistulas diagnosed, 40.4% were simple and 59.6% were complex. All patients were treated with antibiotics such as metronidazole and/or ciprofloxacin, associated, in 61.4% of cases, with the insertion of non-cutting setons. 45.6% of patients received infliximab. This therapy was combined with azathioprine in 27.1%. Complete and partial responses were obtained respectively in 50% and 20%. The average follow-up was 4.53 ± 3.7 years. Recurrence of perianal fistulas was noted in 5.3% of patients.

Conclusion: In our study, the rate of perianal fistulas in patients with CD was 9.1%. The management of this condition is complex and follows a strategy integrating different therapeutic methods.
Mucosal healing in ulcerative colitis (UC) after infliximab treatment – Ultrastructural study

O.C. Fratila¹, C. Craciun²
¹University of Oradea, Romania
²Babes Bolyai University, Electron Microscopy Center, Cluj Napoca, Romania

Introduction: Crohn’s disease is described as corresponding to Th1-proinflammatory, TNF-α-mediated response while UC is considered to be mediated by Th2 (humoral). Considering these two different pathogenetical ways is infliximab just as suitable in UC as in CD?

Aim: To assess intracellular changes of colonic mucosa in patients with UC, before and after infliximab treatment.

Methods: Our study comprised 10 patients (18–65 years, 6 men) with refractory, moderate to severe UC (Clinical Activity Index > 6, Endoscopic Index > 4) who underwent colonoscopy before and 4 weeks after the initial infusion of infliximab (5 mg/kg body weight). Endoscopically obtained biopsies were processed specifically, stained with uranyl acetate and lead citrate and examined with a JEM-1010 transmission electron microscope.

Results: Before treatment we noticed severe alterations of the epithelium-depletion of microvilli, shattering of the epithelial junctions, cytoplasmic vacuolization, dilatation of the endoplasmic reticulum, pycnotic nuclei, the destruction of mitochondria and Golgi complexes which conduct finally to drastic reduction of cell metabolism. Rarefaction of the goblet cells, together with abnormal mucus formation and secretion was observed. The corresponding chorion showed degeneration of the collagen fibres and smooth muscle cells, obstructed capillaries, neutrophilic and mononuclear infiltration. After infliximab therapy, we noticed improvement in morphology and function of epithelial organelles, rich mucus secretion and recovery of the chorionic components. The clinical response observed in all our patients was supported by a descent in UCAI. The UCAI dropped two weeks after infusion, a tendency kept also at week 4. Endoscopic severity diminished as well – with 9 out of 10 cases entering remission (EI ≤ 4).

Conclusion: At the end of treatment the new ultrastructural assessment clearly showed signs of epithelial barrier recovery – one of the goals of UC treatment. These features may contribute to a better understanding of UC pathogenicity and mechanism of action of the anti-TNF-alpha therapies.
Risks and benefits of the combined therapy in the treatment of severe steroid-refractory Crohn’s disease

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

Introduction: Aim of this study was to evaluate the efficacy and safety of infliximab-azathioprine combined therapy comparative with other therapeutic options in treatment of severe steroid refractory Crohn’s disease (CD).

Methods: We monitored 22 patients with moderate-to-severe steroid-refractory CD (mean age 41.72 ± 3.92 years). In 5 cases steroid-refractory CD was associated with fistulae. Our comparative study was performed on three groups: 13 patients (A group) were received combined therapy with oral mesalazine and azathioprine (Salofalk® 3 g/day and azathioprine 2.5 mg/kg/day), 4 patients (B group) were received infliximab monotherapy (5 mg/kg at 0, 2, 6 weeks) and 5 patients (C group) treated with combined therapy with infliximab and oral azathioprine (2.5 mg/kg/day). We monitored, for a 12 weeks period, the activity disease and evaluated response of therapy. CDAI scores were determined within one week before infusion and after infusion at weeks 2, 4, 8 and 12.

Results: After two weeks, clinical response (defined as a decrease in CDAI more 75 points) was observed only in B and C groups. In B group, 1 patient (25%) responded after a single intravenous infusion of Infliximab. After second infusions 1 patient had complete response and 2 patients had partial response. One patient developed pneumonia. Comparatively in C group 2 patients (40%) had rapid response (complete response after two weeks) and 3 patients (60%) present complete remission after 4 weeks. One patient with fistulizing CD developed delayed hypersensitivity reaction, after second infusion. After 12 weeks complete remission was observed in 8 patients (61.54%) in A group, in 3 cases (75%) in B group and in 4 cases (80%) in C group. The relation between endoscopic activity and C-reactive protein positivity was significant (p = 0.001). C-reactive protein level was correlated with clinical response (p = 0.03) and decreasing of CDAI score.

Discussion/Conclusion: Combined therapy with infliximab plus azathioprine remains the most effectiveness in patients with severe steroid-refractory CD. The incidences of side-effects of this combined therapy was significantly increased comparative with monotherapy.
Alternative for the induction of remission in patients with moderate left-sided ulcerative colitis

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

Introduction: Aim was the assessment of the efficacy and safety of mesalazine-budesonide combined therapy versus mesalazine or azathioprine monotherapy in inducing remission of moderate flare of left-sided UC.

Methods: We studied 32 patients with moderate left-sided UC. A comparative analysis was performed on 3 groups of patients. A group composed of 14 patients were treated with oral mesalazine (Salofalk® 2–3 g/day) and oral budesonide (Budenofalk® 3 x 3 mg/day), for 6–8 weeks. In B group, 11 steroid refractory patients suffering for proctitis were treated with oral plus rectal mesalazine (Salofalk® tablets 2 g/day and suppositories 3 x 500 mg/day, for 8 weeks). C group consists of 7 patients (with contraindicated corticoids therapy) were treated with azathioprine (1–1.5 mg/kg/day). We evaluated the clinical disease activity index (CDAI), Powell-Tuck index and endoscopic classification at baseline, after 1 and 3 months.

Results: In A group, most patients (57.14%) had a rapid response to associated treatment. The rate of clinical and colonoscopically confirmed remission was 85.7%. In B group remission rate after 3 months was 81%. In C group two patients discontinued treatment with azathioprine due to adverse events: leucotrombocytopenia and increased aminotransferases levels. In A group side effects was observed in 2 cases (headache and vomiting). The diminution of the mean Powell-Tuck score at 2 months compared with baseline was: $6.2 \pm 0.92$ in A group, $4.7 \pm 1.09$ in B group and $4.8 \pm 1.3$ in C group. At 3 months, compared with baseline, the diminution of the mean value of this index was: $6.8 \pm 1.07$ in A group, $5.6 \pm 1.12$ in B group and $5.2 \pm 1.24$ in C group. Similar evolution was observed at mean values of CDAI.

Discussion/Conclusion: Mesalazine associated with budesonide achieved high remission rate in short term treatment in moderate left-sided UC. Low-dose azathioprine therapy is most effective alternative for the induction of remission in patients with contraindicated corticoids therapy, but association of oral and rectal mesalazine remain the best tolerated treatment in moderate UC.
Central modulatory role of IL-9 in inflammatory bowel disease

K. Gerlach¹, H.-A. Lehr², A. McKenzie³, M.F. Neurath¹ & B. Weigmann¹
¹Department of I. Medical Clinic, University Erlangen, Erlangen, Germany
²Institut Universitaire de Pathologie, Université de Lausanne, Switzerland
³Laboratory of Molecular Biology, University Cambridge, UK

Introduction: Interleukin 9 is a pleiotropic pro-inflammatory cytokine mainly produced by T cells, beside B cells and mast cells. Also many cytokines have been investigated so far in experimental models of chronic intestinal inflammation, the role of IL-9 is largely unidentified. But high concentrations of IL-9 in the colon tissue during colitis point out the important role of this cytokine.

Methods: For the analysis of Interleukin 9 in the development of chronic intestinal inflammation IL-9 deficient mice were used in oxazolone-colitis model. Miniendoscopic analysis has been done to monitor the manifestation of the colitis. The inflamed colon was isolated and histological sections were taken for immunohistofluorescent staining and real-time PCR analysis. For therapeutically treatment wildtype mice were given 40 µg of specific anti IL-9 antibody to prevent the emergence of colitis.

Results: In the experimental oxazolone-colitis model the IL-9 KO mice were protected. This became evident in the miniendoscopic analysis as well as in the HE staining. Immunofluorescence staining shows a decrease of the IL-9 regulating transcription factor PU.1 in the IL-9 deficient mice, indicating the involvement of PU.1 in the IL-9 production. This is consistent with the fact that PU.1 is higher expressed in human biopsies of colitis patients, indicating a pro-inflammatory role of IL-9 in patients suffering from inflammatory bowel disease. Further analysis of the pro-inflammatory effect of IL-9 showed that the blockage of high IL-9 concentrations with a specific anti IL-9 antibody in wildtype mice lead to a protection in oxazolone-colitis model.

Discussion/Conclusion: Here, we have identified a central pathogenic role for the pro-inflammatory cytokine IL-9 in chronic intestinal inflammation. This is based on the fact that IL-9 is increased in inflamed colon tissue and IL-9 KO mice are protected in the experimental oxazolone-colitis model. Furthermore, administration of a blocking anti IL-9 antibody before the manifestation of colitis has a protective effect. Thus IL-9 emerges as a potentially new therapeutic target for inflammatory bowel diseases.
Anti-TNF-alpha therapy in patients receiving tuberculosis chemoprophylaxis

I. Gîrleanu, A. Trifan, O. Stoica, S. Chiriac, A.-M. Sîngeap, C. Stanciu
Department of Gastroenterology and Hepatology, Grigore T. Popa University of Medicine and Pharmacy, Iasi, Romania

Introduction: A major concern surrounding the use of tumor necrosis factor-alpha (TNF-alpha) inhibitors is their potential to increase the risk of opportunistic infections, particularly tuberculosis (TB), especially in countries with a high prevalence of TB like Romania. All patients with latent TB are receiving 6 months chemoprophylaxis with isoniazid. The aim of this study was to evaluate the efficacy of anti-TNF-alpha therapy in patients receiving TB chemoprophylaxis with isoniazid.

Methods: We conducted a prospective study of 37 patients with inflammatory bowel disease (IBD) who received anti-TNF-alpha therapy in the Department of Gastroenterology of a tertiary hospital, from Romania. Eleven patients diagnosed with IBD who received TB prophylaxis and anti-TNF-alpha therapy were compared with a group of 26 patients treated with anti-TNF-alpha only. All patients had a tuberculin skin test, a postero-anterior chest plain, and Quantiferon determination. When indicated treatment for latent TB was established - 6 months with isoniazid.

Results: Of 11 patients who fulfilled the criteria for chemoprophylaxis, none developed active TB after the beginning of anti-TNF-alpha therapy. Eight of these patients had received Infliximab and 3 patients Adalimumab. Remission rate was 72.8% in the first group and 73.6% in the second group. There was no difference in induction and maintaining the remission between the two groups (p = 0.554). There were no hepatic side effects in both groups.

Discussion/Conclusion: TB chemoprophylaxis does not influence the efficacy of anti-TNF-alpha therapy in patients with IBD.
Risk factors and incidence for low urinary tract infections in patients with inflammatory bowel disease

I. Gîrleanu, A.-M. Sîngeap, C. Cojocariu, C. Sfarti, A. Trifan
Department of Gastroenterology and Hepatology, Grigore T. Popa University of Medicine and Pharmacy, Iasi, Romania

Introduction: A high proportion of patients with inflammatory bowel disease (IBD) are treated with immunosuppressants. Immunossuppresants lead to an increased risk of infections including low urinary tract infections. The aim of this study was to assess the incidence of low urinary tract infections, and the risk factors associated with these infections in patients with IBD and immunossupresant therapy.

Methods: We conducted a prospective study on patients diagnosed with IBD in the Department of Gastroenterology of a tertiary hospital. We included patients with IBD and immunossupresant therapy (corticotherapy, thiopurine, anti-TNF-alpha agents). All patients were evaluated at the inclusion in the study and follow up for 12 months.

Results: Fifty-eight patients (20.9%) out of 277 IBD patients developed low urinary tract infection. *Escherichia coli* and *Enterococcus faecalis* were observed in 34 and 18 patients, respectively. The incidence of low urinary tract infection in male patients aged 60 or over was significantly higher than that in the other age groups (p = 0.02). The use of thiopurine (p < 0.001), and immunossupresant combination therapy (p = 0.03) was associated with the increased rate of low urinary tract infection. The treatment with infliximab or adalimumab was not associated with increased rate of infection (p = 0.86). Multivariated analysis indicated that thiopurine treatment (p = 0.05, HR = 1.54, CI: 0.779–3.275) and hypoalbuminemia (p = 0.028, HR = 1.83, CI: 0.932–2.617) were independent risk factors for development of low urinary tract infection.

Discussion/Conclusion: The incidence of low urinary tract infection in IBD patients treated with immunossupresants was and prophylaxis should be considered. Age ≥ 60 years, hypoalbuminemia and the use of thiopurine are risk factors for low urinary tract infection in patients with IBD.
Clinical course and treatment options of Crohn’s disease patients in Serbia

V. Gligorijevic¹, D. Bojic¹, M. Krstic², D. Tarabar³, A. Nagorni⁴, L. Hadnadjev⁵, P. Dugalic⁶, G. Nikolic⁷, B. Maksimovic¹, T. Brocic³, Z. Milenkovic³, N. Jojic¹
¹Zvezdara Clinical Centre, Belgrade; ²Clinical Center of Serbia, Belgrade; ³Military Academy, Belgrade; ⁴Clinical Center, Nis; ⁵Clinical Center, Novi Sad; ⁶Zemun Clinical Centre, Belgrade; ⁷Bezanijska Kosa Clinical Centre, Belgrade, Serbia

Introduction: The epidemiological study of occurrence, clinical course and treatment options of Crohn’s disease (CD) was conducted from June 2010 till May 2011 in seven centers in Serbia. It was observational, non-interventional, cross-sectional, health outcome study in our country.

Methods: All enrolled patients during one visit completed CRF which was created for CD patients. The data from CRF inserted into data base and descriptive statistics were calculated.

Results: During one year we included 454 patients with CD. Female were 45.3%. Mean age at diagnosis were 30.9 year. Serbian population was predominant (68.2%) and 19.2% were Indo-European. 90% of patients lives in the city. They are mostly workers (47.8%). 9.9% of CD patients reported disability because of the disease itself. 45.6% of patients are smokers. Heredity have 5% of CD pts. The mean duration of symptoms before diagnosis was 1.8 years. At the moment of diagnosis 75% of patients had diarrhea and 78% abdominal pain. Fulminant form at the start of disease had 18.7% of CD patients. Localization of CD was: ileum-colon 47.5%; colon 31.7%; ileum 23.6%; upper GI 2.7%. Most frequent intestinal complications in CD patients were fistulas (25.6%) and bowel obstruction (34.12%). Extra intestinal complications have 12.3% of CD patients (55% arthropathy and 12% eye lesions). 43% of CD patients were operated manly of intestinal complications and 44.4% because of medical therapy failure. Current medical treatments in CD patients were 5-ASA (51.2%); immunomodulatory therapy (17.7%); corticosteroid therapy 32%; infliximab 4.2%.

Discussion/Conclusion: Occurrence of Crohn’s disease is more higher compared to our previous data. We registered more patients with Crohn’s colitis. The main therapy is still 5-ASA and corticosteroid therapy but higher number of patients are on immunomodulatory therapy. Very small number of CD patients was on biologics.
The utility and cost-effectiveness of testing for latent TB infection in UK inflammatory bowel disease patients initiating anti-TNFα agents

K. Greveson¹, S. Capocci², S. Murthy³, C. Smith⁴, S. Morris⁵, C. Murray¹, I. Cropley³, M. Hamilton¹, M. Lipman²
¹Centre for Gastroenterology, Royal Free London NHS Foundation Trust
²Department of Respiratory Medicine, Royal Free London NHS Foundation Trust and University College London
³Department of Infectious Diseases, Royal Free London NHS Foundation Trust
⁴Research Department of Infection and Population Health, University College London
⁵Department of Applied Health Research, University College London, UK

Introduction: Two commercial Interferon Gamma release assays (IGRA) are approved in the UK to detect M. tuberculosis (M.tb) infection. Both may provide borderline or indeterminate results, especially in people taking immunomodulatory therapy. Since 2008, we applied a standard IGRA-based assessment for latent M.tb infection in inflammatory bowel disease (IBD) patients being considered for anti-TNFα therapy. Initially this involved T-Spot.TB (TSTB) but in December 2010, our service switched to Quantiferon Gold In-tube (QFGIT). Here we review the performance and cost-effectiveness of these assays within our protocol.

Methods: Adult IBD patients were assessed using symptom review, chest radiograph and IGRA. Indeterminate/borderline IGRA were repeated and patients with indeterminate/borderline/positive results were referred to TB services. Cost per patient assessment used the average of assay costs and repeated assays plus onward referrals for those with indeterminate/borderline tests. Appointment costs were taken from standard NHS tariffs. Immunomodulators were defined as thiopurines, methotrexate or prednisolone > 20 mg/day.

Results: Between October 2008 and November 2010 90 patients were tested with TSTB, of which 2 had a positive TSTB result and 5 borderline/indeterminate. From December 2010 until July 2012, 82 patients were tested with QFGIT, of which 3 had a positive result and 12 indeterminate/borderline. 170 (99%) had normal CXR and a negative clinical assessment. 4 of 13 patients had two sequential indeterminate IGRA and also required assessment in TB clinic. The average price per patient was £ 60.66 for TSTB and £52.41 for QFGIT. 88% (152/172) have subsequently received treatment with either infliximab or adalimumab. No subjects have gone on to develop active tuberculosis.

Discussion/Conclusion: Using either platform, we find a comparable, low rate of LTBI in our IBD population. There appears to be a higher frequency of indeterminate results using QFGIT. This raises the average cost per patient, but overall, QFGIT remains more cost-effective than TSTB. Despite differing length of follow-up, the average time was sufficient in both, otherwise comparable, cohorts to detect likely development of active TB disease.
The immunohistochemical assessment of MMP-2, MMP-7 and MMP-9 in IBD

K. Guzińska-Ustymowicz¹, K. Niewiarowska¹, A. Pryczynicz¹, W. Famulski², A. Kemona¹, D. Cepowicz³, M. Gryko³
¹Department of General Pathomorphology; ²Department of Medical Pathomorphology; ³2nd Department of General Surgery and Gastroenterology, Medical University of Białystok, Poland

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

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

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

Conclusion: The increased expressions of MMP-9 appear to be more important than MMP-7 and MMP-2 in UC, but MMP-2 was more important in CD. In addition, both MMP-2 is extensively secreted by inflammatory cells in UC and CD.
Cytomegalovirus infection reactivation and IBD: What was the primary?

K. Hospodarska, I. Hospodarskyy
Clinical Immunology, Allergology and General Patient Care Department, Ternopil University Hospital, Ternopil, Ukraine

Cytomegalovirus (CMV) infection as for results of seropositivity (from 25 till 80% of seropositive patients in different countries) is ubiquitary infection predominantly without any clinical or laboratory signs. But in case of virus reactivation due to immunosuppression, stress, surgery etc a wide spectrum of clinical symptoms could be established. The typical group of CMV symptoms are due to lymphadenopathy (such as peripheral and abdominal lymph nodes enlargement, hepatosplenomegaly etc), other typical symptom is subfebril body temperature. On the other hand abdominal lymph nodes enlargement as well as subfebril body temperature are very frequent in patients with chronic CMV infection. So the reactivation of CMV in patients with IBD has been studied.

Simultaneous ELISA (specific antibodies) and PCR (CMV-DNA) methods of virus reactivation have been applied. Frequency of seropositivity to CMV was the same in population with IBD and without IBD. But in patients with IBD frequency of virus replication markers (as ELISA as PCR) were significantly higher than in patients without IBD.

The separate group of patients with IBD could be formed not only according special clinical symptoms (abdominal lymph nodes enlargement and subfebril body temperature), but also due to higher level of pro-inflammatory cytokines than in group without CMV-DNA and CMV-IgM determining. The effectiveness of conventional treatment in such a patients was not satisfied.

So CMV reactivation could play significant role in pathogenesis of IBD in approximately 30–35% of total IBD patient's population.
Is occult hepatitis B infection really a serious problem in patients with inflammatory bowel disease

Department of Gastroenterology, Kocaeli University Medical School Hospital, 41100 Kocaeli, Turkey

Introduction: Hepatitis B virus (HBV) reactivation in patients previously negative for HBsAg have been reported in patients with inflammatory bowel disease (IBD) treated with immunosuppressive agents.

Methods: All IBD patients attending the IBD Clinic of our hospital had their HBV status determined serologically (HbsAg, anti-Hbs, Anti-HBc Ig G). Chronic HBV was diagnosed when HBsAg was positive. Occult hepatitis B infection was defined by negative HBsAg and positive anti-HBc antibody. Patients who had adequate anti-HBs titer without anti-HBc antibody were considered to be previously vaccinated against HBV. Liver dysfunction was defined as abnormal serum ALT levels that were above normal reference range. The proportions of patients with liver dysfunction in different groups were compared and factors associated with liver dysfunction were identified.

Results: A total of 157 patients were analyzed, including 92 (58.6%) patients with ulcerative colitis (UC) and 64 (41.4%) patients with Crohn’s disease (CD). The mean age of these patients was 41 (SD 12.1) years and there were 72 (45.8%) men. Ten patients were HBsAg positive, 33 had occult HBV and 50 had been previously vaccinated against HBV. HBV-DNA was detected in 60% patients who were positive for HBsAg. Liver dysfunction was noticed in 30% HBsAg positive patients and 15% patients with occult HBV, as compared to 16% in previously HBV vaccinated patients. Liver dysfunction was significantly associated with the diagnosis of CD (31.7% vs. 15.5% in UC; p = 0.003). The use of azathioprine (28% vs. 19.5%; p = 0.07) or steroid (27.8% vs. 20.4%; p = 0.18) was associated with a non-significant increase in risk of liver dysfunction.

Conclusion: Occult HBV infection is common than most people think too among patients with IBD. The risk of liver dysfunction was comparable between patients with occult HBV and those previous HBV vaccination. In addition patients with CD was risk factor for liver dysfunction in IBD patients.
Retrospective study of endoscopic polypectomy in ulcerative colitis associated polyps

T. Ilias¹, O. Fratila², D. Puscasu²
¹University of Oradea; ²Emergency Clinical County Hospital, Oradea, Romania

Introduction: There is an increased risk of colorectal cancer in patients with inflammatory bowel disease through a chronic inflammation dysplasia sequence. Dysplasia in ulcerative colitis (UC) is either flat or associated with a raised lesion or mass dysplasia (DALM). One specific subtype of DALM consists of polyps that are difficult to distinguish from sporadic adenomas.

Aim: Assessement of pathologic features of polypoid lesions in UC using histology and to observe the complications and efficacy of endoscopic polypectomy.

Methods: 107 polypectomies of UC polyps (from a ten-year period) were reviewed. Polypectomy was performed with diathermic snare using en bloc or piecemeal technique. Size, shape, location, histology, efficacy and complications were assessed.

Results: We had 44 men and 63 women (mean age 43.2 years). 84 polyps were sessile, most of them located in the sigmoid. Median polyp size was 2 cm. Most of the polyps (> 95%), were resected and cured. Most polyps developed within an area of colitis had a tubulovillous architecture (76–71%), mixed normal-low grade dysplastic epithelium and increased lamina propria mononuclear inflammation. 65 (85.5%) polyps had mild dysplasia and 11 (14.4%) severe dysplasia. Three polyps (2.8%) were malignant. All pedunculated polyps were resected in one session, whereas for sessile polyps we performed 1.3 colonoscopies in average. We had 10 hemorrhages treated by endoscopy and 2 colonic perforations (requiring surgery, 1 resolved with metallic clip).

Conclusion: Colonoscopic polypectomy should be the standard treatment for polyps even in UC, being a prevention of colorectal cancer. It is a safe technique when performed by expert hands using cautious technique and properly working equipment. The polyp size is an important risk factor for malignancy and bleeding. Morphologic features may help to define a dysplastic lesion as a sporadic adenoma or a potential IBD-related neoplasm in a patient with IBD, providing a different management.
Clinical efficacy of two regimens of maintenance therapy in patients with Crohn’s disease aged 7–17 years – Multicenter randomized study


1Children’s Memorial Health Institute, Warsaw, Poland; 2Department of Pediatrics, Gastroenterology and Nutrition, Medical University of Wroclaw, Poland; 3Department of Pediatrics, Gastroenterology and Nutrition Jagiellonian University School of Medicine, Krakow, Poland; 4The Department of Paediatrics, Medical University of Silesia, Gastroenterology Unit, Upper-Silesian Child Health Care Centre in Katowice, Poland; 5Medical University of Warsaw, Department of Pediatric Gastroenterology and Nutrition, Poland; 6Wl. Buszkowski Kielce Province Children's Hospital, Kielce, Poland; 7Department of Paediatric Allergology, Gastroenterology and Nutrition, Medical University of Lodz, Poland; 8Paediatric Nursery Unit of Pomeranian Medical University, Division of Paediatrics, Gastroenterology and Rheumatology of Zdroje Hospital in Szczecin, Poland; 9Chair and Department of Pediatrics, Allergology and Gastroenterology, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Poland; 10Department of Pediatrics, State Hospital, Medical College,University of Rzeszow, Poland; 11Gastroenterology and Pediatric Departments, Polish Mother’s Memorial Hospital, Research Institute Lodz, Poland; 12Department of Pediatrics, Medical University of Silesia, Zabrze, Poland

Background: Optimal use of biologics in Crohn’s disease (CD) requires balance between benefits and risk, and concern of serious side effects may question the concomitant immunomodulators use in pediatric patients. The study was conducted to compare the efficacy of two infliximab maintenance regimens: (1) infliximab alone and (2) infliximab with immunomodulator in pediatric patients with moderate to severe active CD.

Methods: Patients (n = 99; 14.5 mean age, 62% males) with PCDAI > 30 were involved to the study and received induction therapy with infliximab 5 mg/kg at weeks 0, 2, and 6. Clinical (PCDAI score) evaluation were performed at week 10 and patients with clinical response (decrease of PCDAI ≥ 15 AND PCDAI < 30) and/or remission (PCDAI ≤ 10) were randomized to Group I receiving infliximab 5 mg/kg every 8 weeks with immunomodulator until Week 54 (n = 45) or Group II receiving infliximab 5 mg/kg every 8 weeks with immunomodulator stopped at week 26 (n = 39). Clinical assessment (PCDAI score) was performed at week 54 in both groups. Primary endpoint was loss of clinical response defined as increase of PCDAI > 15 points or PCDAI > 30. Secondary endpoint was: necessity to increase/change maintenance therapy.
Results: 84 out of 99 (85%) pts had response, and 58 (59%) clinical remission after induction therapy at week 10. Two out of 45 (4%) pts in Group I and 2 out of 39 pts (5%) in Group II had loss of clinical response at Week 54 (non significant-NS). The increase/change of maintenance therapy was necessary in 13 out of 45 patients (29%) in Group I and 11 out of 39 (28%) in Group II (NS).

Conclusion: Both regimens of maintenance therapy (1. Infliximab with immunomodulator and 2. Infliximab alone) are clinically equally efficient in children aged 7–17 years with moderate to severe CD.
Cell therapy in patients with acute attack of ulcerative colitis

O. Knyazev¹, A.I. Parfenov¹, P. Shcherbakov¹, A. Konoplyannikov²
¹Central Research Institute of Gastroenterology, Moscow; ²Medical Radiological Research Center, Obninsk, Russia

The relapse rate of ulcerative colitis (UC) in the first year after diagnosis is 50% within 3–7 years after diagnosis remains in remission 25% of patients, the annual relapse – 18%. Only 50% of patients have remission for 5 years.

Objective: To assess the effectiveness of culture mesenchymal stromal cells (MSCs) in patients with acute (primary) attack of ulcerative colitis (UC).

Methods: Divided into two groups of patients with acute attack of UC. The first group of MSCs (n = 10) – UC patients who received MSC, the second group 5-amino-salicylic acid/glucocorticosteroids (5-ASA/GCS) (n = 10) – patients treated with standard anti-inflammatory therapy with 5-ASA and corticosteroids. Age from 22 to 44 years (Me – 29 years), medium/heavy degree, the length of lesion – left hand side and total defeat, the observation time – from 24 to 34 months. Clinical activity of UC was assessed on a scale Rahmilevich. Endoscopic picture was assessed on a scale of Mayo. Culture MSCs injected drip dose of 3 million to 1 kg of body weight.

Results: When comparing the "survival curves" in patients with acute attack of UC, within 1 year of observation, the difference in length of remission in treatment groups were observed (p = 0.582). When comparing the "survival curves" for the 2-year follow-up, the first group of patients the duration of remission was 17 months, patients of the second group – 22 months (p < 0.001). The relative risk (RR) of recurrence in patients with UC who received MSCs (I-group) compared with II-nd group (5-ASA/GCS) at 1 year was 0.25 (95% CI: 0.03–1.86) (p = 0.3), (x²=1,07). RR of recurrence of UC within 2 years of observation – 0.33 (95% CI: 0.13–0.88) (p = 0.02), (x²=5.21).

Conclusions: MSCs transplantation improves the efficiency of anti-inflammatory therapy in patients with acute attack of ulcerative colitis. The relative risk of second attack UC for 2 years of observation to 3 times lower in patients who received MSC.
Cell therapy and quality of life of patients with inflammatory bowel disease

O. Knyazev, I. Ruchkina, L. Efremov, A.I. Parfenov
Central Research Institute of Gastroenterology, Moscow, Russia

Evaluation of physical, psychological and social well-being of patients with ulcerative colitis (UC) and Crohn’s disease (CD) at different stages of the disease is used to develop treatments and rehabilitation programs. To assess the quality of life (QL) in patients with chronic inflammatory bowel disease (IBD) in the acute stage and one year after the standard anti-inflammatory therapy, combined therapy with the use of culture mesenchymal stromal cells (MSCs) and infliximab therapy.

Materials and methods: IBD patient surveys were made using a specialized international questionnaire to identify patients with IBD QL (IBDQ) (maximum total value – 224 points). Of the 90 patients with IBD, formed the study group QL in acute disease, 35 patients (38.8%) suffered from CD, 55 (61.2%) – UC, 53 of them (58.9%) males and 37 (41.1%) – females. The median age was 35.2 ± 1.2 years. The average duration of illness of persons interviewed was 9 years old. Patients were divided into age groups as follows: 18–24 – 21 (23.3%), 25–44 – 45 (50%), aged 45 and above – 24 (26.7%). A year later, the surveys were 31 patients (group 1) after therapy with 5-aminosalicylic acid (5-ASA), glucocorticosteroids (GCS), 29 patients (group 2), which carried out a systemic transplantation of mesenchymal stromal cells and 27 patients (group 3), treated with infliximab.

Results: 100% of the observed decrease in QL of patients with IBD in the period of exacerbation. According to the IBDQ average QL in patients with UC and CD was 118.1 ± 11.5 points. During the remission rate was significantly improved QL in 1st group to an average of 169.7 ± 22.3 (p < 0.05). However, there was a significant difference between patients who received 5-ASA drugs (n = 7) and patients who received long-term corticosteroids (n = 24) – 184.8 ± 22.6 and 154.7 ± 21.1, respectively (p = 0.03). The level of QL in 2nd group patients was 198.6 ± 26.3 points, which was significantly higher than in 1st group (p < 0.05). In the 3rd group – 202.4 ± 26.8 balls, which also had a significant difference from 1st group patients with IBD (p < 0.05). Differences in terms of QL between the 2nd and 3rd groups was not (p = 0.6).

Conclusion: All the patients had inflammatory bowel disease during exacerbation has reduced quality of life. The results indicate a higher quality of life in patients with IBD who had received biological therapy – mesenchymal stromal cells and infliximab, than in patients treated with standard anti-inflammatory therapy.
Mesenchymal stem cells increases the effectiveness of anti-inflammatory therapy with newly diagnosed Crohn’s disease – 4 years of observation

O. Knyazev¹, A. Konoplaynnikov², I. Ruchkina¹, A.I. Parfenov¹, P. Shcherbakov¹
¹Central Research Institute of Gastroenterology, Moscow; ²Medical Radiological Research Center, Obninsk, Russia

For Crohn's disease (CD) at the moment there is no sufficiently effective treatment modality. Up to 90% of the patients are exposed to during the life of one or more surgical interventions. However, the treatment of patients with CD at the beginning of the disease is a priority for the gastroenterologist.

Objective: To assess the impact of culture of mesenchymal stem cells (MSCs) in patients with newly diagnosed CD for the duration of remission.

Materials and methods: Divided into two groups of patients with newly diagnosed CD. The first group of mesenchymal stem cells (MSCs) (n = 15) – CD patients who received MSCs, the second group – 5-ASA/GCS (n = 15) – patients who received standard anti-inflammatory therapy drugs 5-aminosalicylic acid (5-ASA) and corticosteroids (GCS). Age of patients ranged from 19 to 34 years (Me – 22), the severity of the attack of the disease – moderate and severe, the length of the defeat – ileocolitis, ileitis and colitis, the observation time ranged from 28 to 48 months. Clinical activity was assessed by the Crohn's disease activity index (CDAI). The culture of allogeneic MSCs injected drip in doses of 3 million per 1 kg of body weight on 0–1–26 week.

Results: CDAI in group 1 was 242.6 ± 11.7 points, in the 2nd group – 240.9 ± 12.9 points (p = 0.83), CRP levels in group 1 was 29.3 ± 6.4 mg/l, the 2nd – 27.8 ± 4.8 (p = 0.47). After 1 year of follow- CDAI in group 1 was 70.0 ± 11.0 points in the 2nd – 133.8 ± 22.2 points (p < 0.001), CRP levels in group 1 was 6.36 ± 1.5 mg/l, the 2nd – 12.2 ± 2.9 (p < 0.001). After 2 years of CDAI in group 1 was 99.6 ± 19.3 points in the 2nd – 147.1 ± 22.1 points (p < 0.001), CRP levels in group 1 was 16.0 ± 6.0 mg/l, the 2nd – 18.8 ± 4.4 (p = 0.156). After 3 years, the CDAI in group 1 was 110.5 ± 21.9 points in the 2nd – 180.6 ± 20.3 points (p < 0.001), CRP levels in group 1 was 10.9 ± 2.6 mg/l, the 2nd – 16.9 ± 3.0 (p < 0.001). After 4 years – the CDAI in group 1 was 120.0 ± 22.3 points in the 2nd – 208.7 ± 17.6 points (p < 0.001), CRP levels in group 1 was 11.3 ± 2.6 mg/l, the 2nd – 15.5 ± 2.4 (p < 0.001). The relative risk (RR) of recurrence in patients with CD receiving MSCs (group 1) compared to the 2-nd group (5-ASA/GCS) at 1 year RR – 0.14 (95% CI: 0.02–1.02) (p = 0.04), (x²–4.26). RR of relapse after 2 years observations – 0.38 (95% CI: 0.12–1.15) (p = 0.13), (x²–2.3), after 3 years RR – 0.36 (95% CI: 0.15–0.89) (p = 0.03), (x²–4.8), after 4 years RR – 0.38 (95% CI: 0.18–0.81) (p = 0.009), (x²–6.81).

Conclusion: MSCs increase the effectiveness of anti-inflammatory therapy in patients with newly diagnosed Crohn's disease, helping to increase the duration of remission. Risk of recurrence of CD within 3 years after achieving remission in 3 times and 4 years after remission 2.5 times significantly lower in patients who received MSCs.
The safety of biological treatment of IBD

M. Konecny, V. Prochazka
Department of Internal Medicine II, Gastroenterology and Hepatology, University Hospital Olomouc, Czech Republic

Introduction: The present clinical practice of biological treatment (BT) of inflammatory bowel disease (IBD) in the Czech Republic includes using of two drugs (infliximab and adalimumab), where the active substance are antibodies against tumor necrosis factor alpha (TNF-α). The therapeutical effect is very good. For some patients, however, BT is associated with the occurrence of sometimes serious side effects. Their pathogenesis is not known yet and in some cases these serious side effects are the cause of the termination of the treatment.

Methods: In the period 2007–2012, 126 patients with IBD TNF-α were treated at the University Hospital in Olomouc. In this set of patients, the occurrence of serious side effects of TNF-α was observed within the dispensarization. The difference in the occurrence of side events was compared with the control set of 102 patients with IBD, who underwent only conventional therapy. The observed side effects included skin, articulary, ocular, infectious, metabolic and hematopoietic disorders. The data were statistically processed using standard descriptive methods for continuous data.

Results: The serious side effects were documented in 11 (8.7%) patients with TNF-α therapy; the most common complications were skin complications (54.3%). In the set of patients under the conventional therapy, the side effects of the treatment have been reported in 7 (6.9%) patients, mostly involving hematopoietic disorders (61.2%). The observed difference of occurrence of serious side effects was not statistically significant (p = 0.11).

Discussion/Conclusion: In the last decade, the introduction of BT has caused a significant change in the routine clinical treatment of IBD. It turns out that this treatment is relatively safe, the incidence of serious side effects is not higher than when using conventional drug therapy. It is necessary to indicate the TNF-α treatment properly, the patient must be carefully examined before the initiation of the treatment and intensively monitored during the course of the treatment.
Pseudotumoral colonic form of Crohn's disease: A series of 16 cases

S. Matri, M. Fekih, B. Ben Slimene, A. Laabidi, N. Ben Mustapha, M. Serghini, J. Boubaker, L. Kallel, A. Filali
Department of Gastroenterology A, La Rabta Hospital, Tunis, Tunisia

Introduction: Pseudotumoral colonic or rectal form of Crohn’s disease is a rare entity. Preoperative diagnosis is very difficult and is usually based on the pathological examination of the surgical specimen.

Aim: Assessing the frequency, circumstances of diagnosis and management of pseudotumoral form of Crohn’s disease.

Materials and methods: We have conducted a retrospective chart review of patients who were admitted to hospital for Crohn’s disease over six years (2005–2011). Only patients with pseudotumoral form of Crohn’s disease were included.

Results: Over the 6-year period, 387 cases of Crohn’s disease were reviewed. Sixteen patients with pseudotumoral form inaugurating Crohn’s disease were included. The prevalence of this form was 2%. There were 9 males and 7 females. Mean age was 43 years (14–65 years). Obstruction and pseudo-obstruction were the presenting symptoms of the disease in respectively 9 and 3 patients. Fever and acute right iliac fossa pain were identified in 4 patients. In patients who were operated on immediately, the intra-operative diagnosis was right colonic tumor (9 cases). The remaining patients were investigated with colonoscopy and CT scanner and were diagnosed with colonic or ileal tumors, nevertheless biopsies were negative. In the latter patients surgery was referred to for diagnostic and therapeutic aim. Diagnosis of pseudotumoral form of Crohn’s disease was made only on the basis of the pathology examination of the surgical specimen.

Conclusion: Pseudotumoral form of Crohn’s disease are extremely rare. Despite the improvement of morphological investigation, definitive diagnosis could be made only after pathological examination of the surgical specimen.
Crohn’s disease of the upper gastrointestinal tract: Is this location more severe?

Department of Gastroenterology A, La Rabta Hospital, Tunis, Tunisia

Crohn’s disease (CD) affects mainly the terminal ileum and colon. The involvement of the upper gastrointestinal (GI) tract rarely occurs. This location occurs frequently in young patients and is associated to a severe form of the disease. The aim of our study is to determine the frequency of this location in our department, its medical management and the evolution.

Methods: We included retrospectively all patients with upper gastrointestinal (GI) tract location of Crohn’s disease, hospitalized in our department between January 2000 and January 2010 (to have a necessary delay for follow-up). Demographic, clinical and therapeutic data was obtained. The effectiveness of treatment was evaluated.

Results: 20 patients were included (17 men and 3 female) with a mean age of 26 years. The patients were classified as A2 (5%), 70% as A3, and 25% as A1 (Montreal classification). Upper CD involvement tract was diagnosed with a median delay of 1.7 years (range 0–9) after CD diagnosis. In this study, 11/9 patients showing upper CD involvement were asymptomatic. Typical clinical symptoms suggestive of upper GI tract involvement were found in 55% of patients [epigastralgia (20%), dyspepsia (10%), upper GI bleeding (10%), vomiting (5%) and symptoms of gastroduodenal obstruction (10%)]. Endoscopic lesions were ulcer (60%), erosions (10%), stenosis (5%) and congested mucosa (15%). These lesions were found in the body stomach, gastric antrum, duodenum and jejunum in respectively 5%, 15%, 60% and 20% of patients. Specific granulomas were observed in 50%. The upper GI location was associated to ileal involvement in 11 patients (55%), Colonic in 5%, and ileocolonic in 40%. In respect to disease behavior, 10 patients (50%) were allocated in B1 group. Strictureing disease (B2) was found in 4 patients. Penetrating behavior of disease (B3) was present in 2 patients (10%), and two patients had perianal disease. Proton pump inhibitors and oral or systemic corticosteroids are used, often in combination with azathioprine or 6-mercaptopurine in the most patients (85%). Two patients received an infliximab infusion. Dilation of stenotic lesions has been described in only patient. The mean duration of follow up after treatment was 29 months. The clinical improvement and mucosal healing was observed in 80% and 25% of the cases, respectively.

Conclusion: The frequency of upper gastrointestinal location of CD in our study is higher than expected from the literature. This location was associated for a need of immunomodulator treatment in the majority of patients.
Colon polyps distribution analyse in patients with inflammatory bowel diseases

V. Mokricka, I. Ozola-Zalite
Gastroenterology Center, Pauls Stradins Clinical University Hospital, Riga, Latvia

Introduction: Patients with ulcerative colitis have increased risk of developing colorectal cancer. Factors associated with increased risk include long duration of colitis, extensive colonic involvement, a family history of colorectal cancer, early disease onset and more severe active inflammation. The study aim was to analyze colon polyps frequency, risk factors (age, disease duration) and their different type distribution among patients in Latvian Gastroenterology Centre, who underwent colonoscopies in period 2007–2012 years.

Methods: The retrospective study was conducted in Pauls Stradins Clinical University Hospital, Latvia. The study included 262 patients [male 147 (56.2%), females 115 (43.8%), median age 46] with ulcerous colitis where diagnoses were confirmed with clinical course, radiology and endoscopy examinations and histological approved.

Results: Polyps were founded in 19 cases. From histological conclusions there were hyperplasiogen polyps (35%), tubular adenomatous polyps (19%), serrated polyps (12%). Mean disease duration was 5.6 years with serrated polyps, 4 (95% CI: 4.3) years with tubular polyps. Detected tubular adenomatous polyps size was 8 mm (min 3, max 15, 95% CI: 8.3), serrated 5.6 mm (min 4, max 7, 95% CI: 3.5). Most of all cases tubular adenomatous polyps were found in the sigmae (44%), serrated polyps in the proctosigmoidium area (67%). In 6 cases (8%) in ulcerative colitis were found adenocarcinoma. Localization of malignancy – 67% in the sigmae, 17% colon descendens, 17% proctosigmoidium area.

Discussion/Conclusion: Screening colonoscopies for patients with inflammatory bowel diseases in higher risk group can avoid late dysplasia and already adenocarcinoma findings. However, hyperplasiogen polyps rate are high, there still can find cureable adenomatous polyps.
Age distribution analyses in adult patients with onset Crohn’s disease

I. Ozola-Zalite, V. Mokricka
Gastroenterology Center, Pauls Stradins Clinical University Hospital, Riga, Latvia

Introduction: The age of onset of Crohn’s disease has a bimodal distribution – the first peak occurs between age 15–30 years and the second peak 60–80 years. Most cases begin before the age of 30 years, and approximately 20–30% of all patients with Crohn’s disease are diagnosed before the age of 20 years. A greater proportion of colonic and distal Crohn’s disease has been diagnosed in older patients, whereas younger patients have predominantly ileal disease. The study aim was to analyze age distribution in patients with onset Crohn’s disease and age, gender correlation with disease localization.

Methods: The retrospective study was conducted in Pauls Stradins Clinical University Hospital, Latvia. Colonoscopies data were gained from Endoscopy center data base. During 2008–2011 years were 132 patients with Crohn’s disease diagnoses. The study included from all 25 patients older than 18 years (male 9.36%, female 16.64%, median age 39) with onset Crohn’s disease. Diagnoses were confirmed with clinical course, endoscopy examinations and hystological approved. Data were statistical processed by MS Excel program.

Results: Age range was from 21 until 65 year old patients with mean age 39 years (95% CI: 4.89). In the age groups 18–25 years were 3 patients; 26–35 years 6 patients; 36–45 years 6 patients; 46–55 years 9 patients; 56–65 years 1 patient. Peak was 46–55 years of age. Most often in younger patients (18–35 years) were found ileal disease (44%), ileocolitis (33%) and proctitis (12%). In the older patients (36–55 years) total colitis (54%), ileocolitis (28%). More often was detected ileal disease in males (33%), than females (6%); total colitis in females (38%) than males (33%); ileocolitis in males (33%), in females (25%). From all patients were detected 3 cases with strictures (12%), 2 cases with parcial stenosis (8%). 80% from patients was urban, 20% from rural areas.

Discussion/Conclusion: Study showed more dominant age group from 46–55 years in patients with onset Crohn’s disease. These data suggest that second age peak for this disease can be earlier than 60 years age. Ileal diseases are predominantly in younger patients and as well in male patients.
Is anxiety and depression responsible for some symptoms in patients with inflammatory bowel disease (IBD)?

A. Păcurari, C. Banciu, A. Munteanu, C. Serban, I. Romoșan
University of Medicine and Pharmacy Victor Babeș, IVth Medical Clinic, Timișoara, Romania

Introduction: The presence of anxiety and depression as psychological co-morbidities are frequent in IBD patients. There for symptoms of functional gastrointestinal disorders (FGID) are highly prevalent in those patients. The aim of this study was to determine whether there is any inter-relationship between the presence of FGIDs and psychological status.

Methods: The study was carried out on a group of 32 patients diagnosed with IBD (37.5% had ulcerative colitis, 18.8% Crohn’s disease and 43.7% not differentiated IBD), admitted in our clinic. The patients were aged between 31–62 years. We applied in all patients a psychological test for personality (E.P.Q.), a stress test and a depression scale (Beck) in order to evaluate the psychological status. Disease activity and functional symptoms according to Rome III criteria were also collected.

Results: Of all patients, 68.8% had functional bowel symptoms. Anxiety was present in 59.3% of those patients and depression was present in just 18.2% of those patients. We observed that anxiety was more often present in women than in men and the prevalence was higher in older patients. 72.7% of the selected patients were introverts.

Discussion/Conclusion: Functional gastrointestinal disorders are highly prevalent in IBD patients. Most of the patients had an introvert personality. Anxiety was more frequent than depression in our group.
Inflammatory bowel disease – A risk factor for low bone mineral density

A. Păcurari, A. Munteanu, C. Banciu, C. Serban, I. Romosan
University of Medicine and Pharmacy Victor Babeș, IVth Medical Clinic, Timișoara, Romania

Introduction: Patients with inflammatory bowel disease (IBD) are at increased risk of developing osteopenia and osteoporosis. The aim of the study was to investigate the prevalence of decreased bone density (BMD) and related risk factors in IBD patients.

Methods: The study was carried out on a group of 23 patients diagnosed with IBD, admitted our clinic. We measured in all patients the bone mineral density, expressed by the T-score and blood samples were obtained to measure biochemical markers.

Results: In the studied group 16 (69.6%) patients had ulcerative colitis (UC) and 7 (30.4%) had Crohn’s disease (CD). From all patients included in the study, 21.8% had normal bone mineral density, 60.8% had osteopenia and 17.4% had osteoporosis. Osteopenia was more pronounced at the femoral neck (69.6%) followed by the ultra-distal radius and the lumbar spine (L1–L4). There were no significant differences between men and women or between patients with UC or CD. We performed a correlation and regression analysis for determining the risk factors of low BMD in IBD patients. The analysis revealed that the T score was predicted by age ($p < 0.0001$), chronic corticosteroid use ($p < 0.002$), body mass index (BMI) ($p < 0.005$), hypocalcemia ($p < 0.005$) and smoking ($p < 0.009$).

Discussion/Conclusion: Osteopenia and osteoporosis is highly prevalent in patients with IBD. Corticosteroid use, age, smoking, and increased BMI are predictive factors for low bone density.
Osteo-articular affecting in IBD – Importance and treatment

O. Petrescu, V. Birlutiu
Medical Clinic II, County Clinical Hospital Sibiu; Faculty of Medicine, Sibiu, Romania

Introduction: Of the extraintestinal manifestations of the inflammatory bowel diseases, arthropathies are of extreme importance. Because of the painful symptoms, these require adequate therapeutic measures, which would alleviate discomfort and improve life quality.

Methods: We have examined and followed (from September 2007 to September 2013) 57 patients with inflammatory bowel diseases: 47 (82.4%) with ulcerative colitis and 10 (17.6%) with Crohn's disease. The osteo-articular manifestations that were present were clinically, immunologically and radiologically evaluated. We assessed their relation with the inflammatory bowel disease, with other extra-intestinal manifestations, the therapeutic methods and the patients’ response to treatment.

Results: Of the patients with ulcerative colitis, 8 (17%) showed osteo-articular manifestations, 4 (8.5%) had pauciarticular peripheral arthropathies, 3 (6.4%) had polyarticular peripheral arthropathies, and 1 patient (2.1%) was diagnosed with ankylosing spondylitis (HLAB27 positive). Only 1 patient with Crohn's disease showed asymptomatic sacroiliitis. In the patients with pauciarticular peripheral arthropathy, the clinical manifestations were present in the stages of activity of ulcerative colitis, while polyarticular peripheral arthropathies also evolved independent of the phases of activity of ulcerative colitis. 2 patients with peripheral pauciarticular manifestations also had erythema nodosum.

The treatment consisted of measures common to arthritis in order to alleviate symptoms in the acute stage. These included analgesics, non-steroidal anti-inflammatory agents (classical ones and COX II inhibitors) over a period of 7–10 days, without negative effects on the inflammatory bowel disease. Sulfasalazine had a benefic effect in the treatment of 2 patients with pauciarticular peripheral arthropathies, as well as in the case of a patient with polyarticular affecting. The other patients had a favourable evolution of the articular symptomatology, under treatment with anti-TNF agents. The patient with ankylosing spondylitis received treatment with Infliximab, and had a favourable evolution.

Conclusions: The therapeutic measures common to arthritis in patients with severely painful manifestations (over a period that would not exceed 10 days) and the medicine used in the treatment of the inflammatory bowel diseases (sulfasalazine, anti-TNF agents) had benefic effects irrespective of the type of arthropathy associated with the inflammatory bowel disease. We have identified neither arthropathies induced by the medication used for the inflammatory bowel diseases, nor the aggravation of the inflammatory bowel disease after the anti-inflammatory treatment over short periods of time.
Efficacy of infliximab in the treatment of inflammatory bowel disease (IBD) in children

A. Potapov, M. Venediktova, E. Tsimbalova, A. Anushenko, M. Varichkina
Gastroenterology and Hepatology, Scientific Centre of Children's Health, Moscow, Russia

Introduction: Infliximab, a chimeric monoclonal antibody against tumor necrosis factor-α, is available for treatment of patients with moderately to severely active inflammatory bowel disease (IBD). Biological therapy significantly improved the management of IBD refractory to conventional therapies. The principal purpose of the study was to investigate efficacy of infliximab to achieve an endoscopic remission of IBD in children.

Methods: The study included 58 children with IBD aged 6–18 years (mean 11.9 ± 4.1 years): Crohn's disease (CD) – 45 and ulcerative colitis (UC) – 13. Patients received infliximab (5 mg/kg) in three repeated infusions at 0, 2, 6, 8 weeks. The endoscopic activity was scored using the Simple Endoscopic Score (SES-CD) and Rachmilewitz endoscopic activity index.

Results: At the beginning of infliximab therapy in 37 children with CD (82.2%) had severe activity disease (PCDAI > 30), 8 children (17.8%) – moderate activity (PCDAI > 10); in children with UC 9 (69.2%) had severe activity of disease (PUCAI 65–85) and 4 children (30.8%) – moderate activity (PUCAI 30–65). Efficacy of infliximab induction therapy in CD was 98% (65% children achieved clinical remission) and in UC efficacy was 85% (62% clinical remission). After 1 year therapy efficacy of therapy CD was 96% (clinical remission was reduced to 77%) and in UC efficacy of therapy was 89% (clinical remission was in 67%). Endoscopic remission in CD after induction therapy was 52.5% and in UC – 15%. After 1 year treatment. endoscopic remission was observed in 43% and in UC – 78%.

Conclusion: Based on these data, anti-TNF-α biologic therapy by infliximab showed high effectiveness for the induction and maintenance of remission in both CD and UC. Anticytokine treatment with infliximab allows to reach clinical and endoscopic remission and secure its maintenance.
Switching patients with ulcerative colitis to once daily mesalazine improves outcome and reduces cost in primary and secondary care

H. Prasher*, P. Savania*, R. Jazrawi**
*Medicines Management Solutions Ravenstone, Leicester; **Dr. Falk Pharma UK, Ltd. Bourne End, Bucks, UK; E-Mail: jazrawi@drfalkpharma.co.uk, Fax: +44(0)1628536601

Background: Oral mesalazine formulations offer similar efficacy and tolerability for acute and maintenance therapy of UC patients. Therefore choice of mesalazine is based on other factors such as adherence to therapy and cost. Once daily dosing and reduced pill burden are the best determinants of improved adherence to therapy. Newer mesalazine formulations such as Salofalk® Granules have unique release characteristics allowing them to be administered once daily for both acute and maintenance therapy of UC and have, therefore, been recommended1.

Aims: Two pilot studies were carried in UC patients in primary care. The aims were to assess in patients inadequately maintained on mesalazine therapy, the effect of changing to a “Once Daily” oral mesalazine on disease outcome (pilot study 1), and on outpatient and hospital visits and cost saving (pilot study 2).

Methods: UC patients from 7 general practices covering a population of 103,000 were reviewed by independent clinical pharmacists “Medicines Management Solutions Ltd”. Disease activity was assessed (Walmsley Index) and following patient and GP consent; eligible patients were switched to a once daily mesalazine (Salofalk® Granules 1.5 g/day). A second review after 6 months assessed disease activity, number of visits to hospital and general practice, steroid use and cost of treatment.

Results: In total, 363 UC patients were reviewed, change was recommended in 130 patients (36%) and was actioned in 87 (24%). The main reasons for changing to once daily mesalazine were adherence issues (52%), patient preference (36%) and symptoms (12%). In the first pilot study the second review 6 months later demonstrated that 70% of the patients improved their UC severity score (Walmsley Index) and 30 had no change. There was no worsening of the UC score in any patients. In the second pilot study review after 6 months in patients switched to once daily mesalazine maintenance therapy demonstrated: 47% reduction in all hospital visits, 60% reduction in hospital visits due to flare up of UC, 45% reduction in GP visits and 50% reduction in steroid courses used. The majority of patients preferred once daily dosing and 85% of patients admitted no prior knowledge of the availability of alternative dosing regimes. Both pilot studies demonstrated a substantial cost saving.

Conclusions: Maintenance therapy of UC in the community is inadequate in more than one third of patients. Optimising maintenance therapy by switching to a once daily mesalazine leads to improved patient and disease outcomes as well as cost saving.

References: DTB 2011; Vol. 49, No. 1
The expression of various apoptotic proteins in inflammatory bowel diseases

A. Przyczynicz¹, K. Niewiarowska¹, K. Guzińska-Ustymowicz¹, W. Famulski², A. Kemona¹, D. Cepowicz³, M. Gryko³
¹Department of General Pathomorphology; ²Department of Medical Pathomorphology; ³2nd Department of General Surgery and Gastroenterology, Medical University of Białystok, Poland

Introduction: In physiological conditions, apoptosis plays an important role in the control of cell numbers during their maturation and allow to remove damaged or cancerous cells as well. The process involves caspases and the proteins of Bcl-2 family. The deficiency or dysfunction of caspases may result in an extension of the inflammatory process. Therefore, the aim of our study was to evaluate apoptotic proteins (Bax, Bak, Bcl-xl, pro-caspase-3, active caspase-3, kspazy-8) in patients with ulcerative colitis and Crohn's disease.

Materials and methods: The study group included 18 patients with ulcerative colitis and 10 patients with Crohn's disease. The expression of Bax, Bak, Bcl-XL, pro-caspase-3, caspase-3, caspase-8 in tissue sections were assessed by immunohistochemical methods. The color reaction was observed in cytoplasm of the glandular epithelium and inflammatory cells.

Results: Patients with ulcerative colitis showed the increased expression of Bax, Bak and Bcl-xl in dysplastic epithelial cells compared to normal glands. In addition, the lack and weak expression of caspase 8 (41.2% and 35.3%, respectively), medium and strong expression of pro-caspase-3 (41.2% and 35.3%, respectively) and the weak reaction of active caspase -3 (80%) were observed. The increased expression of Bax, Bak and Bcl-XL were found in patients with Crohn's disease too. In this disease, the weak, medium and strong reaction of caspase-8 (30%, 40%, 20%, respectively), strong expression pro-caspase-3 (100%) and a weak reaction of active caspase-3 (60%) were shown in dysplastic epithelium. In addition, it was observed the weak reaction of the caspase-8 and pro-caspase-3 (58%, 58%) in patients with ulcerative colitis as compared to the strong reaction of these proteins in patients with Crohn's disease in inflammatory cells (90%, 80%, respectively).

Conclusion: The increased expression of pro-apoptotic in IBD may suggest to start the preventing processes of development of dysplastic glandular epithelium. However, the increased expression of anti-apoptotic Bcl-xl protein which protects dysplastic cells against death was observed too. The expressions of active caspase were high levels in dysplastic epithelium in IBD that may suggest about the dysfunction of regulatory process responsible for cell abnormality.
Long-term outcome of eradication of complex perianal fistula by mucosal advancement flap in IBD patients

O. Ryska, Y. Serclova, J. Marvan*, J. Kalvach
Department of Surgery, 2nd Faculty of Medicine and Central Military Hospital; *Department of Surgery, Bulovka Hospital, Prague, Czech Republic

Introduction: The surgical management of perianal fistulas remains challenging in patients with inflammatory bowel disease (IBD). Fistula recurrence rate varies between 10–40% after advancement flap (AF) procedure. Pre-treatment with non-cutting seton drainage prevents residual abscesses and enables good timing of AF which may improve the results. The aim of the study was to evaluate the long-term results of AF followed by noncutting seton drainage in IBD patients.

Methods: All IBD patients indicated for AF procedure for complex fistula in the period: 6/2006–6/2012 were included in the retrospective analysis. After initial examination under anesthesia and seton placement, re-drainage was performed in case of recurring abscesses or to simplify secondary fistula tracts. Afterwards fistula was eradicated by mucosal AF method. Patients were followed for 21 (1–70) months. Continuing fistula secretion up to 3 months was assessed as a healing failure otherwise as a recurrence.

Results: Forty eight patients, 16 (33%) female and 32 (67%) male in median age of 34 (20–52) years diagnosed with Crohn’s disease - 43 (90%) or ulcerative colitis – 5 (10%) were enrolled. Median number of drainages prior to AF were 2 (1–9) and the period between first drainage and AF was 11 (1–58) months. Primary healing was achieved in 43 (89%) patients; afterwards 2 primary non-healed cases were successfully managed with repeated AF. Four (8.3%) patients suffered from fistula relapse. Recto-vaginal fistula was recognised as a risk factor of primary surgical failure (RR: 8.471; 95% CI: 1.02–70.2; p = 0.047). In only 2 of 9 patients (in 4 for luminal disease) with stoma creation the bowel continuity could not be restored.

Conclusion: Staged procedure: AF followed after seton drainage is effective in fistula eradication in IBD patients with low recurrence rate (8.3%). After an AF re-do AF, long-term fistula eradication was observed in 42 (88%) of patients.
The levels of long and short pentraxins in inflammatory bowel disease


*University of Medicine and Pharmacy, Craiova, Romania
**Titu Maiorescu University, Faculty of Medicine, Bucharest, Romania
***Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

Introduction: The pentraxin superfamily is a group of proteins divided in two subgroups, according to the length of the amino acids chain: long pentraxins (including PTX-3) and short pentraxins such as C protein reactive (CRP) and serum amyloid P (SAP). PTX-3 is an acute-phase protein, a key component of innate immunity produced especially by fibroblasts, neutrophils, and macrophages. CRP and SAP are produced primarily in the liver while PTX3 is produced in a variety of tissues during inflammation.

The aim of this study was to measure the levels of pentraxin-3 (PTX-3) and CRP in serum of patients with inflammatory bowel diseases (IBD) comparative with healthy subjects, and to analyse if these values could be markers of differentiation in bowel diseases.

Methods: The samples were collected from 16 Crohn’s disease (CD) patients, 10 patients with ulcerative colitis (UC) and 14 healthy persons. PTX-3 serum levels were determined using a commercial ELISA Quantikine kit R & D systems, Minneapolis; INOVA kit, SUA has been used for dosage of hs-CRP.

Results: The results showed an increase of mean ± SD serum PTX3 levels from IBD patients than that of healthy control. Long pentraxin PTX3 was a good inflammation marker in the patients. Plasma PTX3 levels were significantly lower in men than in women. CRP concentration was higher in patients with CD active than in patients with active UC. Serum CRP level were normal in inactive ulcerative colitis and inactive CD. High levels of PTX3 were associated with unfavorable outcome. There was a significant correlation between PTX3 and CRP levels in 6 of CD patients. (r = 0.60, p < 0.01).

Discussion/Conclusion: PTX3 and CRP could likely be used in the evaluation of inflammatory status in IBD. CRP and PTX3 may be considered markers useful in differentiation of Crohn’s disease by ulcerative colitis.
The role of the Tec-family kinase Itk in the development of inflammatory bowel disease

S. Steiner, R. Atreya, M.F. Neurath, B. Weigmann
Departement of I. Med. Clinic, Research Campus, University Erlangen, Erlangen, Germany

Introduction: Itk, a member of the Tec-family kinases, is expressed in T lymphocytes and involved in Th2 mediated immune responses. Furthermore, Itk interacts with cyclophilin A, which build a complex with the immunosuppressive drug cyclosporine A. Colitis patients can be successfully treated with cyclosporine A, but Crohn's disease patients not. Therefore we started to investigate the role of Itk in different experimental colitis models as well as in human samples.

Methods: Human cryosections were taken for fluorescent staining of Itk and cyclophilin A. ItkKO mice were treated with oxazolone or were taken for cell transfer to induce Th2/Th1 mediated colitis. DSS-induced colitis, caused by the damage of epithelial cells, was also performed. The manifestation of inflammation was determined by miniendoscopic analysis. The colon was isolated and used for RNA isolation to determine the cytokine profile by qPCR analysis.

Results: By staining of human tissues Itk and cyclophilin A showed a higher expression in tissue of patients compared to control tissue, which indicates an important regulatory role for these components. In the oxazolone colitis and in the transfer colitis ItkKO mice were protected compared to the wildtype mice. This can be seen in the miniendoscopic analysis as well as in the histological sections, which show an increased cell infiltration in the wildtype mice. The Th2 mediated cytokines were increased in the control mice. In the DSS-colitis both groups were nearly equally inflamed, which can also be seen in the miniendoscopic analysis and the histological sections.

Discussion/Conclusion: Because the ItkKO mice are protected in the oxazolone and the transfer colitis, but show distinct signs of inflammation in the DSS colitis, it can be concluded, that Itk has an essential function in T cell-mediated colitis. The immunofluorescent staining of human tissue indicates a crucial role for Itk and cyclophilin A in IBD. Thus Itk seems to play a critical role in the signalling pathway, which induces Th2 mediated colitis and is impaired by cyclosporine A treatment.
Mannan-binding lectin (MBL) in inflammatory bowel disease

A. Szala¹, L. Bak-Romaniszyn²,3, A. Sokolowska¹, A. Swierzko¹, L. Durko⁴, E. Malecka-Panas⁴, M. Cedzynski¹
¹Laboratory of Immunobiology of Infections, Institute of Medical Biology, Polish Academy of Sciences; ²Department of Paediatrics and Clinical Immunology, Polish Mother’s Memorial Hospital Research Institute; ³Unit of Nutrition in Digestive Tract Disease, Medical University of Lodz; ⁴Department of Gastroenterology Medical University of Lodz, Lodz, Poland

Introduction: An increase of incidence of Crohn’s disease and ulcerative colitis is still observed. The etiology of inflammatory bowel disease has not been elucidated clearly. The role of genetic, environmental and immune factors is considered. Data concerning the significance of mannan-binding lectin (MBL) are limited and contradictory. Our preliminary data suggest that MBL2 gene mutations may be connected with Crohn’s disease incidence in children. The aim of the study is an investigation of single nucleotide polymorphisms of the MBL2 gene, and MBL serum concentrations in patients suffering from Crohn’s disease and ulcerative colitis.

Methods: Patients were classified basing on clinical examination, colonoscopy and histological examination. MBL2 gene polymorphisms were investigated with the help of PCR or PCR-RFLP method while MBL concentrations were estimated in ELISA.

Results: Among patients with Crohn’s disease, MBL2 gene exon 1 mutations were found in 11 (45.8%) cases. None of them had mutation of both alleles (O/O), however 4 (16.7%) had LXA/O variants, also associated with MBL deficiency. In UC group, 2 patients (20%) were A/O heterozygotes while 1 (10%) was B/D (O/O) heterozygote. Thirty-eight (35.8%) controls were A/O heterozygotes, including 8 (7.5%) LXA/O. One (0.9%) had O/O genotype. Thus, 9 (8.5%) healthy adults had MBL-deficiency associated genotypes. The statistical analysis revealed no significant differences between patients and controls.

Among IBD patients, median MBL concentrations were 843 ng/ml (CD), 1272 ng/ml (UC), while among controls: 1245 ng/ml. MBL levels did not differ significantly among these groups.

Discussion/Conclusion: These preliminary data suggest that MBL2 gene polymorphism and MBL protein levels are not connected with inflammatory bowel disease incidence in adults.
Infliximab therapy in children with moderate-to-severe ulcerative colitis

M. Szychta¹, M. Dadalski¹, P. Landowski², B. Klincewicz³, M. Sladek⁴, K. Karolewska-Bochenek⁵, G. Czaja-Bulsa⁶, E. Jarocka-Cyrta⁷, B. Korczowski⁸, J. Kierkus¹

¹Department of Gastroenterology, Hepatology and Feeding Disorders, The Children’s Memorial Health Institute, Warsaw; ²Chair and Department of Pediatrics, Pediatric Gastroenterology, Hepatology and Nutrition, Medical University of Gdansk, Gdansk; ³1st Chair of Pediatrics, Department of Pediatric Gastroenterology and Metabolism, Poznan University of Medical Sciences, Poznan; ⁴Department of Pediatrics, Gastroenterology and Nutrition, Jagiellonian University School of Medicine, Cracow; ⁵Department of Pediatric Gastroenterology and Nutrition, Medical University of Warsaw, Warsaw; ⁶Pediatric Nursery Unit of Pomeranian Medical University, Division of Pediatrics, Gastroenterology and Rheumatology of Zdroje Hospital in Szczecin, Szczecin; ⁷Department of Pediatrics, Gastroenterology and Allergology, Medical University of Bialystok, Bialystok; ⁸Department of Pediatrics, State Hospital no 2, Medical College, University of Rzeszow, Rzeszow, Poland

Background: Ulcerative colitis (UC) in children has a variable clinical course ranging from mild to severe phenotype. Treatment of UC depends on disease activity determined by Pediatric Ulcerative Colitis Activity Index (PUCAI) and the extent of mucosal inflammation assessing in colonoscopy. Some clinical data from USA and Western Europe demonstrate that infliximab is efficient in children with moderate-to-severe ulcerative colitis and reduces the quantity of colectomies in this group. The aim of the study was to assess the efficacy and safety of induction therapy with infliximab in Polish children with moderate to severe ulcerative colitis.

Methods: The retrospective analysis of 44 patients (23F, 21M) aged 14 ± 3.9 y [mean ± SD] with moderate-to-severe ulcerative colitis (PUCAI > 0 points; 58.8 ± 15.1 points [mean ± SD]) and endoscopic evaluation who received induction therapy with infliximab 5 mg/kg at weeks 0, 2, and 6. According to Paris classification the endoscopic extension were: E1 – 0 pts (0%); E2 – 11 pts (25%); E3 – 10 pts (23%); E4 – 23 pts (52%); and the severity S0 – 7 pts (16%); S1 – 37 pts (84%). Endoscopic severity according to Baron classification was: Baron 1 – 1 pts (2%); Baron 2 – 17 pts (39%); Baron 3 – 26 pts (59%). Clinical (PUCAI score) and endoscopic (Baron classification) evaluations were performed at week 10 after 3 doses of infliximab. The primary endpoint was clinical remission defined as PUCAI < 10. The secondary endpoints were: clinical response defined as decrease of PUCAI > 19, mucosal response defined as improvement in Baron classification and mucosal remission defined as Baron classification 0 (no endoscopic changes).

Results: Eleven out of the 44 (25%) patients had clinical remission at week 10. Twenty-eight out of the 44 (64%) patients had clinical response, 25 out of 44 (57%) had mucosal response and 5 out of 44 (11%) had mucosal remission. 6 patients did not receive three doses of infliximab, 3 had allergic shock and 3 had to have colectomy performed.
**Conclusion:** Infliximab is efficient and safe as an induction therapy in children with moderate to severe ulcerative colitis and improves mucosal appearance in about 60% cases. Clinical remission is not equivalent to mucosal remission in children with UC.
Inducing role of mucosal mast cells during colitis-associated colorectal cancer

B. Weigmann¹, M. Stassen², M.F. Neurath¹
¹I. Med. Clinic, University Hospital Erlangen-Nürnberg, Nürnberg, Germany
²Department of Immunology, Johannes Gutenberg University Mainz, Mainz, Germany

Introduction: Colorectal cancer is one of the most malignancies accompanied colitis. However, the molecular pathogenesis of colorectal cancer is poorly understood. In order to investigate the functional role of mast cells, which play a more prominent role in immunological processes, we used a previously established murine colon carcinoma model (DSS/Azoxy methan) with mast cell deficient mice.

Methods: Accordingly, mice were treated with AOM followed by three consecutive cycles of orally administrated dextran sulfate sodium (DSS) over a period of 7 days. To monitor tumorigenesis in mice in vivo, we used our mini-endoscopic system.

Results: By using this system together with methylene blue staining, we were able to detect aberrant crypt foci in DSS plus AOM-treated wild-type mice at early time point before macroscopically visible lesions were seen. First visible lesions associated with inflammation appeared in wt mice around 4 weeks, which were followed by the development of more and growing tumors until 9 weeks. In contrast, mast cell deficient mice are protected against tumor development and although they showed colitis-similar symptoms. The possibility, that mast cells play a tumor-promoting role in the development of colon tumors led us to perform a screening of the expression of involved cytokines in colons and tumors of treated mice vs. untreated mice. Even in long term study, a marginal increase of the tumor prevalence concerning mast cell deficient mice could be observed.

Discussion/Conclusion: Our data contribute extensively the understanding of mast cells in colitis-associated colon cancer and encourage of rethinking the role of mast cells in colitis-associated colorectal cancer.
The adaptive potential of organism in patients with ulcerative colitis and anemia

E.V. Zigalo, L.V. Demeshkina, V.M. Zigalo
State Institution “Institute of Gastroenterology of AMS of Ukraine”, Dnipropetrovsk, Ukraine

Introduction: An anemia syndrome at ulcerative colitis (UC) might be a marker of disease severity and predictor of its resistance to treatment. The purpose of this study was to investigate adaptive potential in patients with UC combined with anemia syndrome.

Materials and methods: 38 patients with UC with moderate and severe anemia and 22 patients with UC without anemia (control group) were examined. Vegetative tonus (VT), vegetative reactivity (VR), exertion index (EI), and activity of vegetative provision (AVP) were studied by the method of variating pulsometria and loading tests. Statistical analysis was carried out in SPSS.

Results: The imbalance of vegetative nervous system (VNS) with considerable prevalence of sympathicotonic link was revealed in patients with UC with anemia syndrome. According to VI and EI data, sympathicotonic vegetative tonus was in 68.4% of patients with moderate anemia and in 73.3% of patients with severe anemia (p < 0.05). Patients with UC and anemia had hypersympathicotonic VR (73.7%), asympathicotonic VR (26.3%) that testified about tension of vegetative regulation and weakening humoral link.
Disorder of VPA was revealed at more quantity (71.0%) of patients with UC and anemia in comparison with control group. It was also evidence of exertion of adaptive mechanisms in patients with initial sympathicotonia and increasing EI on the average to 72.9 ± 6.1%. At the same time quantity of compensatory reactions because of tension reaction which became in 2 times more. It means that patients with UC and anemia had vegetative dysadaptation and less unfavorable outcomes than patients in control group.

Conclusion: Disorder of vegetative adaptation was revealed in patients with UC and anemia syndrome.
Author Index to Poster Abstracts
(Name - Poster Number)

Al-Sulttan, F.M. 1
Anushenko, A. 36
Atreya, R. 41
Aydogdu, S. 4
Azzouz, H. 2
Badea, A. 13, 14
Badea, D. 13, 14
Badea, M. 13, 14
Bak-Romaniszyn, L. 42
Banciu, C. 33, 34
Baran, M. 4
Ben Ammar, H. 10
Ben Mustapha, N. 2, 3, 9, 10, 11, 29, 30
Ben Slimene, B. 2, 29
Biciusca, V. 40
Birlutiu, V. 35
Bogdanos, D.P. 1
Bojic, D. 18
Boldeanu, V.M. 40
Boubaker, J. 2, 3, 9, 10, 11, 29, 30
Boussetta, A. 10
Brocic, T. 18
Cakir, M. 4
Capocci, S. 19
Cedzynski, M. 42
Celebi, A. 22
Cepowicz, D. 20, 38
Cerban, R. 5
Cheikh, M. 3, 11
Chiriac, S. 16
Cojocariu, C. 17
Cojocaru, I.M. 40
Cojocaru, M. 40
Cotruta, B. 5
Craciun, C. 12
Cropley, I. 19
Czaja-Bulsa, G. 6, 24, 43
Czkwianianc, E. 6, 24
Dadalski, M. 6, 24, 43
Debbabi, H. 9, 30
Demeshkina, L.V. 7, 45
Dindar, G. 22
Dinler, G. 4
Dornhoff, H. 8
Doyle, S. 8
Dugalic, P. 18
Duman, A.E. 22
Durko, L. 42
Efremov, L. 26
Famulski, W. 20, 38
Fekih, M. 2, 3, 9, 10, 11, 29, 30
Filali, A. 2, 3, 9, 10, 11, 29, 30
Forbes, A. 1
Fragkos, K.C. 1
Fratila, O.C. 12, 23
Genunche- 13, 14
Dumitrescu, A.
Gerlach, K. 15
Gheorghe, C. 5
Gheorghe, L.S. 5
Girleanu, I. 16, 17
Gligorijevic, V. 18
Greveson, K. 19
Gryko, M. 20, 38
Gryzburgska- 6, 24
Chlebowczyk, U.
Guzinska- 20, 38
Ustymowicz, K.
Hadjadjev, L. 18
Hamilton, M. 19
Haouet, S. 2
Hospodarska, K. 21
Hospodarskyy, I. 21
Hülagu, S. 22
Ilias, T. 23
Iwanczak, B. 6, 24
Jarocka-Cyryta, E. 43
Jazrawi, R. 37
Jojic, N. 18
<table>
<thead>
<tr>
<th>Name</th>
<th>Pages</th>
<th>Name</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kalayci, A.G.</td>
<td>4</td>
<td>Petrescu, O.</td>
<td>35</td>
</tr>
<tr>
<td>Kallel, L.</td>
<td>3, 9, 10, 11, 29, 30</td>
<td>Potapov, A. S.</td>
<td>36</td>
</tr>
<tr>
<td>Kalvach, J.</td>
<td>39</td>
<td>Prasher, H.</td>
<td>37</td>
</tr>
<tr>
<td>Karolewskas-Klocek, K.</td>
<td>43</td>
<td>Prochazka, V.</td>
<td>28</td>
</tr>
<tr>
<td>Bochenek, K.</td>
<td></td>
<td>Pyczynicz, A.</td>
<td>20, 38</td>
</tr>
<tr>
<td>Kasirga, E.</td>
<td>4</td>
<td>Puscasiu, D.</td>
<td>23</td>
</tr>
<tr>
<td>Kemenon, A.</td>
<td>20, 38</td>
<td>Rogozi, S.</td>
<td>40</td>
</tr>
<tr>
<td>Kierkus, J.</td>
<td>6, 24, 43</td>
<td>Romosan, I.</td>
<td>33, 34</td>
</tr>
<tr>
<td>Klineczewicz, B.</td>
<td>43</td>
<td>Ruchkina, I.</td>
<td>26, 27</td>
</tr>
<tr>
<td>Knyazev, O.</td>
<td>25, 26, 27</td>
<td>Ryska, O.</td>
<td>39</td>
</tr>
<tr>
<td>Koc, D.</td>
<td>22</td>
<td>Savani, P.</td>
<td>37</td>
</tr>
<tr>
<td>Konecny, M.</td>
<td>28</td>
<td>Siebler, J.</td>
<td>8</td>
</tr>
<tr>
<td>Konoplaynikov, A.</td>
<td>25, 27</td>
<td>Silosi, C.A.</td>
<td>40</td>
</tr>
<tr>
<td>Korczowski, B.</td>
<td>6, 24, 43</td>
<td>Silosi, I.</td>
<td>40</td>
</tr>
<tr>
<td>Korkmaz, U.</td>
<td>22</td>
<td>Singap, A.-M.</td>
<td>16, 17</td>
</tr>
<tr>
<td>Kovaleva, A.V.</td>
<td>7</td>
<td>Sirin, G.</td>
<td>22</td>
</tr>
<tr>
<td>Krstic, M.</td>
<td>18</td>
<td>Sladek, M.</td>
<td>6, 24, 43</td>
</tr>
<tr>
<td>Krzesiek, E.</td>
<td>6, 24</td>
<td>Sfarti, C.</td>
<td>17</td>
</tr>
<tr>
<td>Labidi, A.</td>
<td>9, 29, 30</td>
<td>Shcherbakov, P.</td>
<td>25, 27</td>
</tr>
<tr>
<td>Labidi, A.</td>
<td>2</td>
<td>Siebler, J.</td>
<td>8</td>
</tr>
<tr>
<td>Landowski, P.</td>
<td>43</td>
<td>Silosi, I.</td>
<td>40</td>
</tr>
<tr>
<td>Lazowska, I.</td>
<td>6, 24</td>
<td>Silosi, C.A.</td>
<td>40</td>
</tr>
<tr>
<td>Lehr, H.-A.</td>
<td>15</td>
<td>Singap, A.-M.</td>
<td>16, 17</td>
</tr>
<tr>
<td>Lipman, M.</td>
<td>19</td>
<td>Sirin, G.</td>
<td>22</td>
</tr>
<tr>
<td>Maksimovic, B.</td>
<td>18</td>
<td>Sladek, M.</td>
<td>6, 24, 43</td>
</tr>
<tr>
<td>Malecka-Panas, E.</td>
<td>42</td>
<td>Smith, C.</td>
<td>19</td>
</tr>
<tr>
<td>Manuc, M.</td>
<td>5</td>
<td>Sokolowska, A.</td>
<td>42</td>
</tr>
<tr>
<td>Marvan, J.</td>
<td>39</td>
<td>Stanciu, C.</td>
<td>16</td>
</tr>
<tr>
<td>Maslana, J.</td>
<td>6, 24</td>
<td>Stassen, M.</td>
<td>44</td>
</tr>
<tr>
<td>Matri, S.</td>
<td>10, 29, 30</td>
<td>Steiner, S.</td>
<td>41</td>
</tr>
<tr>
<td>McKenzie, A.</td>
<td>15</td>
<td>Stoica, O.</td>
<td>16</td>
</tr>
<tr>
<td>Mierzwa, G.</td>
<td>6, 24</td>
<td>Swierczko, A.</td>
<td>42</td>
</tr>
<tr>
<td>Milenkovic, Z.</td>
<td>18</td>
<td>Szalai, A.</td>
<td>42</td>
</tr>
<tr>
<td>Mitrut, P.</td>
<td>13, 14</td>
<td>Szyczta, M.</td>
<td>43</td>
</tr>
<tr>
<td>Mokricka, V.</td>
<td>31, 32</td>
<td>Szymanska, E.</td>
<td>6, 24</td>
</tr>
<tr>
<td>Morris, S.</td>
<td>19</td>
<td>Tarabar, D.</td>
<td>18</td>
</tr>
<tr>
<td>Munteanu, A.</td>
<td>33, 34</td>
<td>Toporowska-Egloff, S.</td>
<td>6, 24</td>
</tr>
<tr>
<td>Murray, C.</td>
<td>19</td>
<td>Kowalska, E.</td>
<td>6, 24</td>
</tr>
<tr>
<td>Murthy, S.</td>
<td>19</td>
<td>Trifan, A.</td>
<td>16, 17</td>
</tr>
<tr>
<td>Nagorni, A.</td>
<td>18</td>
<td>Tsimbalova, E.G.</td>
<td>36</td>
</tr>
<tr>
<td>Neurath, M.F.</td>
<td>8, 15, 41, 44</td>
<td>Tümgor, G.</td>
<td>4</td>
</tr>
<tr>
<td>Niewiarowska, K.</td>
<td>20, 38</td>
<td>Ünal, F.</td>
<td>4</td>
</tr>
<tr>
<td>Nikolic, G.</td>
<td>18</td>
<td>Vadan, R.</td>
<td>5</td>
</tr>
<tr>
<td>Ozola-Zalite, I.</td>
<td>31, 32</td>
<td>Varichkina, M.</td>
<td>36</td>
</tr>
<tr>
<td>Pacurari, A.</td>
<td>33, 34</td>
<td>Venedikto, M.</td>
<td>36</td>
</tr>
<tr>
<td>Parfenov, A.I.</td>
<td>25, 26, 27</td>
<td>Wegner, A.</td>
<td>6, 24</td>
</tr>
<tr>
<td>Name</td>
<td>Page</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
<td>------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wiecek, S.</td>
<td>6, 24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yılmaz, H.</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yükselkaya, H.A.</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zabka, A.</td>
<td>6, 24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zalila, H.</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zigalo, E.V.</td>
<td>7, 45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zigalo, V.M.</td>
<td>45</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Innovative Drugs
for bowel and liver diseases
Modern formulations and specially designed delivery systems ensure targeted release of the active drug

Scientific Dialogue
in the interest of therapeutic progress
Falk Symposia and Workshops
over 250 with almost 130,000 international participants since 1967
Continuing medical education seminars
over 15,500, attended by more than 1.2 million physicians and patients in Germany alone
Comprehensive literature service for healthcare professionals and patients with more than 200 publications