IBD in Different Age Groups

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Abstracts
Poster Abstracts
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IBD IN DIFFERENT AGE GROUPS

Madrid (Spain)
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Scientific Organization:
M. Gassull, Badalona (Spain)
A. Levine, Holon (Israel)
A. López San Román, Madrid (Spain)
G. Rogler, Zurich (Switzerland)
CONTENTS

Session I

Insights from epidemiology

Chair:
M. Gassull, Badalona
M. Sans Cuffi, Barcelona

Epidemiology of IBD – Is there a shift towards younger ages?
C.P. Braegger, D. Rogler, M. Friedt, Zurich; P. Ballabeni,
V. Pittet, Lausanne

Disease behavior in adult patients – Are there predictors for stricture or fistula formation?
I. Dotan, Tel Aviv

Pediatric IBD – Is it different?
A. Levine, Tel Aviv

Environmental factors affecting IBD – Have we made progress?
P.L. Lakatos, Budapest

Chair:
J.-P. Hugot, Paris
F.M. Ruemmele, Paris

State-of-the-Art Lecture I
Susceptibility genes and overall pathogenesis of inflammatory bowel disease – Where do we stand?
C. Fiocchi, Cleveland
Session II

Pathophysiology of IBD and age of onset

Chair:
C. Fiocchi, Cleveland
G. Rogler, Zurich

Genetic determinants of pediatric IBD – Is age of onset genetically determined?
S. Kugathasan, Atlanta 29

The epithelial barrier – Is it impaired in older ages?
A. Sturm, Berlin 30 – 31

The link between autophagy and innate immunity
V. Deretic, Albuquerque 32 – 33

The microbiota in IBD in different age groups
S. Cucchiara, Rome 34

Session III

Differences in the diagnostic procedures

Chair:
S. Danese, Rozzano
M. Zeitz, Berlin

What role do serological markers play in IBD – Pediatric and adult data
M.C. Dubinsky, Los Angeles 37

Controversies in use of diagnostic procedures
B. Vucelic, Zagreb 38 – 40

The risk of radiation and choice of imaging
H. Herfarth, Chapel Hill 41 – 42

Non-invasive monitoring of mucosal healing in IBD – The role of bowel ultrasound
F. Parente, S. Greco, Lecco 43– 44
Session IV

Management of Crohn’s disease

Chair:
A. Levine, Tel Aviv
G. Veereman-Wauters, Antwerp

State-of-the-Art Lecture II
Risk/benefit strategies must be employed in the management of pediatric Crohn’s disease
J.S. Hyams, Hartford 47

Enteral nutrition as primary therapy in pediatric Crohn’s disease
R. Heuschkel, Cambridge 48 – 49

Top-down therapy – Is the evidence strong enough?
E. Domènech, Badalona 50

Immunomodulation with methotrexate – Underused and undervalued?
F.M. Ruemmele, Paris 51 – 52

Partial enteral nutrition as a maintenance therapy?
P. Lionetti, Florence 53 – 55

Session V

Management of ulcerative colitis

Chair:
A. López San Román, Madrid
F. Gomollón Garcia, Zaragoza

Treatment of severe ulcerative colitis
S.R. Vavricka, Zurich 59

Severe pediatric ulcerative colitis
D. Turner, Jerusalem 60

Treatment of ulcerative colitis in the elderly
A.N. Ananthakrishnan, D.G. Binion, Pittsburgh 61 – 72

Surgery in ulcerative colitis – Indication and timing
J.D. Söderholm, Linköping 73 – 74
Session VI

Tailored therapy for specific subgroups?

Chair:
B.G. Feagan, London (Ontario)
V. Motilva, Sevilla

Management of IBD during pregnancy
A.U. Dignass, Frankfurt 77

Mild-to-moderate Crohn’s disease – Still room for step-up therapies? – Adult perspectives
S. Bar-Meir, Tel Hashomer 78 – 79

Anti-TNF non-responders – Therapeutic strategies
E. Louis, Liège 80

Early IBD: Different treatment response to specific or all medications?
J.F. Markowitz, New Hyde Park (NY) 81

State-of-the-Art Lecture III
After TNF: Next generation biologics
D.K. Podolsky, Dallas 82 – 83

Session VII

Specific management issues

Chair:
G. Rogler, Zurich
B. Vucelic, Zagreb

How do we manage vaccinations in patients with inflammatory bowel disease?
M. Esteve, Barcelona 87

Non-colorectal malignancies in IBD – More than meets the eye?
L. Beaugerie, Paris 88

CRC prevention in patients with ulcerative colitis – Are pediatricians doing enough?
M.D. Rutter, Stockton-on-Tees 89 – 90

Transition from pediatric to adult health care
J.C. Escher, Rotterdam 91 – 92
Session VIII

Are we approaching solutions for unresolved problems?

Chair:
E. Ricart, Barcelona
C.J. van der Woude, Rotterdam

Fistula treatment: The unresolved challenge
P. Michetti, Lausanne

Drug monitoring in IBD: Helpful or dispensable?
T. Bruns, A. Stallmach, Jena

Growth retardation in early onset IBD: Should we monitor and treat these patients differently?
A.M. Griffiths, Toronto

Prebiotics, probiotics and helminths: The “natural” solution?
F. Guarner, Barcelona

List of Speakers, Moderators and Scientific Organizers
Poster Abstracts

1. The effect of infliximab treatment on angiogenic factors levels in patients with inflammatory bowel disease

2. Hepatitis B status and flare in Asian patients with inflammatory bowel disease receiving immunosuppression therapy
   V.J. Appleby, P. Southern, J. Healey, D. Patterson, S. Moreea (Bradford, GB)

3. The behavior of ulcerative colitis (UC) in elderly patients
   A. Atanassova, I.A. Kotzev, B. Manevska (Varna, BG)

4. Role of upper GI endoscopy in the initial diagnosis of children with IBD
   C. Banciu, I. Simedrea, L. Marian, I. Romosan (Timisoara, RO)

5. Adverse effects of pharmacologic treatment in children with inflammatory bowel disease

6. Glutathione peroxidase activity in ulcerative colitis
   G. Baskol, M. Baskol, F. Dogruel, A. Yurci, S. Gursoy, E. Torun (Kayseri, TR)

7. Adenosine deaminase and xanthine oxidase activities in ulcerative colitis
   M. Baskol, G. Baskol, A. Caniklioglu, F. Dogruel, A. Yurci, S. Gursoy, E. Torun (Kayseri, TR)

8. *CARD15/NOD2* gene mutations and the onset Crohn's disease in Slovak patients
   M. Batovsky, L. Bartosova (Bratislava, SK; Brno, CZ)

9. What factors influence adhesion to therapy in inflammatory bowel disease?

10. Mercaptopurine rescue after azathioprine-induced liver injury in inflammatory bowel disease

11. Folate and B₁₂ vitamin deficiency in Crohn's disease: Prospective controlled analysis of their prevalence and risk factors
12. Infliximab versus parenteral methotrexate for maintenance and induction therapy in pediatric inflammatory bowel disease  
B. Bidmon-Fliegenschnee, B. Raubal, J. Pichler, W.-D. Huber (Vienna, A)

13. Long-term budesonide treatment of collagenous colitis  
O.K. Bonderup, J.B. Hansen, P.S. Teglbjaerg, J. Fallingborg (Randers, Aalborg, DK)

14. Idiopathic pancreatitis at or before inflammatory bowel disease is more frequent in pediatric patients  
E. Broide, B. Weiss, I. Dotan, M. Wilschanski, B. Yerushalmi, A. Klar, A. Lerner, A. Levine (Zerifin, Tel Aviv, Jerusalem, Beer Sheva, Holon, IL)

15. Pregnancy and IBD patients  
A. Chavoushian, H. Kadian, Z. Spassova, S. Stoinov, P. Penchev (Sofia, BG)

16. Biological agents in Greek children with inflammatory bowel disease  

17. Comparative intestinal anti-inflammatory effects of different probiotics in the TNBS model of rat colitis  
M. Comalada, B. Arribas, E. Bailón, D. Camuesco, A. Zarzuelo, L. Perán, M.E. Rodríguez-Cabezas, A. Nieto, A. Concha, J. Gálvez (Granada, E)

18. Oral tacrolimus in steroid-refractory pediatric ulcerative colitis  
D. Comito, A. Famiani, V. Raffa, P. Rossi, R. Gallizzi, C. Romano (Messina, I)

19. Lymphoproliferative disorders diagnosed in an inflammatory bowel disease unit  
M. Van Domselaar, A. López San Roman, E. Garrido (Madrid, E)

20. Colorectal cancer incidence during 10 years surveillance among IBD patients  
V. Draganov, L. Tankova, P. Penchev, C. Velikova (Sofia, BG)

21. Oral beclomethasone dipropionate in pediatric active ulcerative colitis: A comparison trial with mesalazine  
A. Famiani, C. Romano, D. Comito, P. Rossi, V. Raffa, W. Fries (Messina, I)

22. Interest use of pelvic magnetic resonance imaging in patients with Crohn's disease perineal fistulae  
M. Fekih, S. Ouerdiane, K. Nouira, S. Matri, L. Kallel, J. Boubaker, A. Filali (Tunis, TN)

23. Epithelial barrier impairment in ulcerative colitis - Ultrastructural comparison between young and elderly  
O. Fratila, T. Ilias, C. Craciun, G. Avram, R. Mihaila (Oradea, Cluj-Napoca, Sibiu, RO)
24. The immunomodulatory properties of Escherichia coli Nissle 1917 are not restricted to the gastrointestinal tract
J. Gálvez, M. Comalada, B. Arribas, M.E. Bailón, D. Camuesco, A. Zarzuelo, P. Utrilla, M.E. Rodríguez-Cabezas (Granada, E)

25. Infliximab in ulcerative colitis: Concomitant cytomegalovirus infection, life's quality, PPD positive have an influence on the treatment with infliximab?
S. Gómez Senent, L. Adán Merino, E. Martín Arranz, M.D. Martín Arranz, C. Froilán Torres, J.M. Segura Cabral (Madrid, E)

26. Ulcerative colitis associated with aphthous stomatitis

27. Immune deficiency in infants' malnutrition associated with inflammatory bowel disease
S.R. Gotia, M. Cucuruz, S.L. Gotia (Timisoara, RO)

28. Linoleic acid, a dietary n-6 polyunsaturated fatty acid, and the etiology of ulcerative colitis - A European prospective cohort study
A.R. Hart (Norwich, GB)

29. Enteral nutrition vs. corticosteroids in pediatric patients with CD - Retrospective comparison study
I. Hojsak, Z. Misak, S. Abdovic, A. Jaklin-Kekez, O. Jadresin, S. Kolacek (Zagreb, HR)

30. Ulcerative colitis in elderly: Epidemiological, clinical, endoscopic and immunohistochemical study in a population from Western Romania
T. Ilias, O. Fratila, C. Craciun, G. Avram, R. Mihaila (Oradea, Cluj-Napoca, Sibiu, RO)

31. Incidence, phenotype and surgery in pediatric inflammatory bowel disease patients: Changes over a 44-year period
C. Jacobsen, A. Paerregaard, P. Munkholm, V. Wewer (Copenhagen, DK)

32. Impact of biliary and nutritional lack of phospholipids in a colitis mouse model
J. Jahnel, T. Claudel, A. Baghdasaryan, D. Silbert, J. Gumhold, A. Fuchsbichler, C. Langner, M. Trauner (Graz, A)

33. Anorectal lesions in Crohn's disease: Are there age-specific differences?
J. Jongen, A. Eberstein, J.-U. Bock, H.-G. Peleikis, V. Kahlke (Kiel, D)

34. Psychoemotional peculiarities in adolescents with inflammatory bowel diseases
L. Jorjoliani, E. Chkhartishvili, M. Tskhakaia, R. Karseladze, L. Saginadze (Tbilisi, GEO)

35. Prognostic value of intestinal bacterial flora and mucosal immunity during infancy in the development of inflammatory bowel diseases in adults
L. Jorjoliani, R. Karseladze, L. Saginadze, T. Bigvava, T. Arakhamia, E. Chkhartishvili (Tbilisi, GEO)
36. Particularities of Crohn's disease in young patients compared to adults
L. Kallel, N. Nija, S. Matri, M. Fekih, N. Ben Mustapha, S. Karoui, J. Boubaker, A. Filali (Tunis, TN)

37. Fecal calprotectin remains stable in inactive Crohn's disease patients: Results of a prospective study

38. Protease inhibitors genetic system phenotypes in inflammatory bowel disease
R. Karseladze, L. Jorjoliani, L. Saginadze, E. Karseladze (Tbilisi, GEO)

39. Diagnoses of ulcerative colitis in dependence on the age of patients
M. Konecny, V. Prochazka, J. Ehrmann (Olomouc, CZ)

40. Autophagy 16-like 1 (ATG16L1) is associated with inflammatory bowel disease (IBD) in children
M. Lacher, S. Schröpf, A. Jurik, D. von Schweinitz, A. Ballauff, P. Lohse, H. Baurecht, R. Kappler, S. Koletzko (Munich, Essen, D)

41. The role of aluminum in bacterial-induced colitis in young IL-10-deficient mice
A. Lerner, S. Eruli, D. Perl, S. Moalem, D.B. Sachar, S. Tonkonogy, R.B. Sartor (Haifa, IL; Chapel Hill, New York, Raleigh, USA)

42. Implementation of a day care unit for inflammatory bowel disease: Patients' satisfaction
M.D. Martín Arranz, E. Martín Arranz, S. Gómez Senent, L. Adán Merino, C. Froilán Torres, J.M. Segura Cabral (Madrid, E)

43. Risk factors associated with failing to enteral nutrition in pediatric Crohn's disease
Z. Misak, I. Hojsak, S. Abdovic, A. Jaklin-Kekez, O. Jadresin, S. Kolacek (Zagreb, HR)

44. Clinical course of adult ulcerative colitis (UC): A Markov model analysis of the multinational population-based prospective cohort of the European Collaborative Study of Inflammatory Bowel disease (EC-IBD)
S. Odes, H. Vardi, M. Friger, B. Moum, T. Bernklev, D. Esser, H. Waters, M.E. Elkjaer, R.W. Stockbrügger, E. Tsianos, P. Munkholm, E. Langholz (Beer Sheva, IL; Oslo, N; Leiden, Maastricht, NL; Malvern, USA; Copenhagen, DK; Ioannina, GR)

45. Risk factors of the low bone mineral density in patients with inflammatory bowel disease
A. Pacurari, C. Banciu, C. Serban, L.M. Susan, I. Romosan (Timisoara, RO)

46. Symptoms of functional gastrointestinal disorders (FGID) in patients with inflammatory bowel disease (IBD)
A. Pacurari, C. Banciu, M. Floare, C. Serban, I. Romosan (Timisoara, RO)
47. Neonatal colitis: Be aware of rare causes other than IBD
   A. Paerregaard, L.F. Hansen, U. Engel (Copenhagen, DK)

48. Pancreatic autoantibodies are associated with reactivity to microbial antibodies, penetrating disease behavior, perianal disease and extraintestinal manifestations, but not with NOD2/CARD15 or TLR4 genotype in a Hungarian inflammatory bowel disease cohort
   M. Papp, I. Altorjay, K. Palatka, J. Tumpek, L. Lakatos, A. Kovacs, T. Molnar, Z. Barta, W. Stocker, J. Papp, G. Veres, P.L. Lakatos, Hungarian IBD Study Group (Debrecen, Veszprem, Budapest, Szeged, H; Lübeck, D)

49. Mannan-binding lectin levels and deficiency in a large Hungarian cohort of inflammatory bowel disease patients
   M. Papp, I. Altorjay, K. Palatka, G. Farkas, J. Harsfalvi, L. Lakatos, K. Farkas, T. Molnar, A. Kovacs, G. Veres, J. Papp, P.L. Lakatos, Hungarian IBD Study Group (Debrecen, Szeged, Veszprem, Budapest, H)

50. Myocarditis and ulcerative colitis: An infrequent association

51. Activated beta1-integrin in normal colonic mucosa and in ulcerative colitis: Immunohistochemical study
   A. Portyanko, J.V. Gorgun (Minsk, WR)

52. Genitointestinal fistulas on Crohn's disease. Clinical characteristics and response to therapy
   G. De La Poza, F. Bermejo, A. López San Roman, M. Van Domselaar, A. Algaba, J. Die, J. Alvarez (Madrid, Fuenlabrada, E)

53. Significance of immunoserological markers in Crohn's disease (CD) according to the age at diagnosis
   C. Preda, S.N. Turchina, M. Manuc, M. Ciocarlan, R. Iacob, R. Vadan, M. Diculescu (Bukarest, Bucharest, RO)

54. Epidemiological characteristics of inflammatory bowel disease in Albania
   S. Prifti, B. Kraja, M. Sina, I. Akshia (Tirana, AL)

55. CD83 as a marker of mature dendritic cells increased in Crohn's disease
   A. Pryczynicz, K. Guzinska-Ustymowicz, J. Czyzewska, D. Cepowicz, A. Kemona (Bialystok, PL)

56. Renal amyloidosis complicating Crohn's disease: Report of three cases
   A. Quaz, L. Kallel, M. Fekih, S. Matri, J. Boubaker, A. Filali (Tunis, TN)

57. Are probiotics useful in the treatment of inflammatory bowel disease (IBD)
   L. Radu, A. Pacurari, B. Pacurari, I. Rosoman (Timisoara, RO)
58. The effect of inflammatory bowel disease (IBD) during pregnancy on long-term health and illness in children of IBD patients - A multicenter Israeli study
S. Reif, A. Alper, D. Rachmilewitz, I. Dotan (Tel Aviv, IL)

59. The activation of iron regulatory protein 1 dominates iron homeostasis in inflamed intestinal epithelium
R. Reifen, O. Savion, A. Kammer, S. Moshe, Y. Bujanover, B. Weiss, E. Meyron-Holtz (Rehovot, Haifa, Tel Aviv; IL)

60. Characteristics of the patients with inflammatory bowel diseases in Romania
E.C. Rezi, A. Fraticiu (Sibiu, RO)

61. Colonoscopy in elder versus younger patients - A retrospective study comparing the risk of developing IBD and colorectal cancer at two different age groups of patients from Sibiu, Romania
E.C. Rezi, A. Fraticiu (Sibiu, RO)

62. Correlation between ileocolonoscopic and video capsule examination in ankylosing spondylitis
M. Rimbas, M. Marinescu, S. Caraiola, M. Parvu, C. Baicus, S. Bucurica, C. Tanasescu, M.R. Voiosu (Bucharest, RO)

63. Profile of Belgian pediatric Crohn’s disease subjects (2): Snap shot at diagnosis

64. Profile of Belgian pediatric Crohn’s disease subjects (1): Demography and background of the first 100 patients

65. Methotrexate for pediatric IBD: Induction and maintenance of remission in a regional cohort study
P. Rogers, A. Tybulewicz, D. Hoole, J. Satsangi, P.M. Gillett, D.C. Wilson (Edinburgh, GB)

66. Early atherosclerosis in inflammatory bowel disease patients
C. Serban, L.M. Susan, A. Pacurari, C. Banciu, V.M. Ancusa, G. Savoiu, I. Romosan (Timisoara, RO)

67. A study of colorectal cancer in inflammatory bowel disease
68. Arachidonic acid increases ulcerative colitis risk - A prospective cohort study in EPIC-Denmark using biomarker data
   (Norwich, GB; Copenhagen, Aarhus, Aalborg, DK)

69. Mucosal healing and complete regression of transmural inflammation with doubling the third infliximab induction dose in refractory Crohn colitis
   M. Sladek, A. Swiat, I. Herman-Sucharska, S. Pieczarkowski, Z. Grzenda-Adamieck, K. Fyderek (Cracow, PL)

70. A two-year longitudinal study of the anemia associated with inflammatory bowel disease

71. Predictive value of serologic markers in inflammatory bowel disease
   L.M. Susan, C. Serban, C. Banciu, A. Pacurari, V.M. Ancusa, G. Savoiu, I. Romosan (Timisoara, RO)

72. Fertility and outcomes of pregnancies fathered by male patients exposed to thiopurines

73. Experience of infliximab therapy for refractory ulcerative colitis in a district general hospital
   I. Tetlay, D. Sadigh, D. Hughes, R. Turner, J. O’Brien, G. Bray, M. McStay (High Wycombe, GB)

74. Ulcerative colitis in young patients - Epidemiological and clinical course in North-Eastern Romania county
   E. Toader, L. Croitoru, O. Arhip, R. Mihaila (Iasi, Suceava, Botosani, Bârlad, RO)

75. Perinuclear anti-neutrophil cytoplasmic antibodies in patients with inflammatory bowel disease and their first degree in North-Eastern Romania areas
   E. Toader, C. Durnea (Iasi, RO)

76. Extraintestinal manifestations in pediatric patients with inflammatory bowel disease

77. Cytokine profile in autoimmune liver disease-inflammatory bowel diseases (overlap syndrome)
   E.A. Torres, O.S. Shifrin, V.B. Zolotatevsky, V.T. Ivashkin (Moscow, R)
78. Endoscopic diagnosis versus histopathologic diagnosis in inflammatory bowel disease (IBD)
   S.N. Turchina, C.M. Preda, G. Becheanu, M. Dumbrava, C. Gheorghe, M. Diculescu (Bucharest, RO)

79. A prospective multicenter study of outcomes and predictors of response in severe pediatric ulcerative colitis

80. Epidemiological risk factors for childhood onset inflammatory bowel disease in Scotland: A case-control study

81. Childhood-onset versus adult-onset inflammatory bowel disease: Phenotype

82. Characteristics of new pediatric IBD patients enrolled in the Hungarian Pediatric IBD Registry (HUPIR)
   G. Veres, P.L. Lakatos, M. Papp, Hungarian Pediatric IBD Registry Group (Budapest, Debrecen, H)

83. Response to medical treatment in patients with Crohn's disease: The role of NOD2/CARD15 mutations, disease phenotype and age of diagnosis
   B. Weiss, O. Lebowitz, H. Fider, I. Maza, A. Levine, R. Shaoul, S. Reif, Y. Bujanover, A. Karban (Tel-Hashomer, Holon, Tel-Aviv, Haifa, IL)

84. Role of the antioxidative enzyme Prdx6 in inflammatory bowel disease (IBD)
   J. Zeitz, I. Frey-Wagner, E. Kresin, M. Fried, G. Rogler (Zurich, CH)
Session I

Insights from epidemiology
Epidemiology of IBD – Is there a shift towards younger ages?

Christian P. Braegger¹, Pierluigi Ballabeni², Daniela Rogler¹, Valerie Pittet², Michael Friedt¹, and the Swiss IBD Cohort Study Group

¹Division of Gastroenterology and Nutrition, University Children’s Hospital Zurich, Switzerland; ²Institute of Social and Preventive Medicine, University of Lausanne and Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

Increasing numbers of paediatric and adolescent patients with Crohn’s disease (CD) and ulcerative colitis (UC) are reported. To test the hypothesis that this observation may be a consequence of a shift towards younger ages at first manifestation and diagnosis during the last decades we analysed data of paediatric and adult patients recruited from the Swiss IBD cohort study (SIBDCS).

The SIBDCS is a population-based cohort in Switzerland, which is prospectively collecting data on a large sample of paediatric and adult IBD patients across Switzerland through physician and patient questionnaires since 2006. Patients are recruited by paediatric and adult gastroenterologists during a routine consultation or by mail invitation, and additionally by patient organizations. Inclusion criteria include diagnosis based on Lennard-Jones diagnostic criteria, confirmed by radiology, endoscopy or surgery. Diagnosis must be established at least four months prior to inclusion.

The patients of the cohort were stratified according to diagnosis CD, UC, and indeterminate colitis (IC), as well as age at first manifestation and diagnosis related to calendar year of first manifestation and diagnosis, respectively. Data were extracted from both Enrolment Physician Questionnaires and Patient Enrolment Questionnaires. Both questionnaires were analysed separately. Linear regressions of age at first manifestation, respectively at diagnosis, on calendar year of first manifestation, respectively of diagnosis, were performed. Analyses were performed separately for each diagnosis and each questionnaire.

All regression coefficients (slopes) for CD and UC were significantly positive, i.e. age at first manifestation and age at diagnosis have increased with time (coefficients ranged between 0.20 and 0.57). Only the coefficients of the IC analyses were statistically not significantly different from zero.

The results of the SIBDCS do not support the hypothesis that first manifestation and diagnosis of both CD and UC patients in Switzerland occur today at younger ages. In the contrary, the results of the SIBDCS show that there is a significant trend for both first manifestation and diagnosis occurring at older ages today compared to the last decades. The results for IC are statistically not significant, probably because of the low number of patients. However, there is also in IC patients a trend towards increasing age parallel to higher calendar years.

We conclude that the observation of increasing numbers of paediatric and adolescent patients with IBD is not caused by a trend towards younger ages. It might rather be a consequence of increasing incidence of these conditions.
Disease behavior in adult patients – Are there predictors for stricture or fistula formation?

Iris Dotan, M.D.
Head, IBD Center, Department of Gastroenterology and Liver Diseases, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

Disease phenotype predictors—why are they required?
In the current era in IBD step-up vs. top-down therapeutic approaches for the treatment of Crohn’s disease (CD) are evaluated. As a consequence, we need to be able to differentiate between patients who will have more aggressive phenotypes to those with potentially more benign CD course. The former would require closer follow up but more importantly—might be the subgroup of patients to whom we would offer biologic and immunomodulator therapy early on. This strategy is the only one currently known to prevent hospitalization and surgical intervention, specifically in patients with fistulae.

Patients with expected fibrostenotic disease phenotype require early identification as well. The data regarding primary prevention of fibrostenosis are scarce; however, the association of biologic therapy with fewer surgeries might suggest that at least a subgroup of these patients would benefit from early, step-up therapeutic strategy. They might also benefit more from early immunomodulator therapy—as this was shown to have a secondary (though modest) preventive effect. The patients with fibrostenotic phenotype are also candidates for the most needed but still practically non-existent anti-fibrotic therapies.

In any case where patients are identified as having a higher chance to develop the more aggressive phenotypes—fibrostenotic and perforating, recommendation to avoid triggers/accelerators of disease progression (smoking, NSAIDS use) should be kept rigorously.

What are the current and near-future tools for disease phenotype prediction?
Until recently we based our attempts to predict disease phenotype mainly on clinical characteristics. As would be the case with many clinical features—some of them are not even predictors, but already manifestations of the condition we are trying to predict. Intervention at this stage might be too late for this patient.

In addition to known demographic and clinical sophisticated predictors reported more recently shall be described. These predictors belong to three major groups: serological markers, genetic markers, mucosal disease/healing.

The major serologic markers used: anti \textit{Saccharomyces cerevisiae} antibodies (ASCA), anti neutrophil cytoplasmic antibodies (ANCA), outer membrane porin C (OmpC), CBir1-flagellin, antibodies against I2 protein and the anti-glycan antibodies: anti laminaribioside carbohydrate (ALCA), anti chitobioside carbohydrate (ACCA) and anti mannobioside carbohydrate (AMCA) and their associations with penetrating and fibrostenotic disease shall be discussed.

The associations of genetic polymorphisms such as CARD15 and TLR4 variants and their association with more aggressive disease phenotype will be described as well.

Finally, the data supporting the relationship between inflamed, in contrast to healed intestinal mucosa and more aggressive disease course will be illustrated.
These predictors may be used in clinical practice and/or research in order to better stratify CD prognosis. Thus they may be significant in our therapeutic decisions. Models for using these predictors would be presented.

**Address for correspondence:**

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: +972-3-6974622  
E-Mail: irisd@tasmc.health.gov.il
Pediatric IBD – Is it different?

Arie Levine
Pediatric Gastroenterology & Nutrition Unit, Wolfson Medical Center, Tel Aviv University, Israel

The clinical manifestations of Crohn’s disease (CD) and Ulcerative colitis (UC) are highly variable, with significant diversity in phenotypes of the diseases. This diversity in adults is manifested by differences in the location and distribution of the diseases, the natural history and outcomes. Patients may also differ by age of onset, and raises the question if age of onset dictates any difference in disease phenotype or outcome. Like adults, children and adolescents are prone to the same diverse array of complications stemming from the disease and its therapy. However, recent evidence indicated that pediatric onset of the disease may be associated with different presentations or behavior of the disease (1–4).

Ulcerative Colitis
Clear evidence exist at present to state that pediatric onset UC may be different than adult onset UC. The primary difference in disease phenotype is extent of the disease. Approximately 60–70% of patients with pediatric onset of UC present with pancolitis, as opposed to approximately 20–30% in adults. Proctitis is an unusual manifestation of the disease. This finding has been replicated in large North American and European registries. Rectal sparing also appears to be more common in pediatric onset disease than in adult onset UC. Clear evidence about the natural history of UC in children is problematic, and interpretation of the natural history is complicated by the fact that it was collected recently during the era of biologics use in UC. However, a recent study demonstrate that about 80% of pediatric UC, had pancolitis, 80% had moderate to severe colitis, and 80% patients receive corticosteroids within 30 days pf diagnosis. Of those receiving steroids, 45% were steroid dependent at 1 year. Colectomy was performed in 5% of patients within a year of diagnosis.

Crohn’s disease
Evidence exists that manifestations of Crohn’s disease may be affected by age. However, as opposed to a pediatric versus adult cutoff seen in ulcerative colitis, the phenotype of Crohn’s disease may be affected by an age gradient, rather than a general cutoff age. There is an inverse linear relationship between age and colonic Crohn’s disease, the younger the patient, the more likely the patient is to have colonic Crohn’s. This inverse relationship is true through age 10. In addition, pediatric patients are more likely to have upper gastrointestinal involvement than their adult peers. Disease behavior in childhood onset, as assessed by the Montreal classification, seems to be similar to adult onset disease, in that duration of disease is the most significant factor associated with stricture or fistula formation. While children with Crohn’s disease may appear to be more responsive than adults to several types of therapies in trials, this may be due to a bias for earlier intervention, shorter duration of disease, and earlier immunomodulation use in pediatric CD. Lastly, growth retardation is a unique complication and management issue in pediatric onset disease, and may correlate with a poorer prognosis.
References:


Environmental factors affecting IBD – Have we made progress?

Peter Laszlo Lakatos
1st Department of Medicine, Semmelweis University, Budapest, Hungary

The pathogenesis of IBD is only partially understood; various environmental and host (e.g. genetic-, epithelial-, immune and non-immune) factors are involved. The critical role for environmental factors is strongly supported by the recent worldwide trends in IBD epidemiology. The most consistent association so far identified is the association between non-smoking and ulcerative colitis (UC) as well as smoking and Crohn's disease (CD). A meta-analysis partially confirmed previous findings that smoking was found to be protective against ulcerative colitis and, after onset of the disease, might improve its course, decreasing the need for colectomy. In contrast, smoking increases the risk of developing Crohn’s disease and aggravates its course. The role for passive smoking however is even more controversial. A recent meta-analysis suggests that there is not a strong association between childhood passive smoke exposure and CD susceptibility. Furthermore, there was no evidence that childhood passive smoke exposure exerts a protective effect against UC. The heterogeneity among the small number of studies limited the ability to draw conclusions about prenatal smoke exposure.

The history of IBD is dotted by cyclic reports on the isolation of specific infectious agents responsible for CD or UC, while others reported on the absence of helminths. Several microorganisms, such as Mycobacterium paratuberculosis, Listeria monocytogenes, Chlamydia trachomatis, Escherichia coli, Cytomegalovirus, Saccharomyces cerevisiae, and many more, have been proposed as having a potential etiologic role. The fascinating cold chain hypothesis on the role for refrigeration is providing an even broader platform by linking dietary factors and microbial agents (psychrotrophic bacteria). Another theory has suggested a breakdown in the balance between putative species of “protective” versus “harmful” intestinal bacteria - this concept has been termed “dysbiosis” resulting in decreased bacterial diversity. In concordance, recent development in IBD genetics/immunology identified altered bacterial sensation of the commensal flora as one of the cornerstones of IBD pathogenesis.

Other factors such as oral contraceptive use, appendectomy, dietary factors (e.g. refined sugar, fat, fast food), perinatal events, childhood infections have also been found to be associated with both diseases but their role is more controversial. Nonetheless, there is no doubt that economic development, leading to improved hygiene and other changes in lifestyle (“Westernized lifestyle”), may play a role in the increase in IBD. Further studies are however needed to better understand the importance of these and other environmental factors in the pathogenesis and during the course of IBD and to explore the interaction between environmental and host factors.
Susceptibility genes and overall pathogenesis of inflammatory bowel disease – Where do we stand?

Claudio Fiocchi
Department of Pathobiology, and Department of Gastroenterology and Hepatology
The Cleveland Clinic Foundation, Cleveland, Ohio, USA

For at least three decades the major components of inflammatory bowel disease pathogenesis (IBD) have been identified and partially characterized, including environmental changes, genetic susceptibility, the enteric commensal flora, and the immune response. Each of these components influences the function and relative input of the others in the overall pathogenesis of Crohn's disease (CD) and ulcerative colitis (UC). The amount of accumulated knowledge and progress achieved in understanding the exact role of the above four components in IBD pathogenesis has been rather uneven. Studying the environmental changes that accompany the increased incidence and prevalence of IBD worldwide has proven the most difficult, given the need to study large populations of patients and unaffected relatives prospectively over long periods of time. Consequently, knowledge in this area is limited and fairly speculative at the moment. The analysis of the enteric microbiota in IBD has also been unexpectedly challenging, considering that the intricate composition of gut flora in normal humans has yet to defined, that each person seems to carry an "individualized" sets of microorganisms, and that reported variations in the types of bacteria populating the IBD intestine have been inconsistent, perhaps with the only exception of an increased number of E. coli. The most investigated and best understood component of IBD pathogenesis is by far the intestinal immune response, both the innate and adaptive immune branches, that has led to the development of novel anti-inflammatory therapeutic strategies - largely based on anti-cytokine approaches – that are the direct result of an improved understanding of how immunity and inflammation are regulated at the systemic and mucosal levels.

The investigation of possible genetic variations and their role in the pathogenesis of IBD has gained a major boost from the development of techniques that allow performing genome-wide associations (GWA) in large human populations in a relatively rapid – though still expensive – fashion. GWA association studies have replicated and confirmed findings achieved with positional cloning strategies based on linkage analysis followed by linkage disequilibrium mapping, like in the case of NOD2 variants. More importantly, GWA have enabled variants at different loci to be associated with particular diseases, and this has had a major impact on IBD, with the discovery of more than 30 genetic variants associated with this condition. So far, the majority is associated with CD, or both CD and UC, although variants exclusively associated with UC have been recently reported. The genetic variants identified by GWA have provided support for or confirmed suspected associations with innate and adaptive immune pathways, like for TLR4 and IL-23/IL-17, respectively, but also disclosed previously unsuspected potential pathogenic pathways related to handling...
or disposing of bacteria – like the ATGL16L1- and IRGM-dependent autophagosome pathways, epithelial cell function – like the PTGER4-dependent pathway, apoptosis - like the TNFRSF6B-dependent pathway, and immune suppression – like the PTPN2-dependent pathway, in addition to several others.

The discovery of multiple new susceptibility genes in CD and UC is unquestionably critical to the investigation of IBD pathogenesis, as it allows the pursuit of specific molecular pathways that will undoubtedly provide novel information on how environmental and microbial factors modulate inflammation. On the other hand, this discovery has also added a new and higher level of complexity to the study of the molecular and cellular mechanisms of IBD. First, the > 30 new associations explain < 30% of all IBD cases, suggesting that many more genetic variants wait to be recognized and, most crucially, that the impact of each variant on IBD pathogenesis is rather small. Second, the investigation of the consequences of each genetic variant at the level of the biology of specific cell types creates enormous logistic problems related to the innumerable experiments that should be carried out in humans – to confirm that a particular pathway is indeed functionally altered, and to the creation of brand new sets of knock-out, knock-in and transgenic animal models to carry out finer experimentations that are not feasible in humans. Third, each genetic variation alone may or may not have a direct impact on IBD pathogenesis, and may only be relevant if associated with other variations in gene-gene or gene-environment interaction systems. Finally, there is the issue of whether enough resources – both human, logistic and financial - are currently available to perform all that appears to be required to implement and coordinate the studies necessary to meet the above challenges. The use of bioinformatics may solve or, at least, alleviate some of these problems, but this approach is still at its infancy and largely untested for complex diseases such as IBD, and its use may generate hypotheses that still need to be tested in vitro and in vivo, and not just in silico.

In summary, while major advances in the field of genetics have generate fundamental new insights into potential mechanisms of IBD pathogenesis, major new challenges have been created that result directly from such rapid progress. Thus, one can only hope that we are not a position now where the carriage has been put in front of the horse.
Session II

Pathophysiology of IBD and age of onset
Genetic determinants of pediatric IBD – Is age of onset genetically determined?

S. Kugathasan
Professor of Pediatrics and Human Genetics, Emory University School of Medicine, Division of Pediatric Gastroenterology, Emory Children's Center, 2015, Uppergate Drive, Room 248, Atlanta GA 30322, USA, Telephone: 404 727 4542, Telefax: 404 727 4069

Inflammatory bowel diseases (IBD) are lifelong conditions with an onset that can occur at any age, but peaking in the late teens and early twenties, the age where childhood transcends from puberty into adulthood. One of the most compelling hypothesis is that pediatric onset IBD is more likely to be influenced by genetics compared to late onset as there is less time for environmental modifiers to have influenced disease. While this question about differing age of onset among the chronic complex inflammatory disorders such as in IBD encourages debate, a fundamental issue in IBD remains unanswered. Does early (pediatric) onset IBD represent the same disease process occurring in adults but merely at an earlier age (ie. age of onset is a random event) or is IBD in children have a very different etiology and pathogenesis (hence different natural history) but just with the same clinical presentation as adults? Although no hard scientific evidence exists about differing etiology, pediatric onset IBD does ‘differ’ from adult IBD in many aspects. In fact, there is growing evidence from clinical observations, as well as, epidemiologic and natural history studies that pediatric onset IBD represents a distinct disease with differences in disease type, disease location, disease behavior, gender preponderance and genetically attributable risk compared to its ‘adult’ counterpart. We will examine the clinical genetics of pediatric IBD by demonstrating how pediatric onset IBD differs from adult disease including evidence from family and population studies, as well as highlighting differences in disease demographics and phenotype. The genome-wide association approach (GWAS) of performing broad, unbiased screening for the contribution of common genetic variation to disease susceptibility in adults has already rapidly identified strong evidence for many Crohn’s disease and ulcerative colitis susceptibility loci. There was no effect of age of onset on these newly discovered susceptibility loci when adult IBD patients were studied. Using the concept that stratifying early onset cases may identify new genes, we have performed and published the first pediatric GWAS IBD scan. Two novel susceptibility loci have been discovered using over 1000 cases of pediatric onset IBD, the TNFRSF6B and PSMG1 genes. The gene TNFRSF6B, which encodes a decoy receptor for the FasL pathway (DCR3), was found to increase the risk for pediatric-onset CD and UC. Our functional studies have suggested that this variant regulates DCR3 protein abundance, lymphocyte JAK/STAT signaling, and serum cytokine levels, and that this effect is most pronounced in patients with pancolitis phenotype of UC or colon-only CD, the two pediatric specific phenotype that differs from adult onset IBD. Another larger pediatric GWAS scan involving nearly 3000 pediatric onset IBD patients has been completed and further new gene discoveries are awaiting publication. In addition, we will review the current knowledge of molecular genetics in pediatric IBD emphasizing the similarities and differences with respect to adult IBD. Lastly, we will highlight possible future directions of genetics in the field of pediatric IBD.
The epithelial barrier – Is it impaired in older ages?

Andreas Sturm
Department of Gastroenterology and Hepatology, Charité Universitätsmedizin Berlin, Campus Virchow-Klinikum; Augustenburger Platz 1, 13353 Berlin, Germany; E-Mail: andreas.sturm@charite.de

The population over 65 years of age is increasing rapidly and malnutrition is a more common problem of elderly patients. The epithelial barrier is the surface of the digestive tract which consists of epithelial cells that constitute an efficient physical barricade between the dietary and enteric flora pathogens found in the intestinal lumen and the individuum, but also allow an exchange between nutrients and the systemic circulation. Epithelial defense mechanism can be categorized into three key components: pre-epithelial, epithelial and post-epithelial, the latter is represented by the lamina propria. The pre-epithelial mucus barrier is composed of mucin associated with other proteins and lipids and forms a continuous gel into which a bicarbonate-rich fluid is secreted, maintaining a neutralizing pH at the epithelial surface. Phosphatidylcholine is the predominant surface bioactive phospholipid found within the gastrointestinal tract. Intestinal epithelial cells secrete mucins and glycocalyx, which contains membrane-anchored negatively charged mucin-like glycoproteins and hydrophobic phospholipids. The tight adherence of mucin to the apical surfaces of epithelia is owed to the existence of the specific complex between mucin oligosaccharides and the mucin binding protein of the apical mucosal membrane. The hydrophobic lining of the luminal surface has an important functional role. It prevents microorganisms to get into contact with and to adhere to the plasma membrane. It furthermore protects the mucosal epithelium against chemical and mechanical injuries. Epithelial cells provide the second line of the mucosal defense system. Whereas in the upper digestive tract this layer consists of a stratified epithelium, the stomach, small, and large bowel are surfaced with a simple epithelial layer sealed by tight junctions. When intact, the uptake of antigens, macro- and microorganism through this layer is restricted by luminal cell-surface structures. The mucosal surface epithelial cells are rapidly proliferating with a complete turnover every 24 to 96 hours. The proliferative compartment of epithelial cells is localized in the crypt region and is segregated from a gradient of increasingly differentiated epithelial cells present along the vertical axis of the functional villus compartment.

Although the GI tract epithelium has a remarkable capacity to rapidly reseal superficial erosions by migration of epithelial cells, damage and impairment of the intestinal surface barrier are observed in the course of various diseases and may result in an increased penetration and absorption of toxic and immunogenic factors into the body leading to inflammation, uncontrolled immune response. Whereas it is clear, that in inflammatory bowel diseases such as Crohn’s Disease or ulcerative colitis, the intestinal barrier function is impaired, no information is available about possibly changed intestinal repair mechanism in the elderly. From a morphometric point of view, Lipski and coworkers (J Clin Pathol 1992) revealed that there is no significant correlation between age and areas of duodenal surface epithelium, crypts and lamina propria, height of villi and surface epithelium, depths of crypts, crypt to villus ratio, number of intraepithelial lymphocytes, duodenal architecture, enterocytes or brush borders. Underlying this finding, data from animal and human studies
suggest that the lipid digestion and absorption are in general well preserved in aging. However, regarding lipid absorption, results are contradictory. In animals, results show a reduced gastric lipase and bile acid secretion, decreasing lipid solubilization and thus decreasing lipid absorption. In humans, a study of only healthy aged showed no correlation between age and 72 h fecal fat excretion. Other studies in humans reported that absorption of fat may take longer in the elderly, and that post-prandial serum bile acid levels may be reduced with aging. The prolonged absorption of fats in elderly may induce post-prandial satiety, reducing overall intake in the elderly. Concerning carbohydrates, D-xylose, a decreased absorption in ageing humans and an age-associated decline in D-glucose absorption in mice has been demonstrated. However, since D-xylose excretion is also dependent on renal function, when stratifying the results to the kidney function, the significance was lost in the different age groups. With regard to amino acids, the absorption of tyrosine, arginine and aspartic acid declines in senescent rodents, however, systematic human studies are missing.

With focus on the intestinal epithelial barrier and its function, functional studies in elderly patients are lacking. Only in other organ systems, dysfunction of the choroid plexuses and the blood-cerebrospinal fluid barrier has been clearly associated to ageing processes (Exp. Gerontology 2008). However, from a clinical point of view, an impaired blood flow, ischemic changes and an increased use of NSAIDs naturally contribute to an impaired epithelial barrier in elderly patients, leading to increased risk for ulcers in those patients. Following a period of stress, like illness or injury, it has been shown that elderly patients continued to underfeed themselves for 10–15 days while younger patients increased their energy intake (Woudstra T and Thomson ABR, Best Prat Res Clin Gastroenterol 2002). Elderly patients may have decreased functional reserve of the intestine and may become undernourished more rapidly during acute hospitalizations, and may require an extended period of intensive nutritional monitoring because of reduced adaptive responses.
The link between autophagy and innate immunity

Vojo Deretic
University of New Mexico School of Medicine, Albuquerque, NM, USA

Autophagy is an evolutionarily conserved, ubiquitous biological process for cleaning the eukaryotic cell’s interior whereby portions of the cytoplasm, including organelles such as mitochondria, get sequestered by autophagic membranes for delivery to lysosomes and degradation (Deretic and Klionsky, 2008). Autophagy affects a wide range of fundamental biological processes and whole classes of human health and disease states, including infectious or inflammatory diseases, cancer, neurodegeneration, diabetes, and aging (Mizushima et al., 2008). Autophagy has been affirmed as an immune mechanism in recent years (Levine and Deretic, 2007; Schmid and Munz, 2007). The following principles have been uncovered: (i) Autophagy functions as an innate defense mechanism against intracellular microbes (Gutierrez et al., 2004). (ii) Autophagy is under control by pattern recognition receptors (PRR), e.g. Toll-like receptors (TLR), and autophagy acts as one of the immunological output effectors of PRR (Delgado et al., 2009; Delgado et al., 2008). (iii) Autophagy is an immune effector of Th1/Th2 T cell response polarization - autophagy is activated by Th1 cytokines (which act in defense against intracellular pathogens) and is inhibited by Th2 cytokines (which render cells permissive to intracellular pathogens) (Harris et al., 2007). (iv) Autophagy has been implicated in central immunological tolerance (Nedjic et al., 2008) and in chronic inflammatory conditions such as Crohn’s disease (Cadwell et al., 2008; Saitoh et al., 2008; Xavier and Podolsky, 2007). (v) Autophagy is one of the effector functions associated with the immunity regulated GTPases (IRG), which have been initially characterized as cell-autonomous defense but remained until very recently orphaned for the mechanism of function. We have described (Gutierrez et al., 2004; Singh et al., 2006) a connection between autophagy and murine Irgm1 and human IRGM, now recognized as a Crohn’s disease risk locus (McCarroll et al., 2008; Parkes et al., 2007). In this presentation we will cover the above areas and present some of the recent finding regarding IRGM function.

References:


The microbiota in IBD in different age groups

Salvatore Cucchiara
Pediatric Gastroenterology & Liver Unit, Department of Pediatrics, Sapienza University of Rome, Rome, Italy

Crohn’s disease (CD) and ulcerative colitis (UC) are chronic, relapsing, immunologically mediated inflammatory bowel diseases (IBD) with unknown aetiologies. It now appears that commensal enteric bacteria, some with increased virulence, cause aggressive T cell responses and chronic inflammation in the setting of genetic polymorphisms that regulate mucosal barrier function, innate microbial killing, and immune responses. Abnormal microbial composition and host-microbial interactions in IBD have been elucidated in experimental rodent models, translational research, clinical trials and research. No specific bacterial agents have been identified as potential factors triggering intestinal inflammation in IBD. Bacterial flora differs between healthy people and IBD patients: the latter have higher amounts of mucosa-attached bacteria, even in non-inflamed mucosa, than controls; furthermore, it has been shown that bacteria are from diverse genera and some of them have been identified in the epithelial layer. The role of Bacteroides spp. in IBD is still unclear: these anaerobic bacteria have been shown to exhibit proinflammatory properties in IBD animal models, but a protective role and even a decrease in the relative proportion of the phylogenetic group have been postulated in other studies. Moreover, distinct adherent or invasive strains of Escherichia coli have been identified in the ileal mucosa of CD patients and the involvement of a new potentially pathogenic group of adherent invasive E coli has been suggested. Recently, a breakdown in the balance between putative species of "protective" versus "harmful" intestinal bacteria ("dysbiosis"), has been postulated.

We have characterized mucosa-associated bacteria in colonoscopy biopsies of ileum, caecum and rectum in 12 CD patients, 7 UC, 6 indeterminate colitis (IC), 10 ileal lymphonodular hyperplasia and 7 controls. Characterisation were carried out by conventional culture techniques for aerobic and facultative-anaerobic microorganisms, and molecular analysis (16S rRNA-based amplification and RT polymerase chain reaction) for the detection of anaerobic bacterial groups or species. A higher number of mucosa-associated aerobic and facultative-anaerobic bacteria were found in specimens of IBD children than controls. An overall decrease in some bacterial species belonging to the normal anaerobic intestinal flora was suggested by molecular approaches: i.e. occurrence of Bacteroides vulgatus was low in CD, UC and IC specimens. This was the first pediatric report investigating the intestinal mucosa-associated microflora in IBD. These results allow a better understanding of changes in mucosa-associated bacterial flora in these patients, showing either a predominance of some potentially harmful bacterial groups or a decrease in beneficial bacterial species.
Session III

Differences in the diagnostic procedures
What role do serological markers play in IBD – Pediatric and adult data

M.C. Dubinsky
University of California, Cedars-Sinai Medical Center, Pediatric IBD Center, Los Angeles, CA, USA

Immune responses were first investigated as tools to differentiate UC from CD given the specificity of ASCA for CD and pANCA for UC. Advances in the sensitivity of the test characteristics lead to studies evaluating antibodies as diagnostic tools to differentiate IBD from non-IBD. Although conflicting, studies do support the use of these markers, particularly in children, to guide clinicians in cases of diagnostic uncertainty. It has become clear, however, that immune responses may also have perhaps a more important mechanistic implication in the pathogenesis of IBD. Immune reactivities, as measured by the serological expression of immune responses to specific bacteria, may be representative of the host gene luminal bacterial interaction characteristic of IBD. Moreover if these immune responses represent the sum of a genetic and environmental predisposition to IBD, quantitative and qualitative expression of these immune responses may serve as an immunologic risk marker for IBD phenotypes. The initial immune-clinical phenotype studies demonstrated that although pANCA has been established as a UC-specific marker, approximately 25% of all CD patients also express pANCA. These CD patients are described as “UC-like” and tend to have an uncomplicated disease course. In contrast, higher ASCA levels were shown to be associated with earlier age of disease onset, both stricturing and internal penetrating disease behaviors and need for small bowel surgery. Further reports have found that patients with CD who are positive for ASCA IgA, IgG, or both, may define a subset of patients with Crohn’s disease at increased risk for early surgery and more aggressive disease course. These studies also demonstrated that both the number of immune responses to the different microbial antigens expressed by a given individual as well as the magnitude (titer level) of these immune responses correlated most significantly with the presence of complicated CD phenotypes. Newer immune responses targeted against bacterial antigens have been introduced and found to be associated with more rapid disease progression among children and adult patients. The identification of those patients at greatest risk for rapid disease progression would be of great value in stratifying patients into more or less aggressive treatment paradigms at the time of diagnosis.
Controversies in use of diagnostic procedures

Boris Vucelic
Division of Gastroenterology and Hepatology, Department of Medicine, University Hospital Rebro, Zagreb, Croatia

Diagnosis of chronic inflammatory bowel disease (IBD) is based on history, physical examination, laboratory investigations, endoscopic findings, histology and radiologic findings. Main treatment goals are rapid control of symptoms, induction of remission, maintenance of remission, reduction of surgeries and hospitalizations and achievement of normal quality of life. In order to achieve these goals, each patient must be assessed in appropriate way to guide the treatment, with main elements of assessment being determination of IBD phenotype, disease extension and distribution (local activity of drugs), extraintestinal manifestations, disease behavior, disease severity and drug responsiveness. Main assessment tools are endoscopy and imaging procedures. Each element of diagnostic process cannot be looked at alone but it has to be incorporated in general clinical assessment, if possibly by using different indexes.

**Endoscopy** is essential for diagnosis of IBD. In ulcerative colitis (UC), endoscopy is used to confirm the diagnosis, to evaluate the extent of disease, to assess disease activity, to evaluate disease unresponsive to therapy and to assess complications like stricture, dysplasia and cancer. Elements of analysis are vascular transparence, light reflex, presence of erosions/ulcers and bleeding on contact or spontaneous bleeding, frequently reported as Baron endoscopic score (1). Baron score, however, is based on rigid sigmoidoscopy, friability test is not standardised and it has a very wide interobserver variation. Since endoscopic findings correlate reasonable well with clinical activity, they tend to be incorporated into indexes like Mayo score (2) which is a combination of clinical Truelove Witts index and endoscopic Baron scale.

Endoscopic features of Crohn's disease (CD) are partially or not involved rectum, asymmetric affection, "skip" lesions, aphthous lesions, linear/serpiginous lesions, ulcerations within normal appearing mucosa, «cobblestone» appearance and presence of fistulae and stenoses. In view of effects of biologic therapy, assessment of mucosal healing becomes important but remains difficult and prognostic value has to be shown in prospective studies. Endoscopic indexes used in clinical practice are Crohn's Disease Endoscopic Index of Severity (CDEIS) (3) and Simple Endoscopic Score for CD (SES-CD) (4). CDEIS is reliable, reproducible and validated and is presently gold standard for evaluation of endoscopic activity. However, it has poor correlation with clinical activity, it is time consuming, elaboration of the score requires analogue scale transformation, and therefore is unsuitable for everyday clinical practice. SES-CD is easier and faster to score and calculate than CDEIS and the results are are reproducible and reliably correlate with clinical activity.

**Imaging Techniques** used in IBD are plain X-rays of the abdomen, contrast studies, ultrasonography, computed tomographic studies, magnetic resonance imaging and capsule endoscopy. Complete opacification and regular distension of the entire small bowel is essential for proper analysis of the bowel wall and 2 techniques used are CT-enterography and CT-enteroclysis. MRI advantages are multiplanar imaging, high
contrast resolution, rapid and multiple sequences, no irradiation (important in young patients and repeated investigations) and excellent contrast resolution (intestinal wall). However, only accepted indication of MRI in CD is perianal disease, while it is not yet accepted as a routine test in luminal disease due to its cost, availability and duration of examination. Potential use of capsule endoscopy in CD is for initial diagnosis in patients with suspected CD but normal prior studies (colonoscopy, EGD, radiological studies) and in microscopic colitis. Its use for evaluation of disease extension, monitoring response to therapy and detection of post-operative recurrence has to be defined.

Activity assessment of IBD is based on noninvasive indices (clinical parameters), invasive indices (include endoscopy), biochemical markers of activity and quality of life measures. The main problem with assessment of activity using indices is the fact that they are combination of subjective and objective measurements (symptomatology, laboratory tests, endoscopic appearances, histology, radiology). The most commonly used activity indeces in CD are CDAI (5), Harvey-Bradshaw index (6) and Van Hees index (7). CDAI is a complex index, difficult to calculate in daily clinical practice, with predominance of subjective symptoms and sizable inter-observer variation (up to 100 points), with poor correlation with endoscopic and laboratory data and with inadequate representation of EIMs, perianal disease and post-operative recurrence. In addition, it is not suitable for measuring perianal disease activity because these patients have low CDAI scores. Therefore, we have to use Perianal Disease Activity Index (8). Perianal disease should be assessed by MRI, proctosigmoidoscopy (to assess inflammatory activity), EUA (examination under anesthesia) which is a gold standard in hands of experienced surgeon and anorectal US (requires expertise, sometimes difficult or impossible due to local complications). Fistulography is not recommended. There are numerous activity indeces used in UC, but no UC index can be clearly recommended. Most commonly used is Truelove-Witts index (9) with Powel-Tuck index (10) as reasonable alternative. Pouch inflammation should be assessed by the Pouchitis Disease Activity Index (11).

References:


Address for correspondence:
Professor Boris Vucelic, MD, PhD, FRCP, FACP, FACG, FACP
Division of Gastroenterology and Hepatology
Department of Medicine
University Hospital Rebro
Kispaticeva 12
10000 Zagreb
Croatia
E-Mail: boris.vucelic@zg.t-com.hr
The risk of radiation and choice of imaging

Hans Herfarth, M.D., Ph.D.
Associate Professor of Medicine, University of North Carolina, Chapel Hill, NC, USA

Radiological imaging especially of the small bowel plays an important role in the diagnosis and management of patients with inflammatory bowel diseases (IBD). The radiographical examination of the small intestine with barium either as enteroclysis or as small bowel follow through are still the mainstays in small bowel imaging. However, abdominal CT or MRI, which has the advantage not utilizing ionizing radiation, or the technique of CT-enteroclysis or MR-enteroclysis are overall comparable with regard to the sensitivity and specificity in detecting intestinal pathologies and have already replaced the conventional techniques in centers dedicated to the management of IBD. Additionally these cross sectional imaging techniques provide in a sense a “one stop abdominal imaging workup”, the diagnosis of extraluminal disease manifestations or complications. Abdominal ultrasound is also a non-invasive, inexpensive and widely available imaging technique. In experienced hands, the sensitivity and specificity of this method in detecting intestinal pathologies is probably comparable with the radiological methods.

Cancer risk associated with diagnostic procedures employing radiation such as CT or conventional x-ray studies has been receiving increasing attention over the last years. A recently published analysis of the increase in number of diagnostic CT exams performed in the US suggested that radiation exposure from CT studies alone may be responsible for 1.5–2.0% of all cancers. The cumulative exposure to ionizing radiation may be a specific concern in patients with IBD, especially since the onset of IBD happens often in adolescence. Several studies have demonstrated substantial exposure to radiation especially in patients with Crohn’s disease mainly caused by CT examinations of the abdomen. For that reason, imaging methods such as MRI or ultrasound should be the preferable diagnostic methods especially in young IBD patients. However, the drawbacks of MRI are limited availability and increased costs compared to CT. The diagnostic accuracy of abdominal ultrasound is clearly operator dependent, which limits the wide application of this method. Therefore, we need to identify subsets of IBD patients, who are at greater risk of a significant lifetime exposure to radiation and we need to develop low-radiation imaging protocols and further improve and facilitate the access to MRI imaging procedures.

References:


Non-invasive monitoring of mucosal healing in IBD – The role of bowel ultrasound

F. Parente¹, S. Greco²
¹Gastrointestinal Unit, A. Manzoni Hospital, Lecco & ²Division of Internal Medicine, Predabissi Hospital Melegnano, Italy

Monitoring of mucosal appearance during medical treatment could be considered as an important step in the therapeutic work-up of IBD patients due to the potential prognostic role of mucosal healing in predicting disease outcome. Indeed, it has been shown that macroscopic appearance of colonic mucosa at endoscopy is an accurate predictor of the anatomical severity of both Crohn’s disease (CD) and ulcerative colitis (UC) during severe disease flare-up¹-³; in addition, recent data suggest that mucosal healing, assessed with endoscopy, after short-term treatment with conventional or biological drugs seems to be associated with a better disease prognosis⁴-⁶. However, IBD patients are often reluctant to be re-endoscoped during follow-up because of the invasiveness of colonoscopy; therefore, there is need for non-invasive surrogate markers of mucosal healing which could replace endoscopy in clinical practice.

During recent years bowel US has become accepted as an important imaging procedure in the diagnostic work-up and follow-up of IBD ⁷. This has been due to the technological advancement of US equipments that has greatly improved resolution capability with good cross-sectional imaging of the gut wall and display of the surrounding mesentery, thus making possible to detect not only bowel wall infiltrations but also peri-intestinal abnormalities. At present, bowel US is being used as screening imaging technique in patients with clinically suspected IBD, where it is highly accurate and well accepted by the patients, in assessing anatomical location of lesions and their extent within the bowel at primary diagnosis and in the detection of abdominal complications of CD such as strictures, abscesses and internal fistulae⁸.

Another important and promising field of application of bowel US is the assessment of IBD activity and the monitoring of response to medical therapy, especially in UC. Two studies of ours have recently addressed this matter: 1) in the first study, 86 consecutive patients with already known UC admitted to our Centres for recurrence of intestinal symptoms were studied with colonoscopy and bowel US before starting any new therapy. Severity of UC was graded 0–3 endoscopically, according to Baron score, for the various colonic segments (rectum, sigmoid, descending, transverse and ascending colon), and ultrasonographically, according to the maximum colonic wall thickening and bowel vascularity measured at Doppler US. Considering endoscopy as the reference test for UC activity, segment-by-segment analysis revealed an high accuracy of bowel US in determining disease relapse: 93%, 90%, 93%, 89% accuracy for the sigmoid, descending, transverse and ascending colon, respectively. By contrast, accuracy of US was very poor for detecting rectal recurrence (42%) due to the well known difficulty of US in exploring the deep pelvis. ROC curve identified a colonic wall thickness > 5 mm as directly associated with the risk of having moderate to severe endoscopic UC flare-up (hazard ratio 9.05; 95% CI 8.16–39.1). This colonic thickness threshold correlated also significantly with the clinical activity (chi-square 26.7, p < 0.001). 2) In the second study, 74 out of 83 patients with severe UC undergoing i.v. high-dose
steroids regimen with favorable clinical response were recruited. All patients underwent baseline colonoscopy and bowel US and severity of disease graded 0–3 according to Baron score and US score (see above), respectively. Steroid therapy was slowly tapered within 4 months and then patients were maintained on mesalazine 1.6–2.4 g/day with a 15 months follow-up by means of repeated colonoscopy and bowel US at 3, 9 and 15 months from entry. Considering endoscopy as the reference test for good response to steroids, in the three visits we showed high and consistent concordance between 0–I Baron scores and US scores (weighted K between 0.76 and 0.90). On logistic regression analysis, patients with severe US scores (2–3) at 3 months, regardless of their clinical score, had a high risk of severe endoscopic activity at 15 months (OR 9.1; 95% CI: 2.5–33.5).

Therefore, these results show that in expert hands bowel US is an accurate tool in diagnosing UC relapse as well as in determining the extension of colonic involvement; it may be therefore proposed as a non-invasive surrogate to colonoscopy in order to assess macroscopic appearance of colonic mucosa (except for the rectum) in UC patients whenever they refer recrudescence of intestinal symptoms.

References:


Session IV

Management of Crohn’s disease
Risk/benefit strategies must be employed in the management of pediatric Crohn’s disease

Jeffrey S. Hyams, M.D.
Professor of Pediatrics, Head, Division of Digestive Diseases, Hepatology, and Nutrition, Connecticut Children’s Medical Center, University of Connecticut School of Medicine, Hartford, CT, USA

Clinicians caring for children with Crohn’s disease must consider the long-term implications of therapeutic interventions and cumulative diagnostic studies in their patients whose disease duration will be measured in decades. Children diagnosed with Crohn’s disease will have the longest duration in which “natural history” will be played out. At the present time there is convincing evidence of the increased severity of pediatric Crohn’s disease compared to its adult counterpart, its frequent co-morbid growth disturbances, and the frequent need for aggressive medical therapies including immunomodulators and biological agents.

Currently the initial management of most children newly diagnosed with Crohn’s disease involves enteral nutritional support, corticosteroids, and immunomodulators. While enteral nutritional support has found favor in some parts of the world, it is not widely utilized in others, and less successful with severe colonic involvement and may be difficult to administer for extended periods of time. Corticosteroids, while initially very helpful in decreasing signs and symptoms of disease, are occasionally ineffective, and frequently associated with a state of corticosteroid dependency. Corticosteroid therapy is generally ineffective in healing inflamed mucosa and can impair growth. Mood disturbances, deleterious effects on bone, and cosmetic changes limit its acceptability and it is has no maintenance efficacy. Budesonide is not as effective as prednisone and also has no demonstrated long term efficacy. Immunomodulators (azathioprine, 6-mercaptopurine, methotrexate) have convincingly been shown to be effective maintenance therapies with corticosteroid sparing effects, but are of little value in the acutely ill newly diagnosed child. Concerns about opportunistic infections and malignancy give physicians, patients, and families pause whenever their use is discussed. The past decade has witnessed the emergence of biological therapy with its impressive record of rapid efficacy and use as maintenance therapy but controversies remain about who are the most suitable candidates, when is the ideal time for initiation, which if any medications can be used concomitantly, and long-term safety.

Not to be forgotten in children with IBD are the frequent diagnostic studies involving ionizing radiation. Repeated barium studies, abdominal and pelvic CT scans, and more recently CT enterography can be associated with a large cumulative radiation burden and convincing evidence exists that this exposure is associated with significantly increased lifetime risk of malignancy. In the setting of therapeutic interventions that may predispose to cancer the clinician and family must consider the risk/benefit of all interventions, while not losing sight of the known devastating effects of poorly treated disease.
Enteral nutrition as primary therapy in pediatric Crohn’s disease

Rob Heuschkel, MBBS MRCPCH
Consultant Paediatric Gastroenterologist, Department of Paediatric Gastroenterology, Addenbrookes Hospital, Cambridge, UK

It is over 30 years ago that patients with Crohn’s disease first received nutritional support as part of their disease management. It became quite clear quite quickly that simple nutritional restitution \textit{per se}, in preparation for surgical intervention, led to disease remission in a number of patients.

Since that time exclusive enteral nutrition (EEN) has been used in both adults and children with Crohn’s disease as an alternative therapy to corticosteroids to achieve a clinical remission. Although optimising nutrition remains a high priority in the management of all children with inflammatory bowel disease, the use of nutrition as ‘therapy’ is limited to acute Crohn’s disease. It is clear that to be an effective induction agent, such nutritional therapy must be given as an ‘exclusive’ liquid formula.

It is in children that EEN has been used most widely and effectively used. Early cohorts demonstrated that EEN was able to achieve clinical remission in a significant proportion of children. At least in part it is their compliance with the exclusive diet that is crucial to its success, although shorter disease duration, milder disease phenotypes and ileal disease distribution all appear to respond better to this treatment modality.

Larger adult studies were carried out, yet subsequent meta-analyses demonstrated oral corticosteroids to be more efficacious in adult practice. Following these publications, few units have continued to use EEN as a first line therapy in adults with Crohn’s disease. Meta-analysis of randomized pediatric data did however demonstrate at least equal efficacy to corticosteroids in children.

Mucosal healing has been assessed endoscopically, by histology and by demonstrating down-regulation of mucosal pro-inflammatory cytokines. Despite impressive results, the mechanism of action remains unclear.

Convincing data has been reported demonstrating very rapid reduction in pro-inflammatory cytokines and systemic inflammatory markers within days of commencing EEN. There must be a very rapid direct anti-inflammatory effect to achieve systemic changes within 3–5 days.

There is currently no robust data supporting nutritional therapy as a maintenance strategy. However small case series and retrospective studies have documented improved growth rates and lower relapse rates in children using intermittent EEN or enteral supplements of at least 30% RDA 5 nights/week.
Given the minimal adverse effects, the direct anti-inflammatory effect and and the potential benefits on growth, as well as its efficacy in achieving mucosal healing, EEN clearly remains an important first line therapy in children with acute Crohn’s disease.

Address for correspondence:

Rob Heuschkel, MBBS MRCPCH
Consultant Paediatric Gastroenterologist
Department of Paediatric Gastroenterology
Box 267
Addenbrookes Hospital
Hills Road
Cambridge, CB2 0QQ
United Kingdom
Top-down therapy – Is the evidence strong enough?

Eugeni Domènech, M.D., Ph.D.
Gastroenterology Department, Hospital Universitari Germans Trias i Pujol, Badalona, Catalonia, Spain

Epidemiologic studies demonstrated that more than 70% of CD patients will develop disease complications (stenosis, abscesses, fistulae) within the first 10 years from diagnosis. The management of such complications usually requires intestinal resection. Chronic or repeated use of steroids (and its collateral effects), persistent disease activity, hospitalizations, and intestinal resections (and ostomies) clearly reduce the patient’s quality of life. That’s why current therapeutic approaches in IBD are focused not only in controlling disease symptoms but also in preventing complications and improving patients’ quality of life.

The development of biological agents and their efficacy in both inducing rapidly and maintaining long-term disease remission, raised the idea that these agents could change the natural history of CD. The study by D’Haens and coworkers in which a “top-down” strategy was compared to the conventional medical management of CD demonstrated that a more intensive medical approach is better in terms of steroid use and mucosal healing. In addition, it showed that, in recently diagnosed CD, almost 70% of patients will require immunomodulators to control disease activity within the first year. However, the study had some weaknesses in its design. First, the steroid regimen allowed a dose-increase in primary non-responders, leading to an unreasonable increase in cumulative steroid dose. Second, the “conventional managed” group did not receive maintenance treatment. Data from clinical practice have showed that early introduction of immunomodulators may be followed by a less disabling course of the disease. Given that CD is a chronic condition and complications will develop in more than one half of the patients within the first 5 years of disease, it seems reasonable that CD therapeutic strategies should always include both a good induction to remission and a long-term (and early introduced) treatment to maintain it. From this point of view, the D’Haens’ study showed that infliximab is a good drug to induce remission and that early introduction of thiopurines is effective in maintaining IFX-induced remission; by the other hand, although steroids may induce CD remission, early relapse in at least 70% of patients if maintenance therapy is not started. If we consider top-down therapy as early introduction of biologicals in CD, the evidence is not strong enough to recommend it as long as it has not been compared to an appropriate strategy with steroids. Nevertheless, strong evidence supports early introduction of thiopurines.
Immunomodulation with methotrexate – Underused and undervalued?

Prof. Dr. Dr. med. Frank M. Ruemmele
University Paris-Descartes, Faculty of Medicine, INSERM U793, Hôpital Necker Enfants Malades, Paediatric Gastroenterology, Program for Intestinal Immunopathology and Inflammatory Bowel Diseases, Hôpital Necker Enfants-Malades, Paris, France

Immunosuppressive or immunomodulatory strategies are now integral part of the treatment of patients with Crohn’s disease (CD). Since the precise molecular basis of CD remains still unclear, different treatment strategies were tested in the past. Best experience was gained with drugs that are able to block or down-regulate the inflammatory cascade within the intestinal mucosa. There is good experimental evidence that active induction of effector T cell apoptosis is a major anti-inflammatory mechanism, allowing to control the inflammatory reactions within the intestinal mucosa of patients. Two well-known drugs with pro-apoptotic effects on T cells are azathioprine and methotrexate (MTX).

Most clinical experience was gained over the last years with the purine analogues azathioprine (AZA)/6-mercaptopurine (6-MP). These drugs are discussed as gold standard for severe CD. Two recent Cochrane-based meta-analyses (five studies including 319 adult CD patients in remission and eight studies analyzing adult CD patients with active disease) clearly underlined the efficacy of AZA/6-MP to induce (after a treatment interval of at least 17 weeks) and to maintain remission. One single randomized placebo-controlled pediatric study confirmed the efficacy of AZA/6-MP in children with CD. However, for patients who do not tolerate or escape therapy with (AZA)/6-MP, there is a marked need for alternative immunosuppressive drugs. Two recent retrospective studies indicate that MTX might be a good second line choice for AZA/6-MP failures or intolerant pediatric patients. The recent French multicenter study showed that MTX improved the clinical course in 49 of 61 CD patients with a clinical remission rate of 39%, 49% and 45% at 3,6 and 12 months, respectively. Follow-up over at least 24 months confirmed a sustained remission on MTX-monotherapy up to 40 months. However, close to 30% of patients experienced a relapse after 13±10 months of treatment in this analysis. Comparable results were observed in the study of Turner et al. with 42% of 60 children responding with steroid-free remission at 6 and 12 months of MTX therapy. Success rates were similar in previously thiopurine-intolerant and refractory patients. These data are in keeping with two placebo-controlled studies in adult CD patients: MTX was shown to be successful in inducing and maintaining remission after steroid tapering in 39 versus 19% of a total of 141 patients with steroid-resistant CD. In the second study, MTX’ potential to maintain remission was about 65% at 40 weeks compared to 39% with placebo. Comparable trials in pediatric CD patients are still missing. Parenteral MTX application (sc or im) seems to be more efficacious in maintaining remission compared to oral MTX.

In summary, MTX seems to be an alternative drug to AZA/6-MP with reasonable good results. Altogether, about 50% of patients respond and remain in prolonged remission under MTX monotherapy. In approx. 10% of patients, the short-time
toxicity of MTX leads to drug discontinuation, indicating an overall acceptable tolerance profile. MTX might be used as first-line therapy. However, there is a great need to perform well-powered placebo-controlled trials as well as trials comparing the efficacy of AZA/6-MP to MTX before definitive recommendations can be given for pediatric CD.

References:


Address for correspondence:

Prof. Dr. Dr. med. Frank M. Ruemmele
University Paris-Descartes, Faculty of Medicine, INSERM U793
Hôpital Necker Enfants Malades,
Paediatric Gastroenterology
Program for Intestinal Immunopathology and Inflammatory Bowel Diseases
Hôpital Necker Enfants-Malades
149, rue des Sèvres
F-75015 Paris, France
E-Mail: frank.ruemmele@nck.aphp.fr
Partial enteral nutrition as a maintenance therapy?

Paolo Lionetti
Pediatric Gastroenterology Unit, University of Florence, Meyer Children’s Hospital, Florence, Italy

Exclusive Enteral Nutrition (EEN) is an effective primary therapy for pediatric Crohn’s disease (CD). More than 30 years ago a group of surgeons discovered fortuitously that it was possible to induce disease remission in patients treated preoperatively with an exclusive elemental formula that was used to improve nutritional status\(^1\). Since then EEN become an increasingly used alternative to corticosteroids and it is regarded as first-line therapy in many pediatric gastroenterology centres\(^2,3\). Liquid diet both elemental and polymeric can induce disease remission, promote linear growth and have steroid sparing capacity in children and adolescents who are at risk of stunting. Several evaluations of the efficacy of EN vs. corticosteroids have been reported. Although a meta-analysis in children suggests at least equal efficacy of these two therapies\(^4\) a systematic review on the existing efficacy data indicate that corticosteroid therapy is more effective\(^5\). However the beneficial effect on growth and nutritional status and the added benefit of lack of medication-induced side effects favor the usage of EN in the pediatric population. Elemental and polymeric diets are equally effective\(^5,6\). It has been suggested that that long-term enteral nutritional supplementation, in addition to unrestricted normal food may prolong remission and reduce number of relapses in patients with CD\(^7,8\). It has been shown retrospectively that providing supplementary enteral nutrition at night by nasogastric tube, with no restriction of normal diet, after successful induction of remission in active Crohn’s disease by EEN, is associated with prolongation of remission and improved linear growth in children and adolescents with Crohn’s disease\(^9\). In a recent study, patients who received half of their total daily calorie requirements as elemental diet and the remaining half by normal diet had a significantly lower relapse rate compared to patients who received unrestricted normal diet (9 of 26 versus 16 of 25; OR 0.3, 95% CI 0.09–0.94)\(^10\). In an other study, elemental and polymeric feeds (providing between 35 and 50% of patients’ pretrial calorie intake in addition to unrestricted normal food) were equally effective for maintenance of remission and allowing withdrawal of steroid therapy (8 of 19 versus 6 of 14; OR 0.97, 95% CI 0.24–3.92)\(^11\). In a recent review of the literature on the efficacy of partial enteral nutrition in maintaining remission in CD authors conclude that available evidence suggests that this therapeutic strategy may be effective for maintenance of remission in CD. Whilst larger studies are needed to confirm these findings, enteral nutritional supplementation could be considered as an alternative or as an adjunct to maintenance drug therapy in Crohn’s disease\(^12\). In a selected group of children with CD by a molecular approach we were able to show profound modification of the intestinal microflora in all children following EEN. Modification of band distribution of different bacterial species was present also in children on partial EN when compared with band distribution before EN\(^13\). Our current approach in children with CD after induction of remission with an 8 week course of EEN with a polymeric formula is to continue to provide 40% of the daily caloric intake as polymeric liquid formula in addition to an unrestricted diet.
References:


Address for correspondence:

Prof. Paolo Lionetti
Pediatric Gastroenterology Unit
University of Florence
Meyer Children’s Hospital
Viale Pieraccini 24
50139 Firenze
Italy
E-Mail: paolo.lionetti@unifi.it
Session V

Management of ulcerative colitis
Treatment of severe ulcerative colitis

Stephan R. Vavricka  
Universitätsspital Zürich, Klinik für Gastroenterologie und Hepatologie, Zürich, Switzerland

The natural history of untreated severe ulcerative colitis shows a mortality of up to 30% and is therefore considered to be a medical emergency. This mortality rate has been reduced to <1% in specialized centres at the present time. The management requires close collaboration between gastroenterologists and surgeons. In adult patients, current evidence supports initial treatment with intravenous steroids. However, only 40% of patients show complete response after corticosteroid therapy and almost 30% come to colectomy. CMV colitis can mimic ulcerative colitis and is thought to be responsible for treatment failure in up to 10% of patients labelled as steroid-refractory. Therefore, sigmoidoscopy and biopsy should be performed as a part of the initial assessment of the patient to rule out this condition. Cyclosporin at 2–4 mg/kg intravenously followed by 5 mg/kg orally still has a first place as salvage therapy because of its short half-life and its established short-term efficacy in about 70% of patients who fail steroids. The long-term benefit of this therapy remains unsatisfactory as colectomy is often only delayed. Infliximab is the choice for those patients with a less severe colitis and less likelihood of urgent colectomy. This is because infliximab has a long duration of immunomodulation that is not desirable after emergency colectomy. Tacrolimus has only been used in case series with similar results to cyclosporin. Surgery is still the definitive procedure for the treatment of ulcerative colitis in adult patients, and its timing is of paramount importance. Morbidity of severe ulcerative colitis results from prolonged ineffective medical treatment and therefore a delay in surgical treatment should be avoided. The surgical procedure most commonly performed is a subtotal abdominal colectomy and ileostomy, followed about 3 months later (when the patient is off steroids with an improved nutritional state) by completion proctectomy and the formation of an ileal-pouch anal anastomosis (IPAA).
Severe pediatric ulcerative colitis

Dan Turner, M.D., Ph.D.
Shaare Zedek Medical Center, Jerusalem, Israel

It is estimated that approximately 15% of adults with ulcerative colitis (UC) will experience at least one episode of severe exacerbation during their lifetime. The prevalence of extensive colitis in pediatric onset UC is twice the rate found in adults. Therefore, it is not surprising that the admission rate for severe UC is higher in childhood onset UC, reaching 28% by the age of 16 years. The optimal dose of intravenous corticosteroids is yet to be determined, however it has been suggested that doses above 60mg of methylprednisolone in adults do not increase response rate. Extrapolating from adult data, the pediatric dosing should range between 1–2 mg/kg up to 40–60 mg daily. Approximately one third of adults will fail steroid therapy and require second line medical therapy or colectomy. In three of four published retrospective studies, the rate of steroid refractoriness has been shown to be higher among children. A recent large prospective multicenter study of 128 children with severe UC indicates that the failure rate may be actually similar to that reported in adults. Predictors of steroid refractoriness in children include nocturnal stools, rectal bleeding, abdominal pain and C-reactive protein, while fever is not as common as in adults. Radiographically, the upper range of colonic luminal width is 40 mm in children younger than 11 years versus 60 mm in older patients. Children with colonic width up to these ranges may still respond to steroid therapy. The recently developed pediatric UC activity index (PUCAI) can guide the introduction of second line medical therapy or colectomy early during the admission. As per the “get set, go!” criteria, the PUCAI, determined at day 3 (> 45 points), should be used to screen for patients likely to fail corticosteroids, and at day 5 (> 70 points) to dictate the introduction of second-line therapy. Infliximab is successful in inducing remission in 75% of steroid-refractory children, of those 70–75% will not require escalation of therapy within 1-year. Tacrolimus may be similarly effective as infliximab in children but should be used preferably as a bridging therapy to azathioprine. In toxic megacolon or in cases refractory to one salvage therapy, the option of colectomy is preferred. Decision making regarding colectomy in children should carefully consider the toxicity of medication consumed over many future years, the quality of life associated with either choice, body self image, and the high infertility rate in females undergoing pouch procedure.
Treatment of ulcerative colitis in the elderly

Ashwin N. Ananthakrishnan, M.D., M.P.H., David G. Binion, M.D.
Division of Gastroenterology and Hepatology, Medical College of Wisconsin, Milwaukee, WI, USA
Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Abstract
Ulcerative colitis has a bimodal age distribution, with the majority of patients being diagnosed between the second and fourth decades of life. However, a second peak in diagnosis occurs in older patients and an estimated 15% of patients present after age 65. Caring for older UC patients who have either presented later in life or who have carried an IBD diagnosis for multiple decades may pose additional challenges in management. Recent studies using nationwide administrative databases from the U.S. have demonstrated that older IBD patients are challenged by worse hospital outcomes. This pattern, seen for both UC and Crohn’s disease, demonstrated increased rates of vascular complications (i.e. venous thrombosis), worse post-operative outcomes and increased rates of complicated and prolonged clinical courses compared to younger IBD patients. This article provides an overview of caring for elderly patients with UC, including diagnostic and therapeutic considerations.

I. UC demographics: The aging colitis population
The percentage of IBD patients who meet criteria for geriatric age, being 65 years of age or older, is not precisely defined. A review of the previously described Medical College of Wisconsin’s IBD Center database demonstrated that approximately 11.8% of 382 UC patients were over the age of 65, while 9% of 916 Crohn’s disease patients were in the geriatric age group. Among the elderly UC patients, 16 out of 45 (36%) were diagnosed at age ≥ 65, while 29 out of 83 (34.9%) elderly Crohn’s disease patients presented at age ≥ 65.

Reviews from populations based samples of patients, including the Olmstead County IBD Database, also demonstrated approximately 10% of their cohort being geriatric [1]. Analysis of the National hospital ambulatory medical care survey and National Ambulatory Medical care survey (NHAMCS/NAMCS) maintained by the National Center for Health Statistics (NCHS) revealed an increasing proportion of ambulatory visits for IBD (both UC and CD) being constituted by the elderly population, suggesting rising burden of disease related to IBD in the elderly [2]. In addition, one quarter of U.S. hospital admissions related to IBD occurred in patients older than age 65.

II. The differential diagnosis of colitis in older patients: Infection, ischemia and SCAD
Ulcerative colitis typically presents with symptoms such as abdominal pain, fecal urgency and bloody diarrhea. However, these symptoms are not specific to UC and similar to the younger IBD patient, it is important to consider a variety of differential diagnoses.
**Infectious colitis**

Similar to younger IBD patients, the majority of cases of bloody diarrhea result from infectious pathogens, with organisms associated with bacterial food poisoning (i.e. campylobacter, E. coli O157H7, salmonella, shigella) being most common. Enteric infection with E. coli O157H7 will often produce more severe illness in elderly individuals and may be associated with renal failure. It is important to perform stool studies identify and distinguish this pathogen prior to initiating immunosuppressive therapy appropriate for UC.

**Clostridium difficile**

An additional enteric pathogen which will mimic an IBD colitis flare which is particularly relevant to the elderly UC population is *Clostridium difficile* (*C. difficile*) [3]. This spore forming anaerobe is classically associated with antibiotic exposure and disturbance in the enteric flora, which will lead to expansion of this organism. *C. difficile* has doubled in incidence in North America over the past 10 years. This infection has classically been associated with patients from high risk environments, specifically long-term care facilities (i.e. nursing homes) and hospitals. Recent research suggests that IBD patients are at high risk of acquiring *C. difficile* infection, and an elderly IBD population may represent one of the highest risk individuals for acquiring this infection [4]. Stool analysis for the presence of *C. difficile* toxins A and B is the most frequent employed modality for diagnosis, but the sensitivity of this assay is fairly low. In IBD patients infected with *C. difficile* in 2005, 54% of patients were diagnosed on the initial stool analysis, and 4 stool samples were required to reach a diagnostic accuracy above 90% suggesting that repeat testing may be indicated in patients where there is a high index of suspicion for this infection [5]. IBD patients with *C. difficile* rarely demonstrated pseudomembranes, which are found in approximately half of *C. difficile* infected patients with no prior history of colitis. The majority of IBD patients who contracted *C. difficile* had pre-existing diagnoses of UC or Crohn’s colitis, and 10% of patient presented with concomitant *C. difficile* infection at the time of the IBD diagnosis. *C. difficile* superinfection will lead to an exacerbation of colitis, and over half of infected IBD patients will require hospitalization. Treatment of the hospitalized IBD patient with *C. difficile* represents a high risk scenario, as high rates of colectomy have been identified in this setting. Use of oral vancomycin as the primary antibiotic regimen targeting *C. difficile* has resulted in improved rates of medical treatment success for hospitalized IBD patients. Rapidly decreasing oral corticosteroid dosing has also improved clinical outcomes, as the ability to mount an antibody response to toxin A is felt to be the critical mechanism for clearing an infection. In severely ill patients, infliximab has been used in conjunction with oral vancomycin and lower dosages of corticosteroids with overall reduced rates of colectomy.

**Ischemic colitis**

A particularly important differential diagnosis to be considered in the setting of colitis in the elderly is ischemic colitis. This is the most common vascular injury seen in the human gastrointestinal tract, occurring at rates varying from 5–44 cases per 100,000 person-years [6]. Ischemic colitis is caused by compromised vascular flow to the large bowel, and may range from mild transient injury to potentially life-threatening transmural infarction [7]. The classic findings of ischemic colitis include the triad of acute abdominal pain, bloody stool and low blood pressure. The classic patient with ischemic colitis in an elderly female older than age 65 [8, 9], but other
subsets of individuals can also manifest injury, with long-distance runners being one example [10], while drug induced ischemic colitis can also affect seemingly low risk individuals (i.e. use of serotonin modulating agents in patients with irritable bowel syndrome) [11, 12].

Multiple etiologies underlie ischemic colitis, but all share the mechanism of decreased perfusion of the large bowel. Key contributing mechanisms include decreased cardiac output, chronic renal failure [13], cardiac arrhythmia, shock [14, 15], arterial thrombosis, embolism, complications of surgery (i.e. failed re-implantation of the inferior mesenteric artery following abdominal aortic aneurysm repair) [16], colonic obstruction with increased luminal pressure leading to impaired mucosal perfusion [12], hypercoagulability [17, 18], vasculitis [19], intra-abdominal inflammation or infection or complications of drugs [17, 20, 21].

The clinical presentation of ischemic colitis depends on the severity of vascular injury and the anatomic segment affected by the ischemic insult [22]. The most commonly affected vascular territory involved with inferior mesenteric artery which supplies blood to the left colon. Ischemic colitis involving the left colon will typically result in abdominal pain, increased bowel movements and rectal bleeding. Ischemic injury to the right colon may manifest with a broader range of presentations including more subtle abdominal symptoms, or conversely more dramatic symptoms in patients with transmural injury to the thinner right colon wall. Mild right colonic ischemia may present with abdominal pain in the absence of bloody diarrhea or altered bowel function.

Physical findings of ischemic colitis are variable, but will frequently present with mild tenderness and/or abdominal distention. More severe injury will present with peritonitis, and this has been estimated to occur in up to 20% of patients experiencing ischemic colitis.

Diagnostic testing is often non-specific in ischemic colitis. In the majority of cases routine laboratories (i.e. blood counts, creatinine phosphokinase, amylase, serum lactate and lactate dehydrogenase) are all normal. Severe ischemic colitis may demonstrate an elevated white blood count and acidosis. Radiologic findings in ischemic colitis are variable, paralleling the severity of the ischemic injury. Most commonly, non-specific radiographic findings are present, which will include bowel dilation, ileus and mural thickening. Thumbprinting, the classic, pathognomonic radiographic finding in ischemic colitis is identified in only 20% cases. CT scanning is helpful in the evaluation of ischemic colitis, as it will help to define the extent of the colonic injury. The diagnosis of ischemic colitis is confirmed by colonoscopy and biopsy, but the decision to evaluate the entire colon must be carefully weighed given the severity of injury and the propensity of the ischemic colon to perforate. The endoscopic appearance of ischemic colitis will manifest a sequence of appearances ranging from friability, petechial hemorrhages and pale appearing mucosa early in the disease. The later appearance of the evolving colitis may demonstrate a hemorrhagic and sloughing mucosa. The most severe ischemic colonic injury demonstrates gangrene, with a bluish-black, dusky mucosal appearance. Histopathology will also demonstrate an evolving tissue injury, with the early process showing mucosal hemorrhage, edema and tissue necrosis and later injury showing leukocytic infiltration, sloughing of the surface epithelium and mucosal ulceration.
During the resolution of ischemic colitis, histology will demonstrate repair with granulation tissue and scarring which may ultimately lead to stricture formation.

Treatment of ischemic colitis is supportive, emphasizing dietary limitation and antibiotics which cover bowel flora [23]. Patients with moderate to severe ischemic colitis, which will manifest radiographic changes, require hospitalization to facilitate bowel rest, administration of intravenous antibiotics and pain control. Restriction of diet is recommended as bacterial translocation can occur in the injured bowel, and avoiding the physiologic demand for increased enteric blood flow required during digestion may also limit further ischemic injury. Likewise, medications which may adversely affect perfusion including non-steroidal anti-inflammatory drugs and aspirin should be avoided during the acute period of bowel injury.

The majority of patients with moderate to severe ischemic colitis requiring hospital admission will recover within 48 hours. Complete resolution of ischemic colitis may require multiple week for resolution to occur. Colectomy and diverting ileostomy should be considered in patients who have failed to resolve over a two week time period, or in the setting of impending sepsis. It is estimated that up to 20% of patients with ischemic colitis will experience this protracted clinical course, and these individuals are at risk for the development of strictures should they finally resolve the injury. The surgical management of ischemic colitis requires a conservative approach, favoring the use of diverting ostomies and avoiding creation of anastomoses which may involve ischemic tissues, due to high rates of anastomotic failure and intra-abdominal sepsis. Close surgical management is necessary in patients with refractory disease, as overt gangrene can emerge in patients who fail to re-establish circulation, which will lead to perforation and high rates of peri-operative mortality.

**Segmental colitis associated with diverticuli (SCAD)**

Diverticulosis is an extremely common clinical finding in Western countries, occurring in 5–10% of the population over age 45, and rising in incidence to 80% of individuals over age 85 [24]. Diverticuli are typically asymptomatic, but episodes of acute diverticulitis may affect up to 20% of patients during their lifetime. Acute diverticulitis is felt to be a microperforation of the bowel wall with associated peritonitis, occurring most commonly where the vasa recta will penetrate across the bowel wall. In distinction from this well characterized acute inflammatory complication, a form of chronic inflammation involving a colonic segment involved with diverticuli has also been described. Segmental colitis associated with diverticular disease (SCAD) was initially described in the 1980’s and 1990’s [25], and this typically resembles IBD at both the endoscopic and histologic levels. SCAD will occur in individuals with a normal rectum and proximal colon [26], and will typically demonstrate a segment of colitis in a field of diverticuli. Patients presenting with SCAD are typically over age 60, are more frequently male and will present with symptoms ranging from painless hematochezia to lower abdominal cramps or altered bowel habits. Occasionally patients with SCAD will demonstrate fever, leukocytosis, nausea and/or weight loss.

Endoscopy is essential to establish a diagnosis of SCAD, and findings will typically include mucosal erythema, granularity and/or friability of the sigmoid colon with sparing of the rectum and more proximal colon. Histology will range from a chronic colitis similar to IBD, to non-specific findings, often similar to mucosal prolapse.
Therapy of SCAD will initially follow the treatment approach for acute diverticulitis [27]. After ruling out potential infectious pathogens with stool testing, including analysis for the presence of *Clostridium difficile* toxin, SCAD patients are typically treated with a regimen of oral broad spectrum antibiotics for 7–10 days, which will include coverage for bowel flora. Following completion of this antibiotic regimen, long-term management of SCAD emphasizes treatment with oral fiber supplementation [28]. The majority of patients with SCAD respond to conservative treatment. Patients who fail to respond to antibiotics can receive mesalamine compounds as well as topical steroid enemas. There is a small subgroup of patients with SCAD who develop more aggressive chronic inflammation, similar to Crohn’s disease, manifesting with non-caseating granulomas and fissuring ulcers or fistulae. These individuals will often require segmental resection, and followup studies evaluating SCAD patients for the subsequent 6–12 months have demonstrated that the majority of individuals do not progress to overt Crohn’s disease.

The etiopathogenesis of SCAD may represent an overlap with either classic IBD or pouchitis, the complication associated with increased mucosal bacterial counts in patients who have undergone ileoanal pouch reconstruction following colectomy. SCAD patients share histologic findings with pouchitis and the initial treatment for both of these conditions employs antibiotics targeting bowel flora. Bacterial stasis in diverticuli may represent a critical etiologic component for the development of diverticular colitis, which drives the development of chronic bowel inflammation in this form of IBD.

**III. Treatment of UC in elderly patients**

**Medical treatment options**

Elderly UC patients are candidates for treatment with all of the therapeutic options available for younger IBD patients. Following induction with corticosteroids, elderly UC patients with mild UC can receive maintenance therapy with agents such as the 5-ASA compounds [29, 30]. Disease of moderate severity may require immunosuppressive drugs such as azathioprine and 6-mercaptopurine [31], with severe, or steroid-refractory disease requiring the most potent class of maintenance treatment, the biologic agent infliximab [32].

All of the major trials for 5ASA compounds as well as infliximab did include elderly UC patients in their study populations, with no specific upper limit for age restriction amongst elderly patients for the majority of the 5ASA trials as well as infliximab (www.clinicaltrials.gov). However, none of these trials have been specifically analyzed to compare the rates of response and remission in elderly patients with those in younger IBD patients. Also importantly, adverse effects of these agents have also not been evaluated specifically in the elderly IBD population. All of the major trials for 5ASA compounds as well as infliximab included elderly UC patients in their study populations, with no specific upper limit for age restriction amongst elderly patients for the majority of the 5ASA trials as well as infliximab (www.clinicaltrial.gov). Data regarding the use of azathioprine and 6 mercaptopurine for the treatment of UC is limited [31], and did not specifically evaluate response rates in elderly patients. Case reports from tertiary referral centers demonstrated clinical efficacy in elderly patients for immunosuppressive agents, and use of these agents should be considered in elderly UC patients.
An important consideration in the management of elderly UC patients, is the loss of physical reserve which accompanies aging. Elderly patients who present with severe colitis flare should have consideration for earlier inpatient management. The rationale for this more aggressive strategy is multiple and includes both pragmatic and therapeutic implications. The ability to handle fecal urgency and multiple nocturnal trips to the bathroom, which are hallmark features of UC flare, may not be readily handled by an elderly individual without assistance. As discussed in the next section, elderly patients may not be able to tolerate the stress of colitis flare and this may translate into worse clinical outcomes. The ability to rapidly induce remission with more potent agents (i.e. intravenous steroids, initiation of biologic therapy with infliximab) compared with a course of oral corticosteroids, can often be more readily initiated in the inpatient setting. Our IBD center recommends immediate assessment of tuberculosis exposure status at the time of admission with either the placement of a PPD skin test or sending the *in vitro* interferon gamma release assay (i.e. Quantiferon Gold TB), so that patients not exhibiting a rapid clinical response can be initiated on infliximab [33]. Our center has emphasized the use of infliximab as an outpatient treatment strategy for refractory UC patients, so the extension of this strategy for early in-hospital initiation follows this paradigm [34].

**Hospitalization outcomes**

Use of all of these treatment modalities for elderly UC patients who are experiencing significant flare is an even more important issue when one considers that hospitalized older IBD patients are at increased risk for worse clinical outcome. Ananthakrishnan and colleagues used the Nationwide Inpatient Sample, an administrative database of approximately 1000 short stay hospitals in the U.S., which is maintained by the Healthcare Cost Utilization Project (HCUP) to determine the impact of age on IBD inpatient outcome [2]. In 2004, there were 105,423 IBD admissions, of which 25% occurred in patients who were over the age of 65. A majority of the elderly IBD patients carried a UC diagnosis.

When the patient populations were adjusted for the presence of co-morbidity, it became apparent that age is an independent predictor of mortality in IBD inpatient admissions. The oldest patients had the highest mortality, even when adjusting for co-morbidities. Factors which were associated with mortality in the oldest cohort of IBD patients included malnutrition and the requirement for bowel surgery during the inpatient stay, while female sex was found to be associated with diminished mortality. In UC, elderly age was predictive of mortality with an odds ratio of 2.84 (1.43–5.63).

**Surgical outcomes for elderly UC patients**

UC patients who have fail to respond to medical treatment will require surgical management with colectomy with either permanent ileostomy or pouch reconstructive surgery. The concern regarding elderly UC patients failing medical therapy, is their overall lack of reserve, and the impact of co-morbid illness which may worsen their surgical outcome. Two studies have evaluated surgical outcomes in elderly UC patients. Almogy reviewed the surgical experience in elderly UC patients at the Mt. Sinai Hospital in New York, and identified 113 consecutive UC patients who underwent surgery between 1960 and 1999 and were age 65 years or older [35]. The authors found that the indication for colectomy changed during the four decades evaluated, as toxic megacolon was significantly decreased in the more recent time period and surgery for dysplasia has replaced adenocarcinoma as the leading reason
for colectomy in elderly UC patients. These authors found that surgery associated adverse outcomes decreased significantly from 50% of cases during the 1960–1984 time period (13% deaths, 37% major complications) to 27% in the most recent time period evaluated (1994–1999; with 3% deaths, 24% major complications). These authors further defined that male sex, albumin level $\leq 2.8$ g/dl and need for urgent surgery were independent predictors of poor outcome.

Page and colleagues evaluated factors affecting surgical risk in elderly IBD patients, using a case-control approach comparing surgical outcome in patients 60 years or older compared with younger individuals using multivariate models [36]. The dataset included 30 IBD patients age 60 or older and 75 IBD patients younger than age 60. These authors found that elderly IBD patients had an increased rate of postoperative complications along with an increased length of hospital stay and increased operating room time. The effect of elderly age persisted after adjustment for comorbidity and use of immunosuppressive therapy. A similar longer duration of post-operative stay was found in the study using a nationwide sample by Ananthakrishnan et al. who also identified a higher incidence of post-operative cardiovascular (OR 2.26, 95% CI 1.13–4.54) and pulmonary (OR 1.66, 95% CI 1.12–2.48) complications in the elderly. As such, it is important to accurate risk stratify elderly patients who may be particularly at a high-risk for these complications and institute early appropriate interventions to minimize the occurrence of these complications.

UC patients who have undergone colectomy may be candidates for ileoanal reconstruction procedures. The ability to successfully rebuild a pouch-reservoir for fecal continence and take down of the end-ileostomy has represented an important advance in the surgical options available for patients with severe/refractory UC requiring total colectomy. However, the prevalence of anorectal dysfunction in the aging population may make the outcome of these procedures less successful. Delaney and colleagues from the Cleveland Clinic Foundation prospectively evaluated the effect of age on surgical results, functional outcome and quality of life after ileal pouch anal anastomosis (IPAA) [37]. Among 1895 patients who underwent the reconstructive procedure, 42 patients were older than age 65. Patients were assessed 1, 3, 5 and 10 years after surgery. The majority of elderly pouch patients had UC (81%). Within 1 year of surgery, elderly UC patients were experiencing on average 1.5 nocturnal bowel movements and 6 daily bowel movements. Nocturnal seepage was described in 44% of elderly patients, and 44% described never being incontinent. These results were slightly worse than those in younger cohorts of patients, but these differences did not achieve statistical significance. When elderly UC patients were asked to describe whether having undergone the ileoanal pouch anastomosis had an impact on their quality of life, 28% said that social restrictions were imposed as a result of surgery, 33% had experienced sexual restrictions, which was significantly higher than in younger age groups. On the positive side, 89% of elderly UC patients stated that they would opt to undergo the pouch reconstruction again, and 96% would recommend the surgery to others. These authors concluded that ileo-anal pouch anastomosis could be safely performed with acceptable results in elderly UC patients.
It is important for physicians and surgeons involved in the management of these elderly IBD patients to discuss the risk-benefits of these procedures with the patients prior to surgery so that a fully informed decision may be taken prior to reconstructive surgery. Patients with pre-existing diagnosis of anorectal dysfunction or incontinence may not be candidates for such reconstructive surgery and may have better function and quality of life outcomes with permanent ileostomy.

IV. Special scenarios relevant to the elderly UC population

**Thrombotic complications in elderly UC patients requiring hospitalization**

IBD is now recognized as a hypercoagulable state [38]. One of the highest risk time period for clotting complications to occur is during inpatient IBD management. Medical admissions for UC are typically focused on the management of severe colitis, where patients experience multiple clinical factors which predispose to clotting. Among these are dehydration, thrombocytosis, and increased inflammatory activity, all of which may contribute to activation of clotting cascades. Surgical management is also associated with increased rates of clotting for all of the above listed reasons, as well as the activation of tissue factor which occurs during the operation itself and decreased mobility in the post-operative period.

In a recent review of clotting complications in IBD patients, Nguyen et al. demonstrated that elderly IBD patients were at significantly increased risk of developing venous clotting complications which rose in a linear relationship to age [39]. Using the Nationwide Inpatient Sample dataset, elderly UC patients demonstrated the highest rates of venous thromboembolism, which occurred in 25% or more of the hospitalizations in patients who were 50 years and older. Approximately 1/3 of the UC patients who were older than age 80 experienced a venous clotting complication during a hospitalization in the year 2004. These high rates of clotting complications suggest that prophylaxis strategies using heparin compounds should be considered in elderly UC patients during hospitalization for medical or surgical management.

**Co-morbid illnesses**

Elderly UC patients are more likely to have co-morbid illness compared to those of a younger age group. In the study of the Nationwide Inpatient Sample by Ananthakrishnan et al., 9.6% of elderly IBD patients had 3 or more comorbid conditions compared to 2.6% of the < 65 year old IBD patients [2]. In concert with this was the finding that fewer elderly IBD patients had no comorbid conditions (46%) compared with younger IBD patients (79%). As such, it is important to take into account the effect of both disease and therapy on underlying co-morbid illness in these patients. Long-term use of corticosteroids may be associated with worsening of diabetes control. Steroid use may also be associated with fluid retention, which may be significant in patients with underlying hypertension, congestive heart failure or renal disease. Elderly patients may also have underlying ocular problems such as glaucoma which may be worsened by steroids. Osteoporosis and osteopenia are prevalent in the older population making it important to consider preventative and treatment measures with use of calcium, vitamin D, and bisphosphonates as indicated. Elderly patients may also be at a higher risk for infectious complications with steroids and the immunosuppressive agents such as azathioprine or infliximab, though such analysis has not been specifically performed from large treatment
registries. Elderly patients may also have a lower reserve to withstand complications from disease such as blood loss and may merit from more active therapy than the younger patient.

**Drug interactions, polypharmacy and medication adherence**

In line with the higher co-morbid burden in the elderly, it is important to consider the fact that these patients are more likely to be on multiple medications raising concerns for both drug interactions and medication adherence [40]. Higher pill burden has been associated with nonadherence. Elderly patients with underlying cognitive defects or with limited functional ability may be especially prone to non-adherence with regimens involving multiple pills spread out over varying times of the day. Visiting nurse programs or other social support mechanisms may be important in this cohort to ensure adherence with therapy and optimal outcomes.

**Preservation of functional independence and quality of life**

A particularly important issue in the management of the elderly UC patient is the importance of preserving quality of life and functional independence. Multiple nocturnal bowel movements or frequency and urgency of bowel movements may be particularly disabling in this population which is also likely to have impaired mobility. Cautious use of antimotility agents may be warranted in this cohort to maximize continence and maintain independence in activities of daily living. According to estimates from the HCUP-NIS, less than 1% of patients aged 18–45 years with a primary discharge diagnosis of UC or Crohn’s required discharged to a nursing home or rehab facility compared to 15.7% of those aged 65–84 years and 35.7% aged 85+ years [2]. Similarly the proportion requiring home health care on discharge was 4.7% for those aged 18–44 years compared to 12.6% for those between the ages of 65–84 years.

**V. Directions for future research**

There are several areas in the management of the elderly UC patients that merit future investigation. It is not yet known if the response rates to treatments as well the susceptibility to adverse effects are different between elderly and younger adult UC patients. The impact of disease activity as well as treatment on quality of life outcomes in the elderly also merits special attention.

**VI. Conclusions**

Elderly UC patients constitute an increasing proportion of patients with IBD. Although they share many similarities with younger IBD patients in regards to treatment options, elderly patients are at risk for worse outcomes related to medical or surgical hospitalizations if they become severely ill. This implies that elderly UC patients have less reserve, and may not tolerate the stress of colitis flare, as well as physiologic challenges of abdominal surgery. Elderly UC patients who are hospitalized are at markedly increased risk for venous thrombotic complications. For all of these reasons, elderly UC patients warrant an aggressive medical approach to achieve and maintain remission. Elderly UC patients are at risk of ischemic and infectious complications, including *C. difficile* colitis, which may complicate their underlying IBD. Future studies are warranted to define the optimal treatment algorithms for the optimal elderly UC population.
VII. Bibliography


Address for correspondence:

David G. Binion, M.D.
Co-Director, Inflammatory Bowel Disease Center
Director, Translational Inflammatory Bowel Disease Research
Visiting Professor of Medicine
Division of Gastroenterology, Hepatology and Nutrition
University of Pittsburgh Medical Center Presbyterian Hospital
University of Pittsburgh School of Medicine
Mezzanine Level – C Wing
200 Lothrop Street
Pittsburgh, PA 15216
E-Mail: binion@pitt.edu
Surgery in ulcerative colitis – Indication and timing

Johan D. Söderholm, M.D. Ph.D.
Professor of Surgery, Linköping University Hospital, Linköping, Sweden

The main indications for surgery in ulcerative colitis remain: 1. fulminant or acute colitis not responding to medical therapy; 2. chronic continuous inflammation; 3. dysplasia and/or cancer; 4. reconstruction after previous surgery.

1. In acute colitis a close collaboration between the medical gastroenterologist and the colorectal surgeon is pertinent. The surgeon should be informed in every case of severe colitis admitted to the hospital, and the patient should also at an early stage be informed that colectomy is an alternative should the medical treatment fail. To be able to make the correct decision the colorectal surgeon must be consulted at any deterioration and/or before rescue treatment with anti-TNF is started. The absolute indications for surgery are toxic megacolon, perforation, and severe colorectal bleeding. In addition, surgery should always be considered upon deterioration during medical therapy. The recommended operation in acute colitis is colectomy and ileostomy, with the rectum left in situ. A proposal of an algorithm for acute colitis will be presented. Reconstruction should be done approximately 6 months from primary surgery, when the patient is back in a good general condition. Currently, many cases of severe acute colitis have been treated with high-dose steroids combined with rescue therapy with infliximab. It must be remembered that there are studies suggesting an increased risk of postoperative complications in pouch surgery for at least 4 months after rescue therapy.

2. In chronic continuous colitis, with long-term steroid therapy, the conditions for healing are poor. The patient should be in an optimized nutritional state and the steroid dose kept at a minimum. Because of the compromised healing, a staged procedure is preferred also in these cases, i.e. primary surgery with colectomy and ileostomy, leaving the rectum intact to consider the options of reconstruction at a later stage.

3. In cases with dysplasia, surgery should be done after carefully verifying the dysplasia since these patients often have little symptoms from their colitis, and proctocolectomy with ileal pouch-anal anastomosis is a procedure with significant risks of postoperative morbidity and lowering of quality of life. The proctocolectomy should in these cases generally include total mesorectal excision. Mucosectomy of the rectal mucosa with a hand-sewn anastomosis of the pouch to the dentate line is often recommended. However, this procedure does not guarantee removal of all mucosa. Therefore the double-stapled technique, leaving a rectal cuff, is acceptable because of its better functional results. The remaining rectal cuff should, however, be no more than 1–2 cm above the dentate line to minimize the mucosal surface at risk of malignant transformation. These patients should be kept under surveillance.

4. Ileal pouch-anal anastomosis (IPAA) is the standard bowel reconstruction in ulcerative colitis. The options to IPAA, ileorectal anastomosis (IRA) or remaining ileostomy, should always be thoroughly discussed, considering the pros and cons in
each individual patient, before a choice is made. The IPAA offers the patients an unchanged body image with no stoma and a preserved anal route of defecation. However, function is often less than perfect, there is a considerable risk of pouchitis, and fertility and sexual function may be affected. The IRA is in select cases (especially in young females not having had their children) a temporary alternative, leaving the pelvis intact and with better anorectal function. To consider this option, however, the proctitis must be easily kept in remission; therefore cases having surgery for chronic continuous disease may not be ideal for IRA. Ileostomy is a valid option if the patient tolerates the stoma. The rectal remnant must be kept in surveillance as if an extensive colitis; if this is not possible, the rectum should be removed.

In conclusion, surgery for ulcerative colitis should be seen as complimentary to medical treatment and will, when used in the right situations, prevent complications, improve the patients’ quality of life and occasionally be life saving.
Session VI

Tailored therapy for specific subgroups?
Management of IBD during pregnancy

Axel U. Dignass
Department of Medicine I – Gastroenterology, Hepatology, Oncology and Nutrition, Markus Hospital, Goethe University, Frankfurt, Germany

Crohn's disease (CD) and ulcerative colitis (UC) have a high prevalence in younger patients with child-bearing potential. Thus, uncertainties and a number of questions regarding medical treatment before and during pregnancy and the nursing period exist in IBD patients. Several studies have demonstrated that most pregnancies in women with IBD will develop normal, if the patient is in remission or has minor disease activity at the time of conception. In contrast, the frequency of normal pregnancies is significantly reduced and the frequency of adverse outcomes like preterm birth or miscarriage is increased, when conception occurs in phases with active IBD. Therefore it is generally recommended to women with IBD to conceive at a time with minor disease activity or in remission.

Because of the observation that adverse outcomes of pregnancy are observed more frequently in IBD patients with active IBD women with IBD, who plan to become pregnant or are pregnant, should be treated adequately for active disease. Currently it is widely accepted that the treatment of IBD with corticosteroids and 5-ASA derivatives does not increase the risk of malformations or adverse outcomes in pregnant IBD patients. However, a slight increase in the number of pre-term deliveries or reduced birth weight is observed. Therefore, corticosteroids and 5-ASA derivatives can be used for the treatment of pregnant patients with active IBD and, when necessary, also to maintain remission during pregnancy. Treatment of active IBD with corticosteroids and 5-ASA derivatives during pregnancy does not significantly differ from treatment considerations in non-pregnant women. More recently, it has also been appreciated that azathioprine and 6-MP and presumably also infliximab and other TNF-alpha blocker can be safely used during pregnancy in IBD, as no significant increase of malformations, miscarriages or adverse pregnancy outcomes are observed. There is no medical indication for a medical termination of a pregnancy, if women become pregnant on these medications. Information on cyclosporine and tacrolimus during pregnancy is more scarce, but it may be continued or started in some situations if clinically needed. Methotrexate is contraindicated, as this drug is known to significantly increase the risk of malformations and spontaneous abortion.

Patients, who wish to nurse their babies, may be treated with steroids and 5-ASA derivatives without a significantly increased risk for the newborn. Immunosuppressants should not be used in nursing women or children should be switched to bottle feeding, because most immunosuppressants are insufficiently metabolized by the newborn because of immature liver function and may cause significant adverse events in the new-born.
Mild-to-moderate Crohn’s disease – Still room for step-up therapies? – Adult perspectives

Simon Bar-Meir, M.D.
Department of Gastroenterology, Chaim Sheba Medical Center, Tel Hashomer, Israel

Step-up therapy refers to the classic therapeutic approach resulting in progressive increase of therapies with the increasing severity of the disease. This approach has been recently challenged by the top-down strategy, where biologicals and thiopurines are used as first line therapy.

Several arguments exist against the top-down therapy. First, data from a large population-based study performed in Copenhagen County, showed that 80% of CD patients maintain high disease activity only in the first year after diagnosis. This percentage decreases dramatically after the first year, with about 55% of CD patients are in stable remission at any given year later on. Prospective studies from the GETAID, including patients in remission after a corticosteroid treatment; the probability of remission off corticosteroid therapy was 60% at 12 months and 53% at 18 months. Taken together, these data indicate that the indiscriminate use of infliximab as first-line therapy would represent an overtreatment for most of CD patients. One should keep in mind that Infliximab is not an innocent medication and the incidence of serious infections during infliximab therapy is increased compared to a control group (4–4.2 vs. 8.2–8.3%, respectively), in particular the risk of active tuberculosis.

ECCO Statement is therefore that budesonide 9 mg daily is the preferred treatment in mild-to-moderate CD patients. The benefit of mesalazine is limited. At this stage 5-ASA should be considered clinically no more effective than placebo for active ileal or colonic CD. Antibiotics cannot be recommended unless septic complications are suspected. No treatment is an option for some patients with mild symptoms. Budesonide 9 mg daily is favored because it is superior to both placebo (OR 2.85, 95% CI: 1.67–4.87) and 5-ASA 4 g/day (OR 2.8, 95% CI: 1.50–5.20) and achieves remission in 51–60% over 8–10 weeks. Budesonide is preferred to prednisolone for mild active CD because it is associated with fewer side effects. Active mild colonic CD may be treated with sulfasalazine and if needed with systemic corticosteroids as well. Topical treatment should be considered for distal disease. Any patient who has an early relapse is best started on an immunomodulator.

Two important trials (The national cooperative Crohn’s disease study and the European co-operative Crohn’s disease study) established corticosteroids as effective therapy for inducing remission in CD. Remission is achieved in 60–83% of the patients.

A Cochrane review of the efficacy of azathioprine and 6-mercaptopurine for inducing remission in active CD showed a benefit for thiopurine therapy compared with placebo with an odds ratio of 2.36 (95% CI: 1.57–3.53). This equates to an NNT of five and a number needed to harm (NNH) of 14. Methotrexate is another effective medication that has been confirmed in a systematic review. In a controlled study,
more of the MTX treated group was able to withdraw corticosteroids and enter remission compared with placebo (39% vs. 19%; \( p = 0.025 \)).

If remission has been achieved with systemic corticosteroids, azathioprine should be considered. For patients in remission on 5-ASA cessation of treatment may be considered after two years of full remission. For patients with extensive colitis, long term treatment is an option as this may reduce the risk of colon cancer, although this is still unproved in Crohn’s disease. For patients in remission on azathioprine as maintenance treatment, cessation may be considered after four years of full remission, but a small treatment benefit persists even after six years.

In conclusion, the natural course of most patients with CD is relatively mild and there is a room for step-up therapy. The efficacy of most medications is similar to the efficacy of infliximab but with less adverse effects. Infliximab should be reserved only for patients where other therapies failed.
Anti-TNF non-responders – Therapeutic strategies

Edouard Louis
Department of Gastroenterology, CHU Liège, Belgium

The absence of response to an anti-TNF treatment can be encountered either as a primary or secondary non-response.

The primary non-response affects 20–40% of the Inflammatory Bowel Disease patients in uncontrolled series and controlled trials, respectively. Best results have been obtained by an association of anti-TNF, immunosuppressant and steroids for the induction. Main reasons for non-response are: inflammation not responding to anti-TNF, strictureing or infectious complications (intrabdominal or perianal abscess in Crohn’s disease (CD), clostridium difficile or CMV colitis in both CD and ulcerative colitis (UC)), absence of significant inflammation with functional symptoms. The primary non-response can thus be minimized by a pre-treatment assessment including biological test of inflammation and if needed endoscopic and/or medical imaging procedure. According to the mechanism of non-response and the induction treatment used, the therapeutic strategy can be either the use of another anti-TNF, another biologics, immunosuppressant or steroids, surgery or symptomatic treatment. In severe UC, infliximab (the only anti-TNF with proven efficacy in UC) failure usually leads to surgery and, for safety reasons, a subsequent cyclosporine trial is not recommended.

The secondary non-response, or loss of response, can be seen in 10–40% of the patients per year of treatment. The main reasons are low anti-TNF trough levels due to either antibody formation or accelerated clearance of the anti-TNF, the development of a strictureing or infectious complication, or the development of an inflammatory pathway escaping anti-TNF treatment. A proper assessment of the patient is useful to define the appropriate treatment strategy. It may include biological test for inflammation, endoscopic and/or medical imaging procedures and, although not widely available, anti-TNF trough levels measurement. If a complication has developed, the treatment is usually surgical, instrumental or antibiotics. If not, the anti-TNF can be optimized by either increasing the frequency of administration or increasing the dosage. If an absence of sustained response occurs despite optimization, a switch in anti-TNF treatment can be attempted. Depending on the therapeutic history of the patients, immunosuppressant or other biologics (when available) may also be an option. Steroids may be used as rescue therapy. In UC, the strategy will depend on the severity of the flare, but surgery will often be the best option.
Early IBD: Different treatment response to specific or all medications?

J.F. Markowitz
Schneider Children’s Hospital, Pediatric Gastroenterology, New Hyde Park, NY, USA

Data suggest that the medications prescribed for the treatment of inflammatory bowel disease may be more commonly efficacious in children than adults. While this may frequently be true, care must be exercised in evaluating the data, as differences in disease duration, drug dose and concomitant therapy can cloud comparisons between studies. In active Crohn disease (CD), corticosteroids acutely induce a response in 84–89% of children and 80–84% of adults. Prolonged response at 1 year may, however, be better in children (50–61%) than adults (32–44%), although differences in duration of CD among the various studies’ subjects and the proportion of subjects receiving concomitant immunomodulators probably explain much of these differences. CD remission rates with thiopurines appear higher in children, whether assessed at 6 months (85% vs. 31%) or 15–18 months (81% vs. 42%), but the duration of CD in the different study populations probably influences the outcomes of these reports as well. Similarly, remission of CD 1 year following initiation of infliximab also appears higher in children than adults (56% [REACH] vs. 28% [ACCENT I]). These differences may be due to the shorter duration of CD in the children in REACH (mean 1.9 yrs) compared to the adults in ACCENT I (median 7.5 yrs), as subanalyses of the major trials of all of the anti-TNF antibodies reveal diminishing rates of response with longer duration of disease. In addition, the apparent enhanced response in children to infliximab can also be due to differences in the rates of concomitant immunomodulator therapy, as 99% of children in REACH received concomitant immunomodulators compared to only 27% of the adults in ACCENT I. Recent data from the SONIC trial appear to confirm this speculation, as the 6 month rate of remission in the adults receiving both infliximab and azathioprine (57%) appears comparable to the 6 month remission rate in REACH (60%).

Conclusion: Understanding the reasons behind the observed differences in treatment responses between children and adults has implications for the treatment of patients of all ages. Children are an important model of early IBD, presenting a largely inflammatory population with little fibrosing disease or complicating social behaviors such as cigarette smoking. Adult trials with corticosteroids, thiopurines and biologics all reveal lower responses than seen in pediatric trials, until correction is made for the generally longer duration of disease characteristic of the adult populations studied, and the effect of concomitant therapies. As a much higher proportion of children than adults receive potent immunomodulators early in their course, the pediatric experience lends weight to the argument that some form of “top-down” therapy offers the best option to maximize remission rates in all patients with IBD.
State-of-the-Art Lecture III

After TNF: Next generation biologics

Daniel K. Podolsky, M.D.
President, Professor of Medicine and Doris and Bryan Wildenthal Distinguished Chair in Medical Science, University of Texas Southwestern Medical Center, Dallas, Texas USA

Even as further refinements of anti-TNF continue to emerge, new biologics targeting alternative mechanisms are progressing through clinical development programs and offer the opportunity for categorically new therapeutics in the years ahead. Several of these target regulatory cytokines which occupy important nodal positions in the intricate pathways mediating immune and inflammatory injury. A number of agents which antagonize the IL-12/23 axis appear to offer promise. One targets the p40 subunit which is common to both IL-12 and IL-23 and the other (ustekimumab) is selective in recognizing only the subunit unique to IL-23. In each instance, there was significant response among patients who received active agent in clinical trials. Future clinical trials may focus on an agent which is directed to the downstream cytokine, a strategic IL-17 which has been found to be effective in preclinical murine models. The apparent efficacy of these anti-cytokine agents has served as a stimulus for development of therapeutics that inhibits the signaling pathway common to their action. Thus, a JAK3 inhibitor has already been found to have a potent activity in rheumatoid arthritis which may predict activity in inflammatory bowel disease. Finally, despite earlier disappointing results from the systemic administration of IL-10, a key down-regulatory cytokine, recent evaluation of local delivery of IL-10 to the mucosa through secretion by engineered lactobacillus suggests that this biologic which down-regulates many immune pathways may yet offer therapeutic leverage.

In addition to the focus on new biologic development on additional components of the cytokine network, the biologics target mechanisms of recruitment of various key cell populations to mucosa involved in inflammatory bowel disease. Natalizumab is already approved for clinical use and targets α4 with proven efficacy in Crohn’s disease. A more specific antibody designated finds α4β7 (also known as MAdCAM) trials has had efficacy in ulcerative colitis and probable efficacy in Crohn’s disease. Finally, an antisense oligonucleotide that selectively prevents expression of ICAM-1, another integrin involved in recruitment of varied cell populations has potential, though as yet unproven, effectiveness in patients with distal colitis.

Efforts continue to exploit increasing understanding of the mechanisms necessary for T-cell activation, and most especially co-stimulatory molecules to intervene in immune related injury. A chimerin in protein encompassing CTLA4 and an immunoglobulin tail (abatacept) has yielded promising results. Another mechanistic strategy to intervene with recruitment of key leukocytes to sites of disease activity has focused on members of the chemokine family that appear to be especially critical to the intestinal mucosa. These include CCR5 and CCR9 that appear to play a particularly critical role. Although initial development efforts for the former were
equivocal, further studies to be designed may yet provide evidence of efficacy. In summary, the expanding knowledge of mechanisms that contribute to the pathogenesis of inflammatory bowel diseases has yielded a wealth of new potential targets and the results of the variety of agents currently being developed offers promise for a rich mix of next generation biologics.
Session VII

Specific management issues
How do we manage vaccinations in patients with inflammatory bowel disease?

Maria Esteve
Hospital Universitari Mutua de Terrassa, Barcelona, Spain

The mortality in Inflammatory Bowel Disease (IBD) has been reported similar or slightly increased as compared to that of the general population. However, deaths related to infectious and parasitic diseases have been repeatedly reported in clinical trials, open series and registries. The IBD patients are exposed to the same infections affecting the community, added to opportunistic infectious related to the immunosuppression. Some of these infectious diseases may be prevented by the appropriate use of a vaccination program. Thus, vaccination status should be assessed at IBD diagnosis, and from time to time, and vaccination should be updated to every patient as soon as possible, since deaths due to preventable diseases should never occur.

Present recommendations include vaccination for influenza (annually), for pneumococcal disease with the 23-valent strain (every five years), for hepatitis B virus (in patients with no detectable hepatitis B surface antibodies), combined vaccination against tetanus, diphtheria and inactivated poliomyelitis (every ten years). The role of human papillomavirus vaccine preventing cervical dysplasia and neoplasia in IBD women taking immunosuppressives are at present unknown.

In patients lacking varicella immunisation, specific vaccination should be considered. Nevertheless it should be taken into account that varicella vaccine contains live attenuated virus that cannot be administered in patients taking immunosuppressives. The same consideration should be kept in mind for patients travelling to endemic areas for yellow fever.

Finally, IBD patients on immunosuppressives may have an altered response to vaccine immunisation. Decreased response has been reported for hepatitis B and pneumococcal vaccination. In those cases, testing for serological responses to vaccine should be performed and booster doses may be required.
Non-colorectal malignancies in IBD – More than meets the eye?

Prof. Laurent Beaugerie, M.D., Ph.D.
Department of Gastroenterology, Hôpital Saint-Antoine, Paris, France

In patients with Crohn’s disease, the risk of small bowel adenocarcinoma is 20 to 40 higher than the low background risk of the general population. In the subset of patients with longstanding small bowel lesions, the absolute risk of small bowel adenocarcinoma exceeds 1 per 100 patient-years after 25 years of follow-up and becomes equivalent to the risk of colorectal cancer. Growing evidence suggests that the pathogenesis of small bowel adenocarcinoma arising in inflammatory lesions of Crohn’s disease is similar to that of colorectal cancer complicating chronic colonic inflammation (inflammation-dysplasia-cancer sequence). However, contrasting with the established endoscopic detection of colonic advanced neoplasias in patients with longstanding extensive colitis, there is no consensus at this time how to face the excess-risk of small bowel adenocarcinoma in patients at high risk. There are no specific clinical or imaging alert signs and endoscopic surveillance of the totality of the inflamed small bowel mucosa would suppose to perform repeated enteroscopies, with the potential limiting factor of stenosis. Very preliminary data suggest that chemoprevention with salicylates could be an alternative way for reducing the risk.

Data from referral centres and from the CESAME cohort suggest that intestinal lymphomas may arise in the chronically inflamed segments in patients with IBD. Regarding non-intestinal lymphoproliferative disorders (LD), it is now established that IBD patients treated with thiopurines have an excess risk of LD, exhibiting in most cases pathological features of LD associated with immunosuppression, including the frequent presence of EBV in neoplastic tissues. There is growing evidence that treatment with thiopurines is responsible by itself for this excess risk. IBD patients receiving immunomodulators, especially young men, are also at risk (0.4 for 10,000 patient-years in the CESAME study) for developing fatal early post-mononucleosis LD, like in Purtilo’s syndrome, may be in association with a background genetic susceptibility. Finally, patients receiving thiopurines and/or TNF-inhibitors are at risk for developing fatal hepatosplenic T cell lymphomas, but this risk is low (no case in the CESAME study). Whether patients receiving a monotherapy with methotrexate and/or TNF inhibitors are at increased risk of LD is not known.

Concordant data suggest that women receiving immunosuppressive therapy are at increased risk for developing uterine cervix dysplasia and require closer surveillance. But it is not established whether the risk of uterine cervix cancer and basal and squamous cell skin cancers (that may be associated with chronic HPV infection) is increased in patients receiving immunomodulators.
CRC prevention in patients with ulcerative colitis – Are pediatricians doing enough?

Matt D. Rutter
University Hospital of North Tees, Hardwick, Stockton-on-Tees, UK

There is an increased risk of colorectal cancer in both ulcerative colitis & Crohn’s colitis. Sadly, when cancers do occur, they tend to develop at a younger age – approximately 10 years earlier than in sporadic colorectal cancer. Suboptimal management of inflammatory bowel disease in childhood will adversely affect a patient’s lifetime risk of cancer. Therefore it is imperative to establish an individual’s risk and to optimize their treatment at an early stage, in order to minimize their future cancer risk.

Established risk factors for cancer in inflammatory bowel disease include disease extent (1), disease duration (2), family history of colorectal cancer (3) and coexistence of primary sclerosing cholangitis (4). Recently, the severity of inflammation has also been shown to be an independent risk factor (5). Whether early age of onset of colitis is an independent risk factor for cancer is controversial: some studies suggest it is (1), others do not (6). Potential confounders include the fact that patients who develop their inflammatory bowel disease in childhood tend to have more severe disease, and that younger patients have more potential life years ahead of them in which to develop cancer.

Recent studies have raised the possibility of chemoprevention in colitis-associated cancer, particularly with 5-ASA drugs, which may have direct anti-neoplastic effects beyond their anti-inflammatory properties (7). Establishing patients on appropriate drugs is important not just for disease control, but for cancer prevention as well.

My talk will review the current literature on colitic cancer risk and provide the audience with a practical guide on how to minimize the lifetime cancer risk of a young patient with inflammatory bowel disease.

References:


Transition from pediatric to adult health care

Johanna C. Escher, M.D., Ph.D.
ErasmusMC-Sophia Children’s Hospital, Rotterdam, The Netherlands

Until the age of 16 or 18, it is the pediatric gastroenterologist who will take care of children and adolescents with inflammatory bowel disease (IBD). The two unique aspects of pediatric IBD, growth and pubertal development are closely monitored by the pediatric gastroenterologist. Parents are often closely involved in decision making, endoscopy is performed under general anaesthesia and adolescents with this disease are used to getting ample attention from their doctor and nursing staff. All this changes after a patient moves to the adult department at the age between 16 and 18.

The GI specialist has many more patients and a clear focus on long-term side effects of medication, risk of malignity, and concomitant need for regular endoscopic surveillance (without anaesthesia), while the presence of parents is often felt as bothersome. Transition is the process where a patient is moving from pediatric health care to the adult caregivers, and transfer is the actual moment of moving. Understandably, adjustment problems sometimes arise if a patient is “handed over” to the adult GI doctor by abrupt transfer. A transitional outpatient clinic (TC), where adolescent IBD patients are seen by both pediatric and adult health care givers, is the ideal setting to overcome these differences. One goal of the TC is to increase the adolescent’s knowledge of his/her disease, as this will encourage independence from the parents. Another goal of the TC is to coach the adolescent towards a higher level of self-efficacy and thereby readiness for transfer. A key figure in the transition process is a IBD-specialised nurse, to coordinate the outpatient clinic, be available for patients and parents by mobile phone and email and to detect and discuss specific age-related issues with the adolescent patients.

In the ErasmusMC-Sophia, we have started a TC in 2006 for IBD patients between age 14 and 18 years. The TC is located in the adult department, and patients are seen together by both the pediatric and the adult gastroenterologist at first visit, and once yearly thereafter. At all other visits (at least 4 per year), the pediatric gastroenterologist sees the patients alone. In addition to this, the IBD nurse has scheduled appointments with all patients.

In a recent pilot study, we tested a self-efficacy questionnaire among 50 patients (mean age 15.6 years) and a mirror-version in 40 parents. Self-efficacy is a person’s belief in his/her capability to organize and execute actions required to deal with prospective situations. For example, if a patient is convinced he capable of talking to his doctor about his disease, self-efficacy is high in this matter. The items on the self-efficacy questionnaire showed good to excellent internal consistency, as demonstrated by Cronbach’s alphas of 0.85, 0.88 and 0.92 for questions relating to independent behavior during outpatient clinic visit, self-efficacy in treatment, and ability to discuss the disease in social environment, respectively.

When patients, parents and doctors were asked to score general self-efficacy on a visual analogue scale (0 to 100%), no significant differences were found: a mean
score of 66%, 71%, and 66% was given by patients, parents, and doctors, respectively.

Good correlation was found between both the number of visits to the IBD transition clinic and the age of the patient and readiness of the adolescent (r = 0.37; p = 0.02, and r = 0.45; p = 0.005, respectively) for transition. Gender differences were not seen, except for knowledge about disease, which was better in boys.

These results suggest that the self-efficacy questionnaire is a new and valuable tool that deserves further validation by assessment of quality and efficacy of IBD transition programs. Second, the results indicate that our IBD transition program is effective in increasing readiness for transfer to the adult caregivers in adolescent IBD patients.
Session VIII

Are we approaching solutions for unresolved problems?
Fistula treatment: The unresolved challenge

Pierre Michetti, M.D.
Division of Gastroenterology and Hepatology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

Fistulas are common complications in Crohn's disease, as their cumulative prevalence reaches two third of the patients on the long term. Fistulas worsen the overall patient prognosis, with permanent sphincter and perineal tissue destruction as well as professional and personal disabilities. The importance of healing these fistulas has been less well appreciated than mucosal healing for luminal disease. Management should not be left to any specialty alone, but requires an optimal combination of surgery, infection control, and immunosuppression. Outcome of therapy beyond fistula drainage is unclear and the means of assessing healing over a long time period poorly characterized. Recent studies suggested that a substantial proportion of patients can achieve fistula healing with surgical and medical therapies. However, studies that measure the benefit of integrated approaches, of early intervention and of precise healing assessment are still missing. Such information is particularly needed in this subset of sick patients that undergo substantial physical and emotional distress because of pain, discharge, incontinence, perineal and genital disfigurement. The advent of adequate pelvic imaging, improved surgical outcomes, and potent biological therapies make it timely to develop best-management strategies and appropriateness of care criteria.
Drug monitoring in IBD: Helpful or dispensable?

Tony Bruns and Andreas Stallmach
Klinik für Innere Medizin II, Universitätssklinikum Jena, Germany

Lately, conventional immunosuppressants have not received the same amount of attention as biological drugs in inflammatory bowel disease (IBD). But, because of their efficacy, safety profile, and relatively low cost they remain the backbone of IBD therapy.

The thiopurine drugs azathioprine (AZA) and 6-mercaptopurine (6-MP) are a well-established, effective treatment of Crohn's disease (CD) and of ulcerative colitis (UC). Both AZA and 6-MP are pro-drugs that undergo extensive metabolism: mercaptopurine is metabolized by thiopurine S-methyltransferase (TPMT), as well as by the hypoxanthine phosphoribosyltransferase (HPRT), the xanthine oxidase (XOD), and the inosine triphosphate pyrophosphatase (ITPase). Thiopurine-related adverse drug reactions are frequent, ranging from 5% up to 40%, in a dose-dependent as well as in a dose-independent manner. Pharmacogenetically guided dosing and metabolite monitoring have therefore been investigated for optimization of individual therapy. Although 23 genetic variants of TPMT have been described, approximately 80% of patients present with a normal TPMT activity. Individuals with a low enzyme activity (10% of patients) or a loss of function (0.45%) are at a high risk of developing severe haematotoxicity due to accumulation of 6-thioguanine nucleotides (6-TGN) and methylated metabolites if standard dosing is performed. Based on cost-benefit analyses, assessment of TPMT enzyme activity is recommended prior to thiopurine therapy in patients with IBD. However, a normal TPMT activity does not exclude the occurrence of a severe haematotoxicity. Furthermore, polymorphisms in ITPAse may predict AZA-intolerance, such as flu-like symptoms, rash, or pancreatitis.

A strong positive correlation between clinical response and high 6-TGN levels (threshold: 230–260 pmol/8 x 10^6 red blood cells) has been shown by a meta-analysis of 12 studies (OR 3.3). At a standard dose of 2 mg/kg AZA patients with a reduced TPMT activity (threshold: 35 pmol/h/mg/Hb) were more likely to achieve clinical response. Remarkably, the use of standard doses regimens with 6-MP (≥ 1 mg/kg) achieves sufficient 6-TGN levels in only 37% of treated patients. However, at present therapeutic drug monitoring of 6-TGN levels is only recommended to estimate patients’ adherence and as a guide to dose escalation in non-responders.

The application of the folate-analogue methotrexate (MTX) to achieve and maintain remission in IBD is complicated by its unpredictable efficacy and toxicity. Serum MTX levels are of no diagnostic value because of its serum half-time of 5-8 hours. MTX is actively transported into cells and polyglutamated by the enzyme folyl polyglutamate synthase (FPGS). In rheumatoid arthritis (RA) intracellular levels of MTX polyglutamates (MTX-PG) in red blood cells (RBC) and polymorphonuclear cells have been shown to correlate with clinical efficacy. Interestingly, a pilot study of MTX-PG levels in patients with Crohn’s disease demonstrated a correlation of higher MTX-PG4/5 levels with a worse disease activity and more frequent adverse effects. Furthermore, numerous variants in MTX transporter genes, in the folate metabolism
pathway, and the adenosine pathway have been reported to be associated with MTX efficacy and toxicity in RA. Drug monitoring in MTX therapy for IBD is not recommended because of a lack of valid data in IBD, the lack of standardized methods, and its high costs. In clinical practice toxicity monitoring is performed by surveillance of pancytopenia and hepatotoxicity.

The calcineurin inhibitors Cyclosporine (CsA) and tacrolimus (FK506) are effective therapeutic options in selected patients with severe UC. Calcineurin inhibitor therapy requires therapeutic monitoring because of highly inter- and intraindividually variable pharmacokinetics and a narrow therapeutic range. CsA and FK506 metabolisms are mainly controlled by the cytochrome P-450 (CYP) isoenzymes 3A4/3A5 and the multidrug resistance-1 (MDR-1) p-glycoprotein, which underlie a variety of gene polymorphisms. Continuous CsA application of 2 mg/kg/d is as efficacious in severe UC as doses of 4 mg/kg, results in lower whole blood levels (230 instead of 300–400 ng/ml), and is potentially less toxic. Especially parenteral application requires frequent monitoring of drug levels, liver function, and creatinine, since it is frequently associated with adverse events although the majority of these are minor and respond to dose adjustment. Besides dose-dependent toxicity, a dose-dependent efficacy has been described for tacrolimus in a controlled trial in chronic active UC patients: Whereas 38% clinically improved at through levels of 5–10 ng/ml whole blood, the improvement rate was 68% at levels of 10–15 ng/ml. Although not all severe adverse events can be clearly attributed to CsA or tacrolimus use alone, its high incidence suggests that vigorous monitoring by experienced clinicians at tertiary care centers may be required.
Growth retardation in early onset IBD: Should we monitor and treat these patients differently?

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

Unique to pediatric patients with IBD is the potential for growth impairment as a complication of the disease and/or its treatment. This is particularly true for Crohn disease (CD), where linear growth often slows prior to recognition of disease. Prevention and management of impaired growth require an understanding of its etiology.

Pathophysiology of growth impairment
Chronic undernutrition (related primarily to inadequate intake) and the effects of pro-inflammatory cytokines released from inflamed intestine are the two major and interrelated factors contributing to growth delay in CD. They do so via interference with the growth hormone (GH) – insulin growth factor 1 (IGF-1) axis, and additionally, in the case of cytokines, via direct effects on growing bones. Inflammatory mediators, moreover, potentiate the puberty-delaying effects of undernutrition via alterations in gonadotropin releasing hormone secretion patterns. Injudicious use of chronic corticosteroid therapy compounds the disease-related causes of growth impairment in CD, creating a state of functional GH deficiency.

There are clearly genetic influences on stature of all children. Whether polymorphisms in IBD susceptibility genes or common polymorphisms, which alter cytokine expression, influence the effects of IBD on growth has been explored but is yet to be conclusively demonstrated.

Monitoring of growth
An appreciation of normal growth is a pre-requisite for accurate recognition of impaired growth. At the time of diagnosis earlier (pre-illness) standard deviation scores (SDS) for height should be obtained and compared with height SDS at diagnosis, so that the impact of disease on growth can be fully appreciated. The greater the deficit prior to recognition of IBD, the greater is the demand for catch-up growth. Following diagnosis, height velocity should be regularly monitored and its adequacy for age and pubertal stage assessed. Restoration and maintenance of a child’s pre-illness growth pattern indicate success of therapy. Timely identification of impaired growth allows adjustment of therapy before the deficit becomes greater.

Management of growth impairment
In the management or prevention of growth impairment attention needs to focus on treatment of inflammatory disease using the most appropriate pharmacologic, nutritional or surgical intervention. Current treatment regimens limit use of corticosteroids, via optimization of immunomodulatory drugs, use of enteral nutrition in Crohn disease, and, if necessary, surgery for ulcerative colitis and for intestinal complications of localized Crohn disease. Biologic agents with the potential for mucosal healing hold promise of growth enhancement even among patients, whose
growth with previously available therapies remained compromised. For all therapies, there is a window of opportunity, which must be taken advantage of before puberty is too advanced.
Prebiotics, probiotics and helminths: The “natural” solution?

Francisco Guarner
Digestive System Research Unit, University Hospital Vall d’Hebron, Barcelona, Spain

The precise aetiologies of the chronic inflammatory bowel diseases remain to be elucidated and therefore, the available medical therapies can only control up to some extent the eruptions of disease activity, but fail completely regarding to the eradication or permanent cure of such diseases. However, the pathophysiological mechanisms that generate chronic inflammatory lesions in IBD have been unveiled at least in part. Abnormal communication between gut microbial communities and the mucosal immune system is being incriminated as the core defect leading to intestinal injury in genetically susceptible individuals. Currently, the most widely accepted hypothesis argues that altered composition of gut microbiota and/or deranged epithelial barrier function elicit pathologic responses from the mucosal immune system.

Experimental evidence indicates that induction and regulation of the immune system occurs primarily in gut-associated lymphoid tissues and the gut-draining mesenteric lymph nodes. The gut is the major site for induction of regulatory T cells, which secrete immunoregulatory cytokines such as IL-10 and TGF-beta and can regulate both Th1 and Th2 responses. Recent findings suggest that some gut commensals, including lactobacilli, bifidobacteria and helminths, play a major role in the induction of regulatory T cells in gut lymphoid follicles. Such T-cell mediated regulatory pathways are essential homeostatic mechanisms by which the host can tolerate the massive burden of innocuous antigens within the gut without responding through inflammation.

Prebiotics, probiotics and helminths can be used to influence the composition of gut microbiota, their metabolic activities and their interactions with the mucosal immune system. In vitro and animal studies have shown that such interventions are able to increase production of immune-regulatory cytokines by Peyer’s patch lymphocytes and increase mucosal secretion of IgA.

The mechanistic studies suggest a role of prebiotics, probiotics or helminths in the prevention of immune-inflammatory disorders. In recent years, the therapeutic manipulation of gut microecology has attracted high expectation as a strategic area for the control and prevention of IBD. The evidence for the use of probiotics or prebiotics is strongest in the case of pouchitis. In addition, one probiotic strain appears to be equivalent to mesalazine in maintaining remission of ulcerative colitis. However, studies of probiotics in Crohn’s disease have been disappointing, and the Cochrane systematic review concluded that currently there is no evidence to suggest that probiotics are beneficial for Crohn’s disease. Further research is needed to optimize the use of probiotics or prebiotics for these indications.
List of Speakers, Moderators and Scientific Organizers

Prof. Dr. S. Bar-Meir  
Chaim Sheba Medical Center  
Department of Gastroenterology  
2 Sheba Road  
52 621 Tel Hashomer  
Israel

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

D.G. Binion, M.D.  
Associate Professor of Medicine  
Division of Gastroenterology, Hepatology and Nutrition  
University of Pittsburgh Medical Center  
Presbyterian Hospital  
University of Pittsburgh School of Medicine  
Mezzanine Level – C Wing  
200 Lothrop Street  
Pittsburgh, PA 15216  
USA

Prof. Dr. C.P. Braegger  
Universität Zürich  
Kinderspital  
Gastroenterologie und Ernährung  
Steinwiesstr. 75  
8032 Zürich  
Switzerland

Prof. Dr. S. Cucchiara  
Università di Roma  
Policlinico Umberto I  
Gastroenterologia Pediatrica  
Viale Regina Elena, 324  
00161 Roma  
Italy

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

V. Deretic, Ph.D.  
University of New Mexico  
School of Medicine  
Molecular Genetics & Microbiology, MSC 08 4660  
900 Camino de Salud, NE  
Albuquerque, NM 87131  
USA

Prof. Dr. A.U. Dignass  
Innere Medizin I  
Markus-Krankenhaus  
Wilhelm-Epstein-Str. 2  
60431 Frankfurt  
Germany

Dr. E. Domènech  
Hospital Universitari Germans Trias i Pujol  
Department of Gastroenterology  
Carretera del Canyet s/n  
08916 Badalona  
Spain

Dr. I. Dotan  
Tel Aviv Medical Center  
Ichilov Hospital  
Department of Gastroenterology  
6, Weizman Street  
64239 Tel Aviv  
Israel
M.C. Dubinsky, M.D.  
Assistant Prof. of Pediatrics  
Univ. of California, Los Angeles  
Cedars-Sinai Medical Center  
Pediatric IBD Center  
8635 West Third Street  
Los Angeles, CA 90048  
USA

Dr. J.C. Escher  
Erasmus Medical Center  
Laboratory of Gastroenterology & Hepatology  
Gravendijkwal 230  
3015 CE Rotterdam  
The Netherlands

Dr. M. Esteve  
Hospital Universitari  
Mutua de Terrassa  
Plaza Dr. Robert 5  
08221 Terrassa/Barcelona  
Spain

Dr. B.G. Feagan  
University of Western Ontario  
Robarts Research Institute  
LCTR  
100 Perth Drive  
London, ON N6A 5K8  
Canada

C. Fiocchi, M.D.  
Professor of Medicine  
The Cleveland Clinic Foundation  
Pathobiology / NC 20  
9500 Euclid Avenue  
Cleveland, OH 44195  
USA

Prof. Dr. M. Gassull  
Germans Trias i Pujol Foundation  
Health Sciences Research Inst.  
Carretera de Can Ruti  
Cami de les Escoles, s/n  
08916 Badalona  
Spain

Dr. F. Gomollón Garcia  
Hospital Clinico Universitario  
Losano Blesa  
Servicio de Gastroenterologia  
Avenida San Juan Bosco 15  
50009 Zaragoza  
Spain

Dr. A.M. Griffiths  
University of Toronto  
The Hospital for Sick Children  
Department of Gastroenterology  
Room 1448  
555 University Avenue  
Toronto, ON M5G 1X8  
Canada

Dr. F. Guarner  
Hospital General Vall d'Hebron  
Servicio de Patologia Digestiva  
Paseo Vall d'Hebron 119  
08035 Barcelona  
Spain

H. Herfarth, M.D.  
Associate Professor of Medicine  
University of North Carolina  
Gastroenterology & Hepatology  
4151 Bioinformatics Bldg.  
130 Mason Farm Road  
Chapel Hill, NC 27599-7080  
USA

Dr. R. Heuschkel  
University of Cambridge  
Addenbrookes Hospital  
Pediatric Gastroenterology  
Hills Road  
Cambridge, CB2 0QQ  
Great Britain

Dr. J.-P. Hugot  
Hôpital Robert Debré  
INSERM U 843  
48, bd. Sérurier  
75019 Paris  
France
J.S. Hyams, M.D.
Professor of Pediatrics
Connecticut Children's
Medical Center
Department of Gastroenterology
282 Washington Street
Hartford, CT 06106
USA

S. Kugathasan, M.D.
Associate Professor of Pediatrics
Emory University
School of Medicine
Department of Pediatrics
201 Dowman Drive
Atlanta, GA 30322
USA

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

Dr. A. Levine
E. Wolfson Medical Center
Pediatric Gastroenterology
& Nutrition
P.O. Box 5
58 100 Holon
Israel

Dr. P. Lionetti
Ospedale Pediatrico Meyer
Department of Pediatrics
Viale Pieraccini, 24
50139 Florenz
Italy

Dr. A. López San Román
Hospital Universitario
Ramon y Cajal
Servicio de Gastroenterologia
Planta-1, izq.
Carretera Colmenar KM 9,100
28034 Madrid
Spain

Dr. E. Louis
C.H.U. Sart Tilman
Gastro-enterologie
4000 Liège
Belgium

J.F. Markowitz, M.D.
Schneider Children's Hospital
Pediatric Gastroenterology
269-01 76th Avenue
New Hyde Park, NY 11040
USA

Prof. Dr. P. Michetti
C.H.U.V.
Département de Médecine Interne
Division de la Gastroentérologie
Rue du Bugnon 46
1011 Lausanne
Switzerland

Dr. V. Motilva
Universidad de Sevilla
Faculty of Pharmacy
Laboratory of Pharmacology
Avda. Dr. Fedrían, s/n
41009 Sevilla
Spain

Dr. F. Parente
A. Manzoni Hospital
Gastroenterology Unit
Via dell’Eremo 9-11
22040 Lecco
Italy

D.K. Podolsky, M.D.
Professor of Medicine
University of Texas
Southwestern Medical Center
5323 Harry Hines Blvd.
Dallas, TX 75390-9046
USA
Dr. C.J. van der Woude
Erasmus Medical Center
Afd. Gastroenterologie
Dr. Molewaterplein 40
3015 GD Rotterdam
The Netherlands

Prof. Dr. M. Zeitz
Gastroenterologie
Charité – Universitätsmedizin
Campus Benjamin Franklin (CBF)
Hindenburgdamm 30
12203 Berlin
Germany
POSTER ABSTRACTS

Poster Numbers 1 – 84

Author Index to Poster Abstracts
The effect of infliximab treatment on angiogenic factors levels in patients with inflammatory bowel disease

A. Algaba¹, P.M. Linares², I. Domínguez², I. De Pousa², F. Bermejo¹, J.P. Gisbert², P. Nos³, J.L. Rodríguez¹

Department of Gastroenterology; ¹Hospital Universitario de Fuenlabrada, Madrid; ²Hospital Universitario de La Princesa, Madrid; ³Hospital La Fe, Valencia, Spain

Introduction: Infliximab (IFX) is a chimeric monoclonal antibody against TNFα effective in the treatment of Inflammatory Bowel Disease (IBD). Effectiveness of this drug could be related to the modification of different angiogenic proteins, such as some members of Vascular Endothelial Growth Factor gene family (VEGF and PIGF), angiopoietins (Ang-1 and Ang-2) and their receptor (Tie-2). Different studies reveal an increase of VEGF serum concentrations in patients with Crohn’s Disease (CD) in comparison with healthy controls. There is only a survey in which a decrement of the VEGF serum concentrations has been observed in the patients with CD after IFX infusion. Our aim was to compare the concentrations of these angiogenic proteins in patients with IBD and healthy controls and to analyze their modifications during the treatment with IFX.

Methods: Prospective and case-control study in 30 healthy controls and 12 patients with IBD that initiate treatment with IFX in induction + maintenance therapy. One serum sample was obtained from each control and 4 from each patient with IBD coinciding with the previous moments to the first 4 doses of IFX (week 0, 2, 6, and 14). VEGF, PIGF, Ang1, Ang2 and Tie2 serum concentrations were determined by ELISA.

Results: Mean age in controls was 43 ± 13 years, 50% men. Of the 12 patients with IBD, 11 were diagnosed as having CD and 1 had Ulcerative Colitis; mean age in this group was 35.4 ± 8 years, 75% women, 50% smokers and 50% in concomitant treatment with corticoids and azathioprine. In all cases there was response to IFX treatment (CDAI/Truelove-Witts). Patients with IBD had significantly higher concentrations of Ang-2 (p = 0.001) and their receptor, Tie-2 (p = 0.000) than controls. No significant differences were found for the rest of proteins. In patients with IBD a tendency to lower values of Ang-1 than those of the controls was observed. Concentrations of VEGF, PIGF, Ang1, Ang2 and Tie2, were unchanged during treatment with IFX.

<table>
<thead>
<tr>
<th></th>
<th>VEGF (pg/ml)</th>
<th>PIGF (ng/ml)</th>
<th>Ang-1 (ng/ml)</th>
<th>Ang-2 (ng/ml)</th>
<th>Tie-2 (ng/ml)</th>
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<tr>
<td>Healthy Controls</td>
<td>335 ± 118</td>
<td>23 ± 9</td>
<td>67 ± 23</td>
<td>3.9 ± 2.0</td>
<td>22 ± 7</td>
</tr>
<tr>
<td>Pre treatment</td>
<td>333 ± 206</td>
<td>21 ± 10</td>
<td>56 ± 17</td>
<td>8.7 ± 5.6*</td>
<td>80 ± 46*</td>
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<tr>
<td>Week 2</td>
<td>231 ± 159</td>
<td>19 ± 7</td>
<td>55 ± 19</td>
<td>8.1 ± 6.5</td>
<td>73 ± 47</td>
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<tr>
<td>Week 6</td>
<td>284 ± 206</td>
<td>17 ± 6</td>
<td>49 ± 19</td>
<td>8.0 ± 4.7</td>
<td>74 ± 47</td>
</tr>
<tr>
<td>Week 14</td>
<td>321 ± 221</td>
<td>18 ± 6</td>
<td>45 ± 17*</td>
<td>8.1 ± 4.4</td>
<td>70 ± 41</td>
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</table>

* Significant values (p < 0.05) respect to healthy controls.
Discussion/Conclusion:
1. There are significant differences of Ang2 and Tie2 serum concentrations between patients with IBD and healthy controls.
2. Effectiveness of the treatment with IFX does not seem to be related to modifications in the concentrations of the angiogenic factors, VEGF, PIGF, Ang-1, Ang2 and Tie2, although a larger sample size might be required to confirm it.
Hepatitis B status and flare in Asian patients with inflammatory bowel disease receiving immunosuppression therapy

V.J. Appleby, P. Southern, J. Healey, D. Patterson, S. Moreea
Bradford Hospitals Foundation Trust, Duckworth Lane, Bradford BD9 6RJ, UK

Background: Bradford has a significant ethnic minority population originating from South Asia where the prevalence of Hepatitis B (HBV) may be 3–4%. It is recognised that HBV can flare during immunosuppressive therapy but data in patients with IBD is sparse.

Aims: To establish the incidence of HBV flare in our Asian IBD patients treated with immunomodulators (azathioprine, methotrexate, 6 mercaptopurine [6MP], infliximab). Secondary outcomes are analysis of characteristics of our Asian patients with IBD, HBV prevalence and outcome of HBV flare.

Methods: Our IBD database and the hospital’s computerised results service were analysed to obtain the following data: demographics, ethnicity, immunosuppression treatment, ALT levels and hepatitis B serology/virology.

Results: There were 1243 patients on the IBD database: 603 (48.5%) males (M) and 639 (51.5%) females (F). 290 patients (23%) were of Asian origin – 167 M, 123 F. 35 (22 F, 13 M) Asians (12%) had a HBsAg test and 2 patients (2 M, 0 F) were HBV positive, prevalence rate 5.7%. There were 58 Asians on immunosuppression therapy (53 on azathioprine, 5 6MP) – this represented 20% of all Asians and 4.7% of the total population. 26/58 (50%) had an ALT flare. 6 of the 23 patients (23%, 4 M, 2 F) were tested for HBV and 1 male patient was found to have HBV (3.8% of patients with an ALT rise), This patient was eAg negative with viral breakthrough and was treated successfully with Lamivudine.

Discussion: The prevalence of IBD in Asians (23%) reflects the ethnic mix of the region. Our figures suggest a HBV prevalence rate of 5.7% in the local Asian population with IBD. This work lends further weight to the calls to screen patients for viral hepatitis prior to initiation of immunomodulator therapy.
The behavior of ulcerative colitis (UC) in elderly patients

A. Atanassova, I. Kotzev, B. Manevska*
Department of Gastroenterology, *Department of Pathology, Medical University of Varna, Bulgaria

Introduction: The aim of the current study was to evaluate the behavior of UC in elderly patients.

Methods: From 2000 to 2007 forty nine elderly patients with UC aged from 60 to 79 at the diagnosis from total number of 528 UC patients were investigated. Clinical, endoscopical, morphological, ultrasonnographical, biochemical data were analyzed.

Results: The age of the diagnosis was from 60–69 year – 29/49 pts; 70–79 year in 20/49 pts. The disease extent at the diagnosis was proctitis (E1) – 6/49 pts, left-sided colitis (E2) – 20/49 pts, extensive colitis (E3) – 23/49 pts, post inflammatory (pseudo) polyps at the diagnosis – 17/49 pts. Typical manifestations were bleeding 47/49 pts, abdominal pain 40/49 pts, diarrhea 36/49 pts, weight loss 42/49 pts, hypochromic anemia 43/49 pts. Forty UC patients had mild (S1) disease with intermittent symptoms and the relapses in this group were one per year and all patients responded to the treatment. Nine patients (all with E3 and post inflammatory polyps) presented more than two relapses per year and the UC was moderate (S2).

Discussion/Conclusion: Most elderly UC patients had mild (S1) disease with intermittent symptoms and well responded to the therapy. To evaluate if the real behavior of UC elderly patients are differed from the average UC patients, we need more studies.
Role of upper GI endoscopy in the initial diagnosis of children with IBD

C. Banciu*, I. Simedrea**, Loredana Marian*, I. Romosan*
*IV. Department of Internal Medicine, **Department of Pediatric Gastroenterology, University of Medicine and Pharmacy, Timisoara, Romania

Introduction: Initial differentiation between Crohn’s disease (CD), ulcerative colitis (UC) and indeterminate colitis (IC) in children can be difficult. Previous studies suggest that esophagogastrroduodenoscopy (EGD) and biopsy prelevation are important in the initial diagnosis of IBD.

Aims: This prospective study wants to confirm the importance of EGD in the initial diagnosis of IBD in children, comparing with other diagnostic methods, such as barium meal (BM), barium enema (BE) and colonoscopy, respectively.

Material and methods: 31 children pts with suspected IBD underwent EGD and biopsies were taken from esophagus, stomach and duodenum. They also underwent, beside laboratory tests, one of other diagnostic tools (BM, BE or colonoscopy with biopsy).

Results: In 17 children upper GI modifications were observed (ulcerations of esophagus and duodenum, cobblestoning of the duodenum, nodularity of the stomach) and CD was confirmed by histology in 15 of these pts (inflammation in two or all three regions in 11 pts and granulomas in 4 pts) and also by another from the above mentioned methods. In 2 pts with CD no histologic alterations at EGD were observed. Nine children were diagnosed with UC, from which 6 pts had upper GI changes at EGD (mild erythema of esophagus and stomach) and histology (increase of inflammatory cells in esophagus/duodenum and mild gastritis). Three pts presented IC, only one child had an erythema at EGD and mild duodenitis at histology.

Conclusions: EGD is a useful and simple procedure in detecting CD and UC in children (in our study 88% and 66% positivity, respectively) and should be used as an obligatory diagnostic method in the work-up of IBD.
Adverse effects of pharmacologic treatment in children with inflammatory bowel disease

Hospital Gregorio Marañón, Madrid, Spain

Introduction: The objective of our study was to describe the frequency of adverse effects during pharmacologic treatment in children with inflammatory bowel disease (IBD) in our hospital in the last five years.

Methods: Retrospective descriptive study including 20 patients with IBD followed in the pediatric gastroenterology service of our hospital in the last 5 years. We describe the adverse effects that appeared in some patients during IBD treatment.

Results: We found adverse reactions in 35% of followed patients. The frequency of side effects was: 2 adverse effects to 6-mercaptopurine (pancreatitis and dermatitis), 3 to mesalazine (toxic hepatitis, fotosensibility and severe acne). 2 to glucocorticoids (diabetes mellitus that requires insulin treatment and vertebral flatten due to osteoporosis).

Discussion/Conclusion: Although adverse effects to drugs are less frequent in children, these could be more severe than in adults. For this reason, this must be considered when we initiate a therapy in these patients.
Glutathione peroxidase activity in ulcerative colitis

Gulden Baskol¹, Mevlut Baskol², Fatma Dogruel², Alper Yurci², Sebnem Gursoy², Edip Torun²
¹Erciyes University School of Medicine, Department of Biochemistry, Kayseri, Turkey
²Erciyes University School of Medicine, Department of Gastroenterology, Kayseri, Turkey

Introduction: The etiology and pathogenesis of chronic inflammatory bowel diseases are still poorly understood. Recently, the role of oxidative stress and antioxidant enzymes come into prominence in the pathogenesis of ulcerative colitis. Glutathione Peroxidase (GSH-Px) (EC 1.11.1.9) enzymes belong to a family of selenoproteins whose function is to catalyze the reduction of various peroxides. There is limited data concerning about antioxidant enzyme glutathione peroxidase in ulcerative colitis. We aimed to evaluate serum GSH-Px activity as an important antioxidant in patients with ulcerative colitis.

Methods: A total of 42 patients with ulcerative colitis and 42 age-and-gender-matched healthy subjects were enrolled in the study as a control group. GSH-Px activity in serum was measured according to the method of Paglia and Valentine. Enzyme activity was determined from the oxidation of reduced NADPH in the presence of H₂O₂ used as substrate. The decrease in concentration of NADPH was monitored and recorded at 340 nm in a mixture containing reduced glutathione and glutathione reductase. Enzymes units were defined as the number of micromoles of NADPH oxidized per minute. Results were defined as U/L.

Results: Serum GSH-Px activities of the patients group were significantly higher than the control group (p < 0.032).

Discussion/Conclusion: A high level of GSH-Px, which is response against oxidative stress, indicates the increase of free radicals in ulcerative colitis. Therefore effective antioxidant therapy to inhibit oxidative stress is necessary and agents to increase antioxidant enzyme may be a therapeutic option in ulcerative colitis.
Adenosine deaminase and xanthine oxidase activities in ulcerative colitis

Mevlut Baskol2, Gulden Baskol1, Aysen Caniklioglu1, Fatma Dogruel2, Alper Yurci2, Sebnem Gursoy2, Edip Torun2
1Erciyes University School of Medicine, Department of Biochemistry, Kayseri, Turkey
2Erciyes University School of Medicine, Department of Gastroenterology, Kayseri, Turkey

Introduction: Oxidative stress is an important pathophysiological mechanism in ulcerative colitis. ADA is an enzyme catalyzing the deamination reaction from adenosine to inosine. Adenosine deaminase (ADA) and xanthine oxidase (XO) are enzymes that play a role in the metabolism of the adenine nucleotides. ADA is a regulatory enzyme in this pathway. The enzyme is widely distributed in human tissues, especially high in T lymphocytes. XO, (EC 1.2.3.2) catalyzes the conversion reactions of hypoxanthine to xanthine to uric acid, the last reactions in the purine metabolism, with by product of toxic superoxide radical (O2-). In this regard, it is a key enzyme between purine and free radical metabolism. We aimed to evaluate serum XO activity (as a generator of reactive oxygen species) and serum ADA activity (as a T lymphocytes activation marker) in patients with ulcerative colitis.

Methods: A total of 31 patients with ulcerative colitis and 20 age-and-gender-matched healthy subjects were enrolled in the study as a control group. ADA activity in serum was measured according to the method of Giusti and Galanti. Results were defined as U/mL. Serum XO activity was measured by the method of Prajda and Weber, where the activity is measured by determination of uric acid from xanthine. Results were defined as U/mL.

Results: Serum ADA and XO activities of the patients group were significantly higher than the control group (p < 0.001).

Discussion/Conclusion: ROS generated enzymatically by xanthine oxidase in the presence of purine enhanced release of ADA activity. Therefore, inhibition of both ADA and XO activities may have a role in understanding the pathogenesis of ulcerative colitis and contribute to development of new drugs.
CARD15/NOD2 gene mutations and the onset Crohn’s disease in Slovak patients

Marian Batovsky†, Ladislava Bartosova‡
†Illrd Med. Clin., Derer’s Fac. Hospital, Bratislava, Slovakia
‡Department of Human Pharmacology and Toxicology, University of Veterinary and Pharmaceutical Sciences, Brno, Czech Republic

Introduction: Interest in genetically determined etiology of Crohn’s disease (CD) has been growing particularly since the discovery of CARD15/NOD2 gene mutations, which are evidently involved in the development of the disease. Clinical gastroenterologists have focused also on the consequence of being a CARD15/NOD2 gene mutations carrier with respect to the early onset CD (under 40 years).

Methods: We evaluated the frequency of CARD15/NOD2 gene mutations in a sample of 31 CD patients with effort to confirm the assumed lower age of CD inception in carriers of this gene mutations. The PCR-RFLP method was used for detection of selected polymorphisms (R702W, G908R, 1007fs). The differences in observed onset CD were statistically analyzed by means of chi-square and Fisher’s exact test with assessment of rm quotient.

Results: CARD15/NOD2 gene mutations were observed in 16/31 of CD patients (in 4 patients two gene mutations). Early onset CD under 40 years occurred in 15/16 patients with CARD15/NOD2 gene mutations and in 12/15 patients without mutations of this gene. The link between CARD15/NOD2 gene mutations carriers and the supposedly lower age at onset CD was not confirmed (chi-square test p = 0.254, Fisher’s exact test p = 0.275, rm = 0.254).

Conclusion: The affirmation that CD often occurs under age of 40 years in patients with CARD15/NOD2 gene mutations was not confirmed in our set of patients.
What factors influence adhesion to therapy in inflammatory bowel disease?


Departments of Gastroenterology, Hospital Universitario de Fuenlabrada, *Hospital Universitario Ramón y Cajal, Madrid, Spain

Introduction: Inflammatory bowel disease (IBD) is a clinical condition associated with a high risk of deficient adhesion to therapy. Our aim was to analyze the degree of adhesion to treatment in a specialized IBD Clinic, and to study which factors could influence it.

Methods: A total of 107 consecutive patients were included during a three-month period. With previous consent and in all privacy, patients filled up an anonymous survey with demographic data, data concerning the disease and therapy, self-applied adhesion declaration and self-medication.

Results: Mean age was 41.3 ± 11 years, 60% were women. The number of years since IBD diagnosis was 8 ± 7; 64% were Crohn’s disease (71% inactive), 36% ulcerative colitis (70% inactive). A 66% was treated with aminosalicylates, 51% with immunosuppressors, 8% with glucocorticoids. A 66% needed an IBD-related hospital admission in the past, and 17% any IBD-related surgical procedure. A 69% (95% CI: 60–77%) showed some type of non-adhesion. A 66% (57–75%) acknowledged some degree of involuntary non-adhesion: either forgetting to take their dose (63%) or being careless about having taken it (27%). A 16% (9–22%) showed some kind of voluntary non-adhesion: interrupting the therapy when feeling better (13%) or when feeling worse (6%). A 25% (17–33%) forgot at least a dose a week (mean weekly number of forgotten doses 1.6), and the most frequent cause was to be away from home when they were supposed to take the medication. This was more frequent under mesalazine therapy (30%) than with azathioprine (17%) (p = n.s.). A multivariate analysis identified as risk factors for a lower adhesion the dosing in three or more times a day (OR 3; 95% CI: 1.1–8.4; p = 0.03) and feeling little informed about their disease (OR 4.9; 95% CI: 1.1-23.8; p = 0.04). On the other hand, immunomodulator therapy was a predictive factor for better adhesion (OR 0.29; 95% CI: 0.11–0.74; p = 0.01). The concordance between patient recall and clinical records was complete in 86%, whereas in 10.3% the patients did not accurately remember the dose and in 3.7% there was confusion about the drug taken. A 9% acknowledged self-medication during flares.

Discussion/Conclusion: In our setting, adhesion to therapy in IBD patients is not satisfactory. Patients treated with immunosuppressors have better adhesion. Optimizing the information on the disease and giving the medication in one or two daily doses could enhance therapeutic adhesion.
Mercaptopurine rescue after azathioprine-induced liver injury in inflammatory bowel disease

F. Bermejo¹, A. López-Sanromán², A. Algaba¹, M. Van Domselaar², J.P. Gisbert³, J.A. Carneros¹, E. Garrido², M.P. Valer¹, M. Rodríguez-Gandía², B. Piqueras¹
¹Hospital Universitario de Fuenlabrada, ²Hospital Universitario Ramón y Cajal, ³Hospital Universitario de La Princesa, Madrid, Spain

Introduction: Thiopurine immunomodulators are widely used in the management of inflammatory bowel disease (IBD). Liver toxicity arises in approximately 3% of patients, and may result in treatment discontinuation. The non-enzymatic reaction converting azathioprine (AZA) into mercaptopurine (MP) gives rise to imidazole derivatives that can be partially responsible for AZA-induced liver injury. Our objective was to describe the tolerance to MP in patients with previous AZA-related liver injury, demanding AZA discontinuation.

Methods: Retrospective description of 30 patients with IBD (14 Crohn’s, 16 ulcerative colitis), in which AZA therapy was interrupted due to the appearance of liver injury, and in which MP was started as alternative therapy, at a dose of 1–1.5 mg/kg.

Results: Mean age was 50 ± 15 yrs; 63% were male; 20% were smokers. The indication for thiopurine therapy was steroid dependence (63.3%), maintenance after cyclosporine or infliximab indicated for steroid-refractoriness (16.7%), fistulous disease (13.3%) and postsurgical prophylaxis (6.7%). Mean AZA dose was 2.2 ± 0.4 mg/kg/d. Mean time of AZA exposure when liver injury was first detected was 3 months (range 0.5–11 mo). The type of AZA-related liver injury was cytolytic in 33%, cholestatic in 40% and mixed in 27%. The mean ALT value in cytolytic injury was 175 U/mL (normal < 40); mean GGT and alkaline phosphatase levels in cholestatic injury were respectively 301 U/L (normal < 85) and 194 U/L (normal < 135). In 40% of cases, liver injury was first approached with a reduction of AZA dose, and in 50% N-acetylcysteine had been prescribed. After a mean time of 2.5 months (range 0–11), the therapy was switched to MP at a mean dose of 1.3 ± 0.3 mg/kg/d. In 86.7% of cases (95% CI: 69–96%), MP was tolerated with normalization of liver tests and without further liver injury; of these, 76.7% (95% CI: 57–90%) tolerated full MP doses, and 10% (95% CI: 2–26%) tolerated lower doses. In a further 13.3% (95% CI: 3–30%), liver injury reappeared (two cases of cholestasis and one of mixed injury), one to three months after the onset of MP exposure.

Discussion/Conclusion: The administration of MP is an excellent alternative in IBD patients with AZA-related liver injury, before thiopurine immunomodulators are definitely discarded.
Folate and B₁₂ vitamin deficiency in Crohn’s disease: Prospective controlled analysis of their prevalence and risk factors

Department of Gastroenterology, Hospital Universitario de Fuenlabrada, Madrid, Spain

Aim: Crohn’s Disease (CD) commonly involves small bowel, which is the site of vitamin B₁₂ and folic acid absorption. Our aim was to define prospectively the prevalence of B₁₂ and folate deficiency in patients with CD and to identify predictive factors associated with such abnormalities.

Methods: One-year prospective study of 98 patients with CD. Deficiency of B₁₂ and folate was defined as levels < 200 pg/ml and < 3 ng/ml, respectively. We analyzed several possible predictive factors: small bowel resection, CD location, disease activity (Harvey-Bradshaw index), duration of CD, gender, age, smoking and need for maintenance treatment. Controls were patients with a diagnosis of Ulcerative Colitis (UC) evaluated at our centre (n = 61). Patients were excluded if they were receiving supplemental B₁₂ and/or folate or they had a known cause of vitamin deficiency other than CD.

Results: Mean age was 36.6 ± 12 years, 57% female, 53% smokers. The prevalence of B₁₂ deficiency in patient with CD was 17.7% (95% CI 10.6–26.8%) compared with 3.3% (95% CI 0.4–11.5%) in patients with UC (p = 0.007). With regard to folate deficiency, the prevalence in patients with CD was 15.6% (95% CI 9–24%) compared with 4.9% (95% CI 1–13%) in control group (p = 0.004). Seventeen percent patients with B₁₂ and/or folate deficiency had macrocytic anaemia (95% CI 3.8–43%). On univariate analysis, ileal involvement (L1 or L3 Montreal’s classification, p = 0.006); CD activity (Harvey-Bradshaw index > 2, p = 0.001) and disease duration (long-standing CD, p = 0.004) were factors associated to B₁₂ vitamin deficiency. Multivariate study revealed that ileal involvement (OR 9.86; 95% CI 1.2–80.8; p = 0.003) and CD activity (OR 5.37; 95% CI 1.6–17.7; p = 0.006) were risk factors associated with deficient B₁₂ concentrations. Only CD activity was significant association with folate deficiency (OR 3.1; 95% CI 1.1–9.8; p = 0.03).

Discussion/Conclusion: A significant proportion of patients with CD suffer from B₁₂ vitamin and/or folate deficiency, and associated anaemia. These findings reinforce the attitude of monitoring these vitamins in the regular blood tests that are performed on patients. Patients with higher risk of deficiency of one or these vitamins are those with active disease, as well as those with ileal involvement (only for vitamin B₁₂ deficiency).
Infliximab versus parenteral methotrexate for maintenance and induction therapy in pediatric inflammatory bowel disease

Bettina Bidmon-Fliegenschnee¹, M.D., Barbara Raubal², M.D., Judith Pichler¹, M.D., Wolf-Dietrich Huber¹, M.D.
¹Division of Pediatric Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Medical University, Vienna, Austria
²Division of Pediatric Cardiology, Department of Pediatrics, Medical University, Vienna, Austria

Introduction: Infliximab and methotrexate are effective agents for induction and maintenance of remission in adult and pediatric Crohn’s disease patients who show intolerance or inadequate response to conventional therapy. At present no study exists that compares the efficiency and safety of methotrexate to infliximab in pediatric Crohn’s disease.

Methods: We therefore analyzed the clinical response to and safety of episodic infliximab versus parenteral methotrexate treatment in pediatric subjects with active Crohn’s disease. We reviewed a total of 32 patients of our pediatric gastroenterologic center who received infliximab infusions or subcutaneously applied methotrexate injections between 2002 and 2008. Clinical outcome, height, weight, daily steroid intake and safety data were recorded before therapy initiation, after 2–3 months and 9–12 months. Hematocrit, C-reactive protein, alpha-1-acid glycoprotein, ferritin and platelet count were used as secondary objective parameters.

Results: 14 patients with a mean age of 13.94 (SD ± 3.32) entered the infliximab treatment group. 18 patients aged 11.93 years (SD ± 3.11) were in the methotrexate treatment group. 6 patients (42.85%) responded to infliximab therapy after 2–3 months, and 5 children (35.71%) achieved full clinical remission. 2 children (11.11%) responded to subcutaneous methotrexate application after 2–3 months, 5 children (27.7%) experienced relapse and 6 (33.3%) achieved full clinical remission. 6 from 8 patients (75%) were in clinical remission after 9–12 months of infliximab treatment compared to 2 from 6 children (33.3%) in the methotrexate group. 69.14% from the initial steroid dosage could be saved in the infliximab treatment group. Steroid dosage per kg bodyweight increased at 9–12 months in the methotrexate treatment group. Body mass index increased during the whole study period in children who were treated with infliximab infusions.

Discussion/Conclusion: Our data confirm previous studies concerning the efficiency and safety of methotrexate and infliximab treatment in pediatric patients with active and therapy refractory Crohn’s disease.
Long-term budesonide treatment of collagenous colitis

O.K. Bonderup, J.B. Hansen, P.S. Teglbjaerg, J.F. Fallingborg
Department of Medicine, Randers Hospital, Randers; Department of Gastroenterology, Aalborg Hospital and Institute of Pathology, Aalborg Hospital Denmark

Introduction: Budesonide is a highly effective and a well tolerated treatment of collagenous colitis. However there is a high risk of relapse of clinical symptoms after stopping 6–8 weeks of treatment. The effect of long-term treatment and the optimal duration of treatment are not established.

Methods: The aim was to study the effect of long-term treatment of collagenous colitis with budesonide. The primary outcome was the effect of 24 weeks budesonide maintenance treatment in keeping patients in remission. Secondary outcomes were the rate of relapse and the time to relapse after stopping treatment. Patients in remission after 6 weeks treatment with budesonide 9 mg/day were randomized to maintenance treatment with budesonide 6 mg/day or placebo for 24 weeks. The patients were controlled until relapse up to 24 weeks after stopping maintenance treatment. Rate of relapse at 24 and 48 weeks among the two groups analyzed by Fischers exact test. Kaplan-Meier estimates and Mantel-Haenszel Logrank test were used for analysis for the length of time to relapse after discontinuation in the two groups.

Results: Thirty-four patients in remission after 6 weeks open treatment with budesonide 9 mg/day were randomized. Seventeen patients were randomized to maintenance treatment with budesonide 6 mg/day and 17 to placebo. Two patients (one in each group) discontinued medication due to adverse events. The numbers of patients in remission after 24 weeks were 14/17 in the budesonide group and 2/17 in the placebo group. At week forty-eighth 15/17 in the placebo group and 13/17 in the budesonide group had relapsed (NS). The median time to relapse in the budesonide group was 207 days compared to 45 days in the placebo group (p < 0.02).

Discussion/Conclusion: Budesonide is an effective for maintenance treatment of collagenous colitis. However, the risk of relapse is unchanged after stopping 24 weeks of maintenance treatment.
Idiopathic pancreatitis at or before inflammatory bowel disease is more frequent in pediatric patients

Assaf Harofeh Medical Center, Zerifin; Safra Children Hospital, Sheba Medical Center, Tel-Hashomer; Soraski Medical Center, Tel-Aviv; Hadassah Medical Center, Jerusalem; Soroka Medical Center, Beer Sheva; Bikur Holim Medical Center, Jerusalem and Wolfson Medical Center, Holon, Israel

Acute pancreatitis (AP) is a rare manifestation of inflammatory bowel disease (IBD), usually associated with the course of the disease. There are only few reports of AP presented before the diagnosis of IBD.

Aims: To characterize IBD patients where AP preceded the onset of IBD, and to compare disease presentation and prevalence between children and adults.

Patients and methods: Pediatric and adult patients, with AP as the first symptom of IBD were identified retrospectively (10 years, 6 University hospitals). We reviewed demographic, clinical and laboratory data as well as imaging methods used for diagnosis, number episodes of pancreatitis and time between onset of first episode of pancreatitis in relation to onset of IBD (weeks).

Results: AP presenting prior to IBD was found in 10/460 IBD pediatric patients (2.17%) with a mean age of 13 (range 3–19 years), compared to only 2/3500 adults (0.06%). Eight children had colonic disease (4 Crohn's colitis, and 4 UC – 3 pancolitis). Mean amylase level was 1419; range 100–1370. Three children (30%) had mild elevated transaminases. Median time between onset of first episode of pancreatitis in relation to onset of IBD was 12 weeks (range 1–156) (in adults range 24–156 weeks). Pancreatitis is most commonly presented with abdominal pain.

Conclusion: AP presenting prior to IBD is more frequent among the pediatric IBD population in comparison to adults. Both in children and adults it was more common in patients with colitis than small bowel disease suggesting that AP is an extraintestinal manifestation of IBD.
Pregnancy and IBD patients

A. Chavoushian*, H. Kadian***, Z. Spassova**, S. Stoinov, P. Penchev***
*Tokuda Hospital, Sofia, Bulgaria
**University Hospital "Sv. Iv. Rilski"
***University Hospital "Tsaritsa Ioanna"

We monitored 12 couples, where one of the spouses had IBD. The outcome of pregnancy in 10 females was 12 births – 13 babies (one mother gave birth to twins). One pregnancy was ended by spontaneous abortion in the 10th gestation week (Crohn’s disease). One pregnancy was ended by surgical operation of extrauterinal pregnancy (ulcerative colitis).

Of the nine couples with ulcerative colitis in 6 cases the UC patient was the mother and in 3 cases the patient was the father. Out of the total of 11 pregnancies one ended with surgical operation of extrauterinal pregnancy, one ended with birth of twins, 2 women gave birth twice and five women gave birth once. Nine of the women gave birth per vias naturalis and one gave birth by caesarean section.

At the time of conception the UC was in remission in 5 couples (no medication), in active stage in 6 couples, where 4 of the patients were given medication (1 with Imuran, 4 with mesalazine, 1 was without medication.

Of the 3 couples with CD, in 2 couples the patient was the father and in 1 couple the patient was the mother, who had a spontaneous abortion in the 12th week of gestation. The other two patients – one was treated with Imuran, the other one was without treatment. The pregnancies ended with birth of healthy babies per vias naturalis (full-term baby).

Our interest is focused on:
F.M.K., 28 years of age, became pregnant soon after colectomy with ileostomy due to severe persistent ulcerative colitis with 9-year period of sterility. She gave birth per vias naturalis of a full-term healthy baby.
A.S.O., 32 years of age, with severe ulcerative pancolitis, Hashimoto thyroiditis, antiphospholipid syndrome which appeared in the course of the second pregnancy with brain stroke. She gave birth of a full-term healthy baby.
I.L.L., 27 years of age, with ulcerative colitis and primary sclerosing cholangitis, she gave birth of a normal healthy baby.

Two of the babies were of fathers treated with Imuran. One of the babies grew up to be a healthy woman, now of 28 years of age, and gave birth to a healthy baby 6 months ago.

Conclusions:
1. Long-term monitoring is required (decades!) in order to evaluate the effect of medication on the development of the fetus.
2. Research and evidence based supportive information is of vital importance for a well-informed decision of the mother-to-be in respect of her pregnancy.
Biological agents in Greek children with inflammatory bowel disease

1st Department of Paediatrics, University of Athens, Greece

Background: The availability of biological agents has contributed significantly in achieving and retaining remission in adults as well as pediatric patients with inflammatory bowel disease (IBD) during the last 10 years.

Purpose: This study aimed at recording and evaluating pediatric data regarding the efficacy and side effects of infliximab which has been the anti-TNFα agent mainly used in our Department since 2003.

Patients and methods: All IBD patients who had received one or more infusions of infliximab until 30/09/2008 were retrospectively included. Clinical and laboratory data for each patient were extracted out of Hospital records which are updated in a standard basis.

Results: A total of 28 patients (43% males) were included and the majority (71%) had Crohn’s disease. Non-responsiveness to previous treatments was the only reason for initiating anti-TNFα therapy. Mean age at the first infusion was 10.9 ± 2.9 (range: 3.9–15.4) while the mean disease duration at the introduction of infliximab was 2.5 ± 2.6 years. The number of infusions per patient ranged from 1–19 (median: 7). Previous treatments included steroids (100% of patients), azathioprine or 6-MP (96.5%), cyclosporine (28.6%) and methotrexate (7.1%). Rate of remission for patients having received > 3 infusions was 80%. Administration of infliximab was discontinued in 9 out of 28 patients (32%) mainly due to adverse reactions (4 out of 9) and lack of maintaining remission (4 out of 9).

Conclusions: Infliximab is the ultimate therapeutic option for IBD patients unresponsive to standard treatment in our department. Results, so far, have been satisfactory although discontinuation due to allergic reactions has proven to be an important issue. Long-term follow up will allow safer conclusions regarding efficacy and safety of infliximab in pediatric IBD patients.
Comparative intestinal anti-inflammatory effects of different probiotics in the TNBS model of rat colitis

M. Comalada¹, B. Arribas¹, E. Bailón¹, D. Camuesco¹, A. Zarzuelo¹, L. Perán¹, M.E. Rodríguez-Cabezas¹, A. Nieto², A. Concha², J. Gálvez¹
¹CIBER-EHD, Department of Pharmacology, University of Granada, Granada, Spain; ²CIBER-EHD, Department of Pathology, Hospital Universitario “Virgen de las Nieves”, Granada, Spain

Introduction: The use of probiotics in the treatment of IBD may be of special interest in children and elderly since they are considered as an effective and safe therapy. However, several studies have revealed that not all probiotics show the same properties as intestinal anti-inflammatory agents. In consequence, it is interesting to compare different probiotics in the same experimental model. This study assays the preventative effects of different probiotics (Lactobacillus salivarius ssp. salivarius, L. reuteri, L. fermentum, Bifidobacterium longum and B. bifidum) in the trinitrobenzenesulphonic acid (TNBS) model of rat colitis.

Methods: Rats were randomly assigned to seven groups (n = 10); two of them (non-colitic and control groups) did not receive probiotic treatment and the rest were administered each probiotic orally (5 x 10⁸ CFU suspended in 0.5 mL of skimmed milk), daily for three weeks. Two weeks after starting the treatment, colitis was induced by intracolonic administration of TNBS (10 mg). All rats were sacrificed one week after colitis induction, and the colonic damage was evaluated histologically and biochemically: colonic myeloperoxidase (MPO) activity and TNFα.

Results: All probiotics assayed showed intestinal anti-inflammatory effects. Macroscopically they significantly reduced the extension of the colonic damaged area and the weight/length ratio, except of B. longum. These beneficial effects were confirmed microscopically. Biochemically, all probiotics decreased MPO activity, thus revealing a reduction of the neutrophil infiltration in the inflamed tissue. When colonic TNFα production was evaluated, all probiotics, except B. longum were able to significantly decrease the production of this cytokine in comparison with control group, showing the highest efficacy L. salivarius ssp salivarius.

Discussion/Conclusion: All the probiotics assayed have shown intestinal anti-inflammatory activity in the TNBS model of rat colitis, although each probiotic shows their own anti-inflammatory profile. Among them, the three lactobacilli have shown to ameliorate all the inflammatory parameters studied.
Oral tacrolimus in steroid-refractory pediatric ulcerative colitis

D. Comito, A. Famiani, V. Raffa, P. Rossi, R. Gallizzi, C. Romano
Department of Pediatrics, University of Messina, Italy

Introduction: Cyclosporine and tacrolimus are used in the treatment of solid organ transplantation and prophylaxis of organ rejection in allogenic transplantation. Bousvaros et al has reported the results obtained in a multicentre trial with oral tacrolimus in moderate-severe pediatric ulcerative colitis (UC) and Crohn's disease (CD) not responding to conventional therapy.

Aim: Evaluate the efficacy of oral tacrolimus in moderate-severe steroid-refractory UC.

Methods: It is enrolled 6 patients (pts, 6–10 yrs old) with a new onset of moderate-severe UC (PUCAI score at admission 60 ± 12). Each patient had failed induction-therapy with steroids (2 mg/k/d). Mayo Score was 2–3 at admission and pancolitis extension (Montreal: E3) was present in all patients. Was started oral tacrolimus 0.1 mg/kg/dose twice daily with plasma levels of 7–10 ng/ml. All patients received prophylaxis for Pneumocystis carinii pneumonia with trimethoprim-sulfamethoxazole. Patients who responded after 2 weeks with improvement of the PUCAI score, continued to receive tacrolimus for 3 months and if clinical remission was obtained, they were shifted to azathioprine for maintaining remission.

Results: A significant clinical (PUCAI < 10) and Mayo score (0–1) improvement was obtained in 5/6 patients (90%) after 2 weeks. No significative adverse effects were reported.

Discussion/Conclusion: Our findings demonstrate that low-dose oral tacrolimus can be considered as an alternative therapy to infliximab or intravenous cyclosporine in moderate steroid refractory UC. It could be considered a bridge-therapy for inducing short-medium term remission and to begin AZA. Randomized and controlled trials are still necessary to confirm these results.
Lymphoproliferative disorders diagnosed in an inflammatory bowel disease unit

Manuel Van Domselaar, Antonio López San Román, Elena Garrido
Gastroenterology Department, Hospital Ramón y Cajal, Madrid, Spain

Introduction: The relationship between inflammatory bowel disease (IBD) and lymphoproliferative disorders (LD) has been previously reported. Our aims were to describe the clinical characteristics and incidence of LD in an IBD unit.

Methods: All the clinical records of patients with ulcerative colitis (UC) or Crohn's disease (CD) followed-up in a tertiary center were reviewed.

Results: We identified 6 cases of lymphoma in 841 IBD patients with a mean follow-up time of 8.6 years (range: 1–53). Four were males, 4 had been diagnosed with UC, 5 were B-cell non-Hodgkin lymphomas and 4 were colorectal lymphomas. Mean time from IBD to lymphoma diagnosis was 5.45 years (range: 0–20). Mean age at lymphoma diagnosis was 56.5 years (range: 41–76). Three cases were associated to Epstein-Barr virus (EBV) infection. Four patients had been treated with thiopurines, and 3 of them also with infliximab. All the EBV-positive patients had been treated with combined treatment (biologics and thiopurines). Estimated incidence of LD was 79.2/100,000/year. After a mean follow-up of 32.3 months (range: 7–57) after the last treatment for the LD, all patients are in remission.

Discussion/Conclusion: Our findings suggest a possible relationship between combined treatment with biologics and thiopurines and the development of EBV-associated LD. The incidence rate of LD was much higher than the expected for the general population.
Colorectal cancer incidence during 10 years surveillance among IBD patients

Vladimir Draganov, M.D.; L. Tankova, M.D. Ph.D.*; P.I. Penchev, M.D.*; C. Velikova, M.D.
National Cancer Centre, Sofia, Bulgaria
*University Hospital “Tzaritza Ioanna”, Sofia

Introduction: The colorectal cancer (CRC) incidence among IBD patients is higher than other population and depends to extent of disease, duration of disease and active inflammation. Years of continuous treatment with 5-ASA provide a protective effect against development of colorectal cancer. Number of studies have demonstrated no protective effect from 5-ASA. Risk of CRC in IBD patients with flat low-grade dysplasia (LGD) or LGD with dysplasia-associated lesion or mass (DALM) and high-grade dysplasia (HGD) remains controversial.

Methods: From 1998 to 2008 years in prospective study we evaluate 108 IBD patients – 32 Crohn’s disease (CD) patients (average duration of disease 12.3 years) and 76 ulcerative colitis (UC) patients (average duration of disease 16.8 years). We performed colonoscopy at time of diagnosis, eight years after the onset of disease and surveillance colonoscopy – every year without dysplasia and every three or six months if dysplasia was found. Patients received permanent treatment – Imuran® for CD and at least 2.0 g. 5-ASA daily for UC.

Results: 486 colonoscopies were performed to evaluate IBD patients. No dysplasia or CRC among CD patients were found. Between UC patients – 4 were with flat LGD, 3 were with DALM and 1 patient with HGD. Extension of colitis was E3 in all these patients, average duration of the disease 15.1 years in non-aggressive course. During follow up from 1.3 to 3.5 years they received maintenance treatment 3.0 g/d 5-ASA and no CRC was detected. In 3 other UC patients, we found CRC. One of them was with two synchronous cancer lesions and two more DALM lesions. The other two were with cancer lesion, several adenomas and no DALM. Cancer patients were with extended (E3) and aggressive disease. Duration of disease was 10.8 years and in first years they didn't receive 5-ASA treatment.

Discussion/Conclusion: Incidence of CRC in our IBD patients is lower than other published data. No progression to CRC was found in LGD and DALM lesions among patients who achieve remission lasting years. DALM lesions and HGD is not indication for proctocolectomy in non-aggressive course of disease. Treatment with 5-ASA for the time of disease provide a protective effect against development of CRC.
Oral beclomethasone dipropionate in pediatric active ulcerative colitis: A comparison trial with mesalazine

Annalisa Famiani, Claudio Romano, Donatella Comito, Paolo Rossi, Vanessa Raffa, Walter Fries*
Department of Pediatrics, University of Messina, *Department of Internal Medicine, University of Messina, Italy

Introduction: Beclomethasone dipropionate (BDP) is a glucocorticoid used for inflammatory bowel disease (IBD) in the form of gastroresistant and enteric-coated capsules. Aim of the study is to evaluate efficacy of oral BDP in inducing clinical and endoscopic remission in children with mild to moderate active ulcerative colitis (UC).

Methods: Thirty patients (pts) with mildly or moderately active UC (pancolitis or left-sided colitis), newly diagnosed or in clinical relapse, were enrolled in an open-labelled, randomized, head to head study. Group 1 (n = 15) received oral BDP (5 mg/day) for 8 weeks, followed by maintenance therapy with oral mesalazine (5-ASA); Group 2 (n = 15) received therapy with oral 5-ASA (80 mg/kg/day). Clinical and endoscopic scores were assessed at 12 weeks, together with a final clinical assessment after one year follow-up.

Results: In Group 1, 12 pts (80%) had clinical remission compared with only 5 pts (33%) of group 2 after 12 weeks treatment (p < 0.025) but the difference, statistical significant, was already present at 4 weeks (pediatric ulcerative colitis activity index, PUCAI score ≤ 10). Colonoscopy, performed at 12 weeks, showed in 11 pts from Group 1 (73%) a significantly improved score, while patients from Group 2, treated with only 5-ASA showed no significant improvement (p < 0.025). Erythrocyte sedimentation rate (ESR) was significantly reduced (p < 0.025 or less) with both treatments, whereas C-reactive protein dropped significantly (p < 0.02) only in Group 1.

Discussion/Conclusion: Oral BDP was well tolerated and significantly more effective than mesalazine in inducing clinical remission and endoscopic improvement in pediatric moderate UC.
Interest use of pelvic magnetic resonance imaging in patients with Crohn’s disease perineal fistulae

M. Fekih, S. Ouerdiane, K. Nouira, S. Matri, L. Kallel, J. Boubaker, A. Filali
La Rabta Hospital, Tunis, Tunisia

Anoperineal lesions occur in 25% of patients with Crohn's disease and are often resistant to conventional treatment including antibiotics and seton drainage. The infliximab is currently the most effective treatment for anoperineal fistulas. However, exhaustive exploration should be performed before its use to detect deep abscesses.

**Purpose:** To study the frequency of asymptomatic collections, under-diagnosed by examining, in patients with anoperineal lesions.

**Materials and methods:** This is a retrospective study including all patients with anoperineal lesions of Crohn's disease treated with infliximab with a record pre-treatment including a pelvic magnetic resonance imaging (MRI).

**Results:** We included 10 patients, 5 men and 5 women aged between 34 and 46 years. The average time of occurrence of perineal fistula from the start of the disease was 5 years (0–13 years). On perineal examination, the number of fistula ranged between 1 and 5 and there was no clinical evidence of a pelvic abscess. All patients were explored by pelvic magnetic resonance imaging. A deep abscess was diagnosed in six of the ten patients. The collection average size was 2.4 cm. All patients had a seton drainage and a control magnetic resonance imaging before starting the treatment with infliximab.

**Conclusion:** MRI should precede systematically infliximab treatment. This exam can accurately identify deep and unsuspected abscesses in order to avoid serious complications such as sepsis or gangrene of the perineum. This method seems to be efficacious and does not expose the patient to X-rays.
Epithelial barrier impairment in ulcerative colitis – Ultrastructural comparison between young and elderly

O. Fratila\textsuperscript{1}, Tiberia Ilias\textsuperscript{2}, C. Craciun\textsuperscript{3}, Gratiela Avram\textsuperscript{1}, Romeo Mihaila\textsuperscript{4}

\textsuperscript{1}University of Oradea, Romania; \textsuperscript{2}Emergency Clinical County Hospital, Oradea, Romania; \textsuperscript{3}Electron Microscopy Center, “Babes-Bolyai” University, Cluj-Napoca; \textsuperscript{4}“Lucian Blaga” University, Sibiu, Romania

\textbf{Introduction}: Several studies suggested that ulcerative colitis (UC) follows a more aggressive pattern in elderly.

\textbf{Aim}: To assess possible differences in ultrastructural changes of the colonic epithelial barrier in patients with UC in whom the diagnosis was made after the age of 60 compared to patients diagnosed before the age of 40.

\textbf{Methods}: The older group consisted of 20 patients (12 men: 8 women, aged 65 ± 3.1 years) and the younger group consisted of 19 patients (10 men: 9 women, aged 28 ± 10.9 years). Rectal biopsies were taken during endoscopy from both groups. The biopsies were contrasted with acetate-uranyl and lead-citrate and studied with a JEM-1010 electron microscope.

\textbf{Results}: In general, both groups expressed similar ultrastructural epithelial changes: rarefaction of goblet cells, depletion of microvilli, destruction of tight junctions, vacuolized cytoplasm, alterations of endoplasmic reticulum, mitochondria, Golgi complexes – resulting in a drastic decrease of mucus formation. The most important difference observed was that dysplasia (enlarged, irregularly shaped nuclei, cell stratification, enlargement of intercellular spaces, luminal surfaces of the cells frequently eroded) was more frequent in younger patients (4:1).

\textbf{Discussion/Conclusion}: In our study, the epithelial barrier in elderly didn’t show any supplementary impairment which might dictate a different course of UC, except for the aforementioned dysplasia which is probably due to longer duration of the disease in young patients. Therefore the ultrastructural insight provided by our research suggests that in elderly UC runs on a rather similar morphological pattern to that in younger patients.
The immunomodulatory properties of Escherichia coli Nissle 1917 are not restricted to the gastrointestinal tract

J. Gálvez, M. Comalada, B. Arribas, M.E. Bailón, D. Camuesco, A. Zarzuelo, P. Utrilla, M.E. Rodríguez-Cabezas
CIBER-EHD, Department of Pharmacology, University of Granada, Granada, Spain

Introduction: Probiotics may constitute an attractive alternative to standard therapy due to its reputed safety, especially in children and the elderly. *Escherichia coli* Nissle 1917 (EcN) has shown beneficial effects in ulcerative colitis. It also exerts systemic immunomodulatory properties, which may be very interesting given the high prevalence of extraintestinal diseases in IBD patients. This study investigates if EcN shows beneficial effect when an altered systemic immune response occurs.

Methods: EcN was administered to rats or mice for two weeks in two experimental models: the trinitrobenzenesulphonic acid (TNBS) model of rat colitis and the lipopolysaccharide (LPS) model of septic shock in mice. The inflammatory status was evaluated both macroscopically and biochemically one week after in the TNBS model or 24 hours after in the LPS. Splenocytes were obtained from mice and stimulated with concanavalin A or LPS to activate T or B cells to evaluate cytokine production (IL-2, IL-5 and IL-10) and IgG secretion.

Results: EcN showed anti-inflammatory effects in both models. In the TNBS model, the probiotic improved the altered histology of the intestine, and it significantly reduced colonic MPO activity (60%) and TNFα production (50%), when compared with control rats. When the probiotic was assayed in LPS model, it significantly prevented the increase in spleen weight induced by septic shock. Both lung MPO activity and colonic iNOS expression was significantly reduced with the probiotic. The increased production of IL-2 and IL-5 in spleen T-cells were inhibited in the probiotic treated mice, and it ameliorated the reduction in IL-10 induced by LPS. The probiotic promoted the downregulation of IgG release from splenocyte-derived B cells.

Discussion/Conclusion: The intestinal anti-inflammatory effects of EcN can be associated to beneficial effects on the systemic altered immune response, ameliorating the extraintestinal manifestations that may occur in IBD patients, with a special relevance in children and elderly.
Infliximab in ulcerative colitis: Concomitant cytomegalovirus infection, life’s quality, PPD positive have an influence on the treatment with infliximab?

S. Gómez Senent, L. Adán Merino, E. Martín Arranz, M.D. Martín Arranz, C. Froílán Torres, J.M. Segura Cabral
Hospital Universitario La Paz, Madrid, Spain

Aim: Results of randomized controlled trials showing efficacy of infliximab in ulcerative colitis (UC) must be confirmed in clinical practice. Our aim was to describe the patients treated with infliximab of the Hospital La Paz of Madrid, looking for clinical predictors of response.

Methods: Retrospective survey of all UC patients treated with infliximab in Hospital La Paz, Madrid followed up for at least 3 months.

Results: 15 UC patients were included (40% males, mean age 37.9 years), with a mean follow up of 18.7 months (range 3–30) and a total number of 148 infliximab infusions. Infliximab was prescribed for steroid-resistance in 46.7% of the patients, and for steroid-dependence in 53.3%. Response rate was, 80% at the 2nd week, 73.3% at the 6th week and 57% at the 8th week. 100% of the patients were treated with concomitant thiopurinic therapy. Four patients did not respond: one of them gave up the treatment in the second session, other began with adalimumab, and the third patient is being treated with adalimumab and the last one with leucocyteapheresis. 66.7% of patients were S2 in Montreal classification, 26.7% were S3 and 6.7% S1 previous of treatment with infliximab. 26.7% of patients had cytomegalovirus infection. All of them response at infliximab after treatment with gancyclovir. All patients filled up a cuestionary of life’s quality before and after induction therapy.100% had improved their life’s quality after treatment. 13.3% of the fifteen patients had PPD positive, these patients were treated with isoniazida during one month before treatment with infliximab, this treatment did not change the response rate at infliximab. Age, gender, disease duration, indication for infliximab, disease severity, C-reactive protein, smoking habit did not influence on efficacy. Extent of the disease was the only predictive factor: patients with pancolitis had better response than those left sided colitis (p = 0.02). We had not adverse events.

Conclusion: Infliximab is safe for UC. Cytomegalovirus infection doesn't get worse the response rate at infliximab. Extent of the disease was the only predictive factor for clinical response.
Ulcerative colitis associated with aphthous stomatitis

Smaranda Laura Gotia¹, Lelia Susan², Smaranda Rodica Gotia¹, Doina Verdes³
¹Department of Physiology, ²IV Department of Internal Medicine, ³Department of Cell and Molecular Biology, University of Medicine and Pharmacy "Victor Babes", Timisoara, Romania

Introduction: The aim of our study was to investigate ulcerative colitis (UC) patients with aphthous stomatitis correlated with some aspects of non-specific defence from blood and saliva.

Methods: There were examined 20 patients with UC, which presented chronic diarrhea, abdominal pain, bloating and nausea. From venous blood samples were performed: erythrocyte sedimentation rate (ESR), leucocytes count and formula, C-reactive protein (CRP). Leucocytes phagocytosis was estimated by nitroblue-tetrazolium dye reduction test (NBT%) from blood and saliva.

Results: Physical examination revealed extraintestinal manifestations in 52% of UC cases: fever, arthritis, spondilitis, and lesions on oral mucosa (aphthous stomatitis, ulcerative lesions, leukoplakia, granulomatous tongue). Accelerated ESR (35 ± 5 mm/h), elevated CRP levels (68.5 ± 2.5 mg/L) were correlated with leucocytosis (12,500 ± 720/microliter), decreased serum albumin (3.2 ± 0.2 g/dl). Phagocytic activity from blood was normal. Leukocyte number from saliva (760 ± 41.8/microliter), the viability of salivary cells (76 ± 4.17%), the phagocytic activity of salivary leukocytes were decreased (NBT = 2.6 ± 0.54%). The number of the epithelial cells was increased (1340 ± 89.4/microliter).

Discussion/Conclusion: These modifications can produce defective mucosal integrity, the decrease of local mechanisms of mucosal defence and can explain the presence and chronic evolution of ulcerative lesions in oral cavity, in UC patients.
Immune deficiency in infants’ malnutrition associated with inflammatory bowel disease

Smaranda Rodica Götia¹, Maria Cučuruz², Smaranda Laura Götia¹
¹Department of Physiology and ²Louis Turcanu Pediatric Hospital, University of Medicine and Pharmacy “Víctor Babes”, Timisoara, Romania

Introduction: Protein-energy malnutrition (PEM) is a nutrient (protein, energy) deficiency state.
The aim of our study was to investigate PEM induced by inflammatory bowel diseases (IBD) in infants correlated with immune modification.

Methods: There were investigated 10 healthy and 34 infants aged 5–15 months, diagnosed with IBD and malnutrition (PEM – 18 cases, energy malnutrition – 9 patients, and protein malnutrition – 7 cases), with decreased ponderal index, admitted in Louis Turcanu Pediatric Hospital, Timisoara. Serum immunoglobulins levels, lymphocytes subsets, and phagocytosis by nitrobluetetrazolium dye reduction assay (NBT%) were performed.

Results: Patients with PEM demonstrated elevated levels of IgG, IgM, IgA, and reduced IgD. Total T and B lymphocytes were decreased, but T helper lymphocytes were increased. NBT test (4.2 ± 0.25%) was significantly lower (p < 0.01) than the values of control group (11.5 ± 1.45%). PEM is one of the most frequent causes of secondary immune deficiency states. In the malnourished organism alterations either in cellular or humoral immune mechanisms increased the susceptibility to infections, especially diarrheal disease.

Discussion/Conclusion: PEM induced profound immunodeficiency, characterized mainly by decreased cell-mediated immunity, and non-specific immunity. Treatment and monitoring IBD evolution, refeeding such patients and the restoration of their nutritional status lead to improvement in all immune responses.
Introduction: Dietary linoleic acid, an n-6 polyunsaturated fatty acid, is metabolised to arachidonic acid, a component of colonocyte membranes. Metabolites of arachidonic acid have pro-inflammatory properties and are increased in the mucosa of patients with ulcerative colitis. The aim of this investigation was to conduct the first prospective cohort study investigating if a high dietary intake of linoleic acid increases the risk of developing incident ulcerative colitis.

Methods: Dietary data from food frequency questionnaires were available for 203,193 healthy men and women aged 30–74 years, resident in the UK, Sweden, Denmark, Germany or Italy and participating in a prospective cohort study (EPIC – European Prospective Investigation into Cancer). These participants were followed up for the diagnosis of ulcerative colitis. Each case was matched with four controls and the risk of disease calculated by quartile of intake of linoleic acid adjusted for gender, age, smoking, total energy intake and centre.

Results: A total of 126 participants developed ulcerative colitis (47% women) after a median follow-up of 4.0 years (range 1.7–11.3 years). The highest quartile of intake of linoleic acid was associated with an increased risk of ulcerative colitis (OR = 2.49, 95% CI: 1.23–5.07, p = 0.01) with a significant trend across quartiles (OR for trend = 1.32, 95% CI: 1.04–1.66, p = 0.02).

Discussion/Conclusion: The data support a role for dietary linoleic acid in the etiology of ulcerative colitis. Approximately 30% of cases could be attributed to dietary intakes higher than the lowest quartile of linoleic acid intake.
Enteral nutrition vs. corticosteroids in pediatric patients with CD – Retrospective comparison study

Iva Hojsak, Zrinjka Mišak, Slaven Abdović, Alemka Jaklin Kekez, Oleg Jadrešin, Sanja Kolaček
Referral Centre for Paediatric Gastroenterology and Nutrition, Children’s Hospital Zagreb, Kliačeva 16, Zagreb, Croatia

Introduction: There are still controversies for optimal induction remission treatment (enteral nutrition vs. corticosteroids) in patients with Crohn’s Disease (CD). The aim of this study was to investigate duration of remission (time until first relapse) in patients treated with enteral nutrition (EN) comparing to children treated with corticosteroids.

Methods: Data of all newly diagnosed CD patients (n = 47) treated in Children’s Hospital Zagreb from 1997 to 2007 were retrospectively analyzed (27 male and 20 female, age range 9–17.8 years). As a first line therapy, for remission induction, EN was introduced in 30 (63.8% of all treated patients) patients vs 16 patients (34.04%) treated primarily with corticosteroids. EN (polymeric formula) was given for 5–6 weeks. Corticosteroids were introduced in the dose 1 mg/kg for 4 weeks, and after that dose was downregulated. All patients received mesalamine or azathiprine with the aim to keep the patient in remission.

Results: From 30 patients who were treated with EN, 21 patients (70%) established remission which lasted from 4 months to 5 years (mean 17.57 months). All patients who failed EN were treated with corticosteroids. In corticosteroid group all patients established remission which lasted from 3 to 12 months (mean 6 months) (p < 0.01). There was no statistical difference between EN and corticosteroid groups regarding age at diagnosis and duration of illness, on the other hand, majority of patients treated with EN had ileal or ileocolic disease (71.4%) comparing corticosteroid group in which 81.25% had ileocolonic and 18.75% colonic disease.

Discussion/Conclusion: Our study showed that all patients with corticosteroids achieved remission comparing to 70% of patients treated with EN. Nevertheless, patients treated with EN established statistically significant longer remission than patients treated with corticosteroids. All results have to be taken with percussion, because it was retrospective study and the number of patients was rather small.
Ulcerative colitis in elderly: Epidemiological, clinical, endoscopic and immunohistochemical study in a population from Western Romania

Tiberia Ilias¹, O. Fratila², C. Craciun³, Gratiela Avram², Romeo Mihaila⁴
¹Emergency Clinical County Hospital, Oradea, Romania; ²University of Oradea, Romania; ³Electron Microscopy Center, “Babes-Bolyai” University, Cluj-Napoca
⁴“Lucian Blaga” University, Sibiu, Romania

Introduction: Previous studies suggested a more aggressive clinical behavior of ulcerative colitis (UC) in elderly and a higher risk of developing cancer.

Aim: to determine characteristics of UC in patients diagnosed after the age of 60 and to check for possible associated dysplasia.

Methods: Our study was conducted in Oradea Clinical County Hospital between 1st January 2003–31st December 2007. The epidemiological, clinical, endoscopic features of all patients with UC diagnosed after 60 years (n = 44) were compared with those diagnosed before 40 years (n = 50). Paraffin-embedded biopsies from 16 elderly and 14 young patients with longstanding UC from the aforementioned group were retrieved from the Pathology Department. Immunohistochemistry was performed with antibodies against p53 and staining was evaluated semiquantitatively with an expression of more than 20% of tumor/epithelial cell nuclei in non-tumor specimens considered positive.

Results: Sex prevalence (male/female ratio = 1/1), extent of disease, (elderly/young-proctitis in 18/19 (40.9%), left sided colitis in 20/22 (45.5%) and subtotal or pancolitis in 6/9 cases) in elderly were similar to those observed in young. No significant differences between the two groups were found concerning the severity and outcome of the initial episode. p53 immunoassay showed: in elderly 3 patients presented high grade dysplasia and 2 patients had low grade dysplasia compared to the young in which 4 patients had HGD and 5 had LGD.

Discussion/Conclusion: UC in Western-Romanian elderly runs a rather similar course to that in younger patients. The malignant potential of UC is partially confirmed by a high prevalence of p53 expression. p53 immunohistochemical documented dysplasia is higher in young people probably due to longer duration of UC.
Incidence, phenotype and surgery in pediatric inflammatory bowel disease patients: Changes over a 44-year period

C. Jacobsen¹, A. Paerregaard¹, P. Munkholm², V. Wewer¹
¹Hvidovre University Hospital, Copenhagen, Denmark
²Herlev University Hospital, Copenhagen, Denmark

Aim: To describe the development in incidence, disease localisation, disease activity and surgery in two Danish pediatric IBD population based cohorts from 1962–1987 (period I) and 1998–2006 (period II) in Copenhagen County.

Material and methods: Incident IBD patients < 15 years were included. The median background population (< 15 years) in period I was 135,235 and in period II 117,216. Incidence rates were calculated per 100,000 person-years under the age of 15. Disease localisation was classified according to the Montreal classification for UC: E1 = proctitis (disease limited to the rectum), E2 = left-sided disease (disease distal to the splenic flexure) and E3 = Extensive disease (proximal to the splenic flexure) and for CD into small bowel only, large bowel only and small + large bowel. Disease activity and need of surgery (colectomy for UC and bowel resections for CD) were assessed during the first year after the year of diagnosis. Disease activity was defined as symptoms at any time leading to a change in medication or surgery.

Results: A total of 119 IBD patients (77 UC and 42 CD) were included in the two periods. Incidence rates were 2.0 and 0.2 for UC and CD, respectively, in period I and 1.6 and 3.1 in period II (incidence rate ratios (period II: period I) of 0.81 (95% CI: 0.5–1.4) and 15.6 (95% CI: 7.5–32.7) for UC and CD, respectively). A significant increase in UC patients with extensive disease E3 (46.7% and 94.1%, p < 0.001) and a decrease in patients with proctitis E1 (28.3% and 0%, p = 0.017) were seen when comparing results from periods II with period I.

No significant difference in disease localisation was found in CD patients, when comparing the two periods.

Disease activity during first year after the year of diagnosis was present in 62% and 22% of UC and CD patients, respectively in period I vs. 47% and 67% in period II (p > 0.05). Nine UC patients (15%) had a colectomy performed in period I compared to none in period II (p = 0.13). No significant difference in the use of surgery was found for CD patients.

Conclusion: A 15-fold increase in incidence of CD was seen over the last 45 years. Despite more extensive disease in UC patients in period II, we found a similar disease activity within the first year in both periods.
Impact of biliary and nutritional lack of phospholipids in a colitis mouse model

Joerg Jahnel¹, Thierry Claudel¹, Anna Baghdasaryan¹, Dagmar Silbert¹, Judith Gumhold¹, Andrea Fuchsbichler², Cord Langner², and Michael Trauner¹
¹Laboratory of Experimental and Molecular Hepatology, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Medical University Graz, Graz, Austria; ²Institut of Pathology, Medical University Graz, Graz, Austria

Introduction: Patients with ulcerative colitis (UC) have low mucus levels of phospholipids (PL); conversely PL therapy has a positive effect on UC. Phospholipid homeostasis requires exogenous PL supply and biliary PL secretion by the hepatic PL floppase Mdr2. We hypothesized, that reduced biliary PL concentration and decreased choline content in nutrition could reduce intestinal PL levels and facilitate colitis genesis.

Methods: DSS colitis was induced in mice lacking biliary PL secretion (Mdr2⁻/⁻) under choline deficient diet (CDD). Control groups included Mdr2⁺/⁺ and Mdr2⁻/⁻ mice without DSS induction or/and CDD. Histological scoring, serum biochemistry, bile flow and composition were determined.

Results: Mdr2⁻/⁻ mice did not develop spontaneously UC, but after 4 weeks of CDD a mild colonic inflammation was observed. DSS colitis in Mdr2⁻/⁻ mice led to similar degree of mucosal damage compared to wild-type and liver histology, serum biochemistry, bile flow (2.5 µl/g/min) and biliary output of bile acids and PL were unchanged. CDD in Mdr2⁻/⁻ mice did not influence the extent of DSS colitis but lowered the bile flow (1.2 µl/g/min).

Summary/Conclusion: Depletion of biliary PL and PL precursors from nutrition did not influence the degree of chemically-induced colitis in mice. Therefore, PL involved in the pathogenesis of colitis originates rather from ileal and jejunal enterocytes secretion than from bile or diet. Finally, PL were found to not have positive properties in our models in contrast to human, either because of species specific differences in PL metabolism or due to different disease course induced by DSS.
Anorectal lesions in Crohn’s disease: Are there age-specific differences?

Johannes Jongen, Anne Eberstein, Jens-Uwe Bock, Hans-Günter Peleikis, Volker Kahlke
Proctological Office Kiel, Kiel and Department of Surgical Proctology, Park-Klinik, Kiel, Germany

Introduction: To investigate specific differences between two age groups of patients with anorectal Crohn’s disease (CD).

Methods: All patients with anorectal CD, who were treated in our office/department from 2002 until 2007 were studied in regard of time of the diagnosis of CD, previous anorectal and abdominal surgery, anorectal lesions, number and type of necessary, anorectal operations.

Results: 170 patients (103 females) with CD were under the age of fifty at the time of first presentation (group A). In 45 of these patients (26%) CD was diagnosed by the anorectal examination.
36 patients (23 females) with CD were 50 years or older at the time of first presentation (group B). In 12 of these patients (33%) CD was diagnosed by anorectal examination.
Findings and diagnoses (group A vs. B): previous anorectal surgery: 57 (34%) vs. 12 (33%), previous abdominal surgery: 42 (25%) vs. 12 (33%), previous both anorectal and abdominal surgery: 18 (11%) vs. 4 (11%), NO anorectal lesions: 6 (4%) vs. 12 (33%), proctitis 57 (34%) vs. 9 (25%), anal fissure 97 (57%) vs. 19 (53%), abscess (106 (62%) vs. 12 (3%), fistula 124 (73%) vs. 21 (58%), stoma for abdominal reasons 9 (5%) vs. 1 (3%), stoma for anorectal reasons 10 (6%) vs. 1 (3%), number of anorectal operations 1 (1–14) vs. 1 (1–4).
Statistically younger patients had significantly more abscesses than older patients. Regarding all other studied parameters there were no significant differences between the groups.

Discussion/Conclusion: Younger patients with CD have more anorectal abscesses than older patients with CD.
Psychoemotional peculiarities in adolescents with inflammatory bowel diseases

Liana Jorjoliani, Ekaterine Chkhartishvili, Mariam Tskhakaia, Rusudan Karseladze, Lali Saginadze
Tbilisi State University, Faculty of Medicine, Georgia
Institute of Pediatrics, Tbilisi, Georgia

Introduction: Inflammatory bowel diseases (IBD) is a well known multietiologic disease with complex psychosomatic symptoms. Disease formation significantly depends on psychological factors as well as motor disturbances in different parts of intestinal tract. During IBD psychical disorders are in 70–90%. In some cases manifestations of the gastrointestinal disorders are on the basis of preliminary psychical pathology. On the other hand, more than 50% of patients respond to stress by gastrointestinal and psychopathological symptoms.

Objective: Assessment of individual-psychological peculiarities, anxiety and stress in adolescents.

Methods: Under observation were IBD 45 patients and 20 controls, aged 11–16 years. Psychoemotional and individual-characteristic data were studied on the basis of Lusher color test, health self-control test and Rieder stress degree test.

Results: In 58.7% of patients evaluated their health as not satisfied, bad in 38%, good in 3.3% of cases. 81% of adolescents revealed moderate degree of stress and 19% high degree of stress. Anxiety data (63.21 ± 4.89) was rather high, which limited personal relationship. Adolescents reveal fear, depression, fear of loosing self-confidence. Parasympathetic influence was dominated and physical activity was rather low.

Discussion/Conclusion: Anxiety, hypochondric mood, limited self-confidence are main signs in IBD adolescents, which worsen disease duration, increases stress, diminishes physical activity.
Prognostic value of intestinal bacterial flora and mucosal immunity during infancy in the development of inflammatory bowel diseases in adults

L. Jorjoliani¹, R. Karseladze¹, L. Saginadze², T. Bigvava¹, T. Arakhamia², E. Chkhartishvili²

¹Tbilisi State University, Tbilisi, Georgia
²Institute of Pediatrics, Tbilisi, Georgia

Introduction: Intestinal microbial and topical immune environment may have some significant influence on inflammatory bowel disease development in future.

Objectives: To determine: 1. the influence of bottle feeding on intestinal micro ecology and mucosal immune defense. 2. the influence of intestinal micro ecology and mucosal immune barrier data on adolescent inflammatory disease development.

Methods: Intestinal microbial flora was determined by microbial culture analysis. In the fecal filtrate secretory Immunoglobulin A (sIgA) was measured by gel radial immune diffusion method. Serum total Immunoglobulin E by radioimmunology test PRIST.

Results: Acid adaptive formula activates intestinal wall mucosal topical immunity and optimal micro ecology status formation, therefore, lowers degree of hypersensitivity during infancy. This was confirmed in main group (80 under 12 months of age children were fed with acid adaptive formula) by increase of SlgA level from 140.2 mg/100 g fecal mass) to 254.2 mg/100 g fecal mass) in comparison with control group (40 under 12 months of age children who got ordinary formula (158.5 mg/100 g fecal mass – 172 mg/100 g fecal mass). Intestinal microbial culture revealed tendency bifid- and lactobacteries intensive growth, decreased growth of pathogenic flora and balanced of dysbiosis in intestinal flora. Observation covered 1993–1995 yy. period. Total IgE content was low in main group in comparison with control group. After 10 years period 2004–2007 study showed that in children who have had revealed diminished fecal filtrate SlgA content and intestinal flora dysbiosis, in 46,4% of cases developed different intestinal inflammatory diseases.

Conclusions: 1. In infancy low SlgA content has a predictive value for intestinal wall mucosal topical immunity status. 2. Misbalanced intestinal microecology and lack of mucosal immunity, which mainly is determined by the nutritional pattern can be a risk factor for intestinal inflammatory process formation in adults.
Particularities of Crohn’s disease in young patients compared to adults

Lamia Kallel, Narjess Nija, Samira Matri, Monia Fekih, Nadia Ben Mustapha, Sami Karoui, Jalel Boubaker, Azza Filali
Department of Gastroenterology A, Rabta Hospital, Tunis, Tunisia

Introduction: Crohn’s disease generally affects adult patients but can occur, though less frequently, in children and teenagers. The aim of the study was to determine the epidemiological, clinical and therapeutic features of Crohn’s disease in patients of less than 18 years old compared with adults.

Methods: A retrospective study was performed including all patients hospitalized in our unit between 1997 and 2007. Patients were separated in two groups depending on their age at disease onset, young patients (0–17 years old) and adult patients (18 years old or more). We examined the epidemiological, clinical and therapeutic features of the disease in both groups.

Results: Among the 332 patients included, 54 (16.26%) were younger than 18 years old and 277 (83.74%) had more than 18 years old at diagnosis. The mean follow-up time was 5.46 yr in the younger group and 4.7 yr in the older group (p = 0.2). Familial form of Crohn’s disease was more frequent in young patients compared to adults (9.3% vs. 2.2%; p = 0.008). The frequency of ileal, colonic and ileocolonic disease subtypes didn’t differ significantly between both groups and upper digestive localization was as frequent in young patients as in adults (7.4% vs. 5.4% p = 0.56). No difference was noted regarding the natural course of the disease (inflammatory, fistulizing or stenosing disease). In addition, a severe acute colitis occurred in 11.1% of the young patients compared to 12.4% of the older group (p = 0.79). In contrast, immunosuppressive drugs prescription was significantly more frequent in young patients (59.3%) compared to adults (33.9%) (p < 0.001). No significant difference was noted regarding the frequency of bowel resection when comparing both groups (38.9% vs. 34.7% in young and old patients respectively, p = 0.55).

Discussion/Conclusion: Compared to adults, young patients with Crohn’s disease had higher familial form frequency and were more often prescribed immunosuppressive drugs in our study.
Fecal calprotectin remains stable in inactive Crohn's disease patients: Results of a prospective study

Lamia Kallel¹, Narjess Nijaa¹, Monia Fekih¹, Samira Matri¹, Sami Karoui¹, Moncef Feki², Jalel Boubaker¹, Naziha Kaabachi², Azza Filali¹
¹Department of Gastroenterology A, Rabta Hospital, Tunis, Tunisia, ²Department of Biochemistry, Rabta Hospital, Tunis, Tunisia

Introduction: Fecal calprotectin is a reliable marker of the intestinal inflammation in both ulcerative colitis (UC) and Crohn's disease (CD) patients. A recent study had already proven that fecal calprotectin level remains stable in UC with inactive disease during 12 months of follow-up. No such study was done in inactive Crohn's disease patients. The aim of the study was to assess fecal calprotectin level variation during long-term follow-up among inactive Crohn's disease patients.

Methods: We included patients with clinically quiescent colonic Crohn's disease patients. Remission was obtained at least 6 months before inclusion. Patients were followed for 12 months. Those who developed clinical relapse during this period were excluded as well as patients who were receiving steroids or sequential anti-TNF treatment. A stool sample was collected at inclusion and was repeated every 3 months until 12 months. Fecal calprotectin concentration was determined by ELISA technique (Calprest test).

Results: Twenty-eight (28) CD patients were included, 9 men and 19 women, with a mean age of 36 years old (17–66 years), in remission since a mean period of 31 months (2–192 months). Among these patients, 16 (57%) were receiving azathioprine. Mean calprotectin concentration was 206 ug/g at inclusion, and 197 ug/g, 188 ug/g, 203 ug/g and 223 ug/g respectively at 3, 6, 9 and 12 months of follow-up. No statistical difference was noted between these concentrations. Interclass correlation coefficient study showed good and very good correlations between the different calprotectin values. Fecal calprotectin levels were not correlated with patient's features or with azathioprine use.

Discussion/Conclusion: Our study had shown that fecal calprotectin level remains stable in patients with clinically quiescent colonic Crohn's disease over a period of 12 months.
Protease inhibitors genetic system phenotypes in inflammatory bowel disease

Rusudan Karseladze¹, Lia Jorjoliani¹, Lali Saginadze², Eka Karseladze¹
¹Tbilisi State University, Georgia
²Institute of Pediatrics, Tbilisi, Georgia

Introduction: Inflammatory bowel diseases (IBD) are multifactorial diseases. Hereditary predisposition plays the most important role in the developing of disease, but it is not everything recognizable. The epithelial cell layer expresses many endo- and exopeptidases at its apical side, colocalizing with proteins and peptides derived from food and microflora.

Methods: Phenotyping of PI-genes was performed in polyacrylamide gel using isoelectric focusing method.

Results: PI-genetic system gens were studied by phenotyping of 53 probands with IBD, 6–16 years of age and 115 healthy individuals. The patients were retrospectively divided into two groups: one with total colitis and another with distal colitis. In patients with total colitis significant increase was revealed in pathological homozygote phenotypes in comparison with control. PI-S allele rate (Px = 0.143, Px = 0.014; p < 0.001), PI-Z allele rate exceeded appropriate index 10 times in the control group (Px = 0.046, Px = 0.005; p < 0.0001). In the blood plasma of carriers of the PI- was observed only 15% of the inhibitor normal content i.e. 0.3 g/l (norm – 2.0 g/l), but in the PI-S allele variant -58–60% i.e. 1.2 g/l (norm – 2.0 g/l). Patients with distal disease, whereas no difference in comparison with control.

Discussion/Conclusion: Study of interrelationship of the PI genetic system and IBD, particularly it clarifies the intimate mechanisms of Inflammatory bowel diseases pathogenesis. It is concluded that the Z-homozygote deficit phenotype in patients with severe total colitis is mainly due to a consumption caused by complex formation with proteases, as in patients with distal colitis. Correct and timely diagnosis, favorable working environment and appropriate genetic consultation will protect the health of PI-deficiency patients and prolong their lifespan.
Diagnoses of ulcerative colitis in dependence on the age of patients

M. Konečný, V. Procházka, J. Ehrmann
IInd Medical Clinic, Faculty Hospital, Olomouc, Czech Republic

Introduction: Ulcerative Colitis (UC) belongs to inflammatory bowel diseases that manifest mostly in younger patients. However the age of patients at the time of the diagnosis varies; the bimodal age distribution of the first finding of UC is described in the third or fifth decades of patients’ lives.

Methods: In 1998–2007, we admitted 128 patients with a new finding of UC. The set of patients was divided into age groups according to decades of patient’s age when UC was diagnosed, and then the occurrence of patients in a particular age decade was observed. We monitored the need of surgical treatment at the time of the first attack of UC.

Results: In more than a half of patients UC occurs in the third age decade. In the above-mentioned age group of 76 patients (59.4%), of which 44 were men (57.9%) and 32 women (42.1%), proctocolectomy was carried out during the first attack in 5 patients (6.6%). In the fifth age decade, UC was found in 19 patients (14.8%), 12 men (63.2%) and 7 women (36.8%), and proctocolectomy had to be carried out during the first attack only in one patient (5.3%). The results achieved in particular age groups were mutually compared and none of found differences was statistically important.

Discussion/Conclusion: In absolute majority, patients with UC were diagnosed until the thirtieth year of age, with increasing age of patients UC is found more often in men, the need of surgical treatment during the first attack of UC does not vary throughout the age decades.
Autophagy 16-like 1 (ATG16L1) is associated with inflammatory bowel disease (IBD) in children

M. Lacher¹, S. Schröpf¹, A. Jurik¹, D. von Schweinitz¹, A. Ballauff², P. Lohse³, H. Baurecht⁴, R. Kappler¹, S. Koletzkö⁵

¹Department of Pediatric Surgery, Research Laboratories, University of Munich, Lindwurmstr. 2a, D-80337 Munich, Germany
²Division of Pediatric Gastroenterology, Universitätsklinikum Essen, University of Duisburg-Essen, Hufelandstr. 55, D-45147 Essen, Germany
³Institute of Clinical Chemistry, University of Munich, Marchioninistr. 15, D-81377 Munich, Germany
⁴Institute for Medical Statistics and Epidemiology, Technical University of Munich, Ismaningerstr. 22, D-81675 Munich, Germany
⁵Department of Pediatrics, Division of Pediatric Gastroenterology, University of Munich, Lindwurmstr. 4, D-80337 Munich, Germany

Introduction: Genome-wide association studies have described a variant within the autophagy 16-like gene ATG16L1 (rs2241880) to be associated with Crohn’s disease in independent IBD cohorts. This locus has been evaluated in three pediatric IBD cohorts with conflicting results. Therefore, the aim of this study was to investigate the association of rs2241880 in a German pediatric IBD cohort and to describe the transcriptional activity of ATG16L1 in colonic tissues.

Methods: Subjects: 232 German Caucasian children with IBD (152 CD, 80 UC) and 253 ethnically matched healthy adult blood donors. Determination of mRNA expression of ATG16L1 in large bowel biopsies of selected IBD patients and controls using real-time PCR. Investigation of the rs2241880 polymorphism of the ATG16L1 gene using a pre-designed TaqMan® SNP Genotyping Assay (Applied Biosystems, Foster City, CA, USA). To verify potential interactions of the T300A variant with the NOD2/CARD15 gene we also tested for epistasis with NOD2/CARD15.

Results: Genotyping for the rs2241880 polymorphism exhibited significant differences in the genotypes between CD patients and controls (p < 0.01), whereas there were no differences between UC patients and controls in genotype or allele frequencies. We could not demonstrate an epistatic interaction between the NOD2/CARD15 gene and the A300T variant of the ATG16L1 gene. The gene expression analysis did not reveal a characteristic overexpression or down-regulation of ATG16L1 in CD and UC patients compared to unaffected controls.

Discussion/Conclusion: We have confirmed the association between CD and the rs2241880 polymorphism in ATG16L1 in a pediatric cohort of German Caucasian children. We could not demonstrate an epistatic interaction between the NOD2/CARD15 gene and the rs2241880 polymorphism. These results mirror the findings in adult patients that even in the absence of NOD2/CARD15 mutations the ATG16L1 variation is a risk factor in pediatric CD thereby supporting a role for autophagy in the pathogenesis of this disease.
Aluminum (Al) is a common immunogenic environmental compound. Since loss of tolerance to commensal intestinal bacteria is involved in the pathogenesis of IBD, we postulate that dietary Al increases luminal bacterial virulence and/or enhances mucosal immune responses to enteric bacteria. Therefore, the capacity of Al preloaded bacteria to enhance immune responses in vitro and the in vivo effect of dietary Al on immune-mediated young murine colitis, were explored.

Methods: Immune responses were studied by $^3$[H] Thymidine incorporation, gamma-interferon by Elisa on young IL-10 KO colitic mouse splenocytes stimulated by murine E. coli grown in increasing Al concentrations. Young 15 IL-10 KO germ free mice colonized with specific pathogen free enteric microbiota, fed a low Al, and exposed to 3 different Al concentrations: low (0.03 uM), middle (5 uM) and high (500 uM) Al L-lactate added to their drinking water. Colitis was measured by blinded histological scores (0–4+) and IL-12 by ELISA.

Results: Bacterial growth was suppressed slightly by high Al concentrations in the media. Lower Al concentrations (150–200 uM) stimulated, while higher concentrations inhibited in vitro T cell proliferation and IFN secretion by splenocytes. In vivo Al feeding worsened colitis, with increased proximal colon histological scores accompanying higher Al intake (2.0 ± 0.2 low vs. 3.8 ± 0.2 high, p < 0.05). Colonic IL-12 secretion by colonic strip cultures increased with higher Al intake (3.5 ± 1.6 vs. 4.9 ± 0.4 ng/ml).

Conclusions: Al stimulates immune responses to enteric bacteria and enhances bacterial-induced experimental colitis in young IL-10 KO mice. Environmental Al might be an inducer of Crohn's disease.
Implementation of a day care unit for inflammatory bowel disease: Patients’ satisfaction

M.D. Martín Arranz, E. Martín Arranz, S. Gomez Senent, L. Adán Merino, C. Froilán Torres, J.M. Segura Cabral
Gastroenterology Department, La Paz University Hospital, Madrid, Spain

Introduction: Patients with IBD require continued attention, with multiple admissions due to activity periods of their illness and to receive treatments, with the following bother and loss of productivity. In order to reduce these admissions a Day Care Unit for IBD was set in our hospital during year 2007, to administer biological treatments and other techniques related to the disease on an outpatient basis, sitting and through the application of a clinical protocol followed by a specialized nurse. Previously these treatments took place during ordinary hospital admission in a medical ward.

Methods: All 50 patients with inflammatory bowel disease receiving biological treatment filled in a satisfaction survey form before the first and after several treatment sessions in the Day Care Unit (DCU). Seven patients refused to answer or did not fulfill it. The form included also the presence of problems in DCU, medical visit or recommendations at home. Three patients reported minor complaints, related with the need for more information. Quantitative variables were compared using Chi square test and qualitative variables with t student.

Results: In the following tables we show the analyzed variables and the results obtained.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>36.9 (18–71)</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>20 (46.5%)</td>
</tr>
<tr>
<td>Study level</td>
<td>Elementary (21%); Secondary (42%); College (37%)</td>
</tr>
<tr>
<td>Previous admissions</td>
<td>86%</td>
</tr>
<tr>
<td>Knowledge of physician’s name</td>
<td>97.7</td>
</tr>
<tr>
<td>Knowledge of nurse’s name</td>
<td>93%</td>
</tr>
</tbody>
</table>

Data are presented as mean (range) or percentage. Satisfaction with different items scored from 1 to 5 with an analogical visual scale.
Discussion/Conclusion: The Day Unit system has improved significantly important outcomes as the number of hospital admissions, adverse reactions attention, and perception of assistance by patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before DCU</th>
<th>After DCU</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assistance by sanitary personal</td>
<td>2.30 ± 0.50</td>
<td>4.63 ± 0.49</td>
<td>0.02</td>
</tr>
<tr>
<td>Medical Care</td>
<td>4.58 ± 0.46</td>
<td>4.60 ± 0.54</td>
<td>0.82</td>
</tr>
<tr>
<td>Nursery Care</td>
<td>2.60 ± 0.90</td>
<td>4.70 ± 0.46</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>3.56 ± 0.96</td>
<td>4.36 ± 0.81</td>
<td>0.05</td>
</tr>
<tr>
<td>Recommendations</td>
<td>3.87 ± 0.81</td>
<td>4.43 ± 0.70</td>
<td>0.06</td>
</tr>
<tr>
<td>Citations</td>
<td>3.66 ± 0.58</td>
<td>4.49 ± 0.59</td>
<td>0.05</td>
</tr>
<tr>
<td>Waiting time</td>
<td>2.87 ± 0.90</td>
<td>4.51 ± 0.67</td>
<td>0.03</td>
</tr>
<tr>
<td>Biologic treatment information.</td>
<td>0.90 ± 0.84</td>
<td>4.36 ± 0.79</td>
<td>0.01</td>
</tr>
<tr>
<td>Biologic treatment informed consent.</td>
<td>0.90 ± 0.58</td>
<td>4.48 ± 0.67</td>
<td>0.01</td>
</tr>
<tr>
<td>Global satisfaction score (1–10 score)</td>
<td>6.70 ± 0.87</td>
<td>8.90 ± 0.10</td>
<td>0.04</td>
</tr>
<tr>
<td>Hospital admissions (6 months)</td>
<td>1.40 ± 0.08</td>
<td>0.20 ± 0.02</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Variables are expressed as mean ± SD.
Risk factors associated with failing to enteral nutrition in pediatric Crohn’s disease

Zrinjka Mišak, Iva Hojsak, Slaven Abdović, Alemka Jaklin Kekez, Oleg Jadrešin, Sanja Kolaček
Referral Centre for Paediatric Gastroenterology and Nutrition, Children’s Hospital Zagreb, Klaićeva 16, Zagreb, Croatia

Introduction: Treatment for remission induction in patients with Crohn’s disease (CD) is still a subject for debate. However, it seems that enteral nutrition (EN) may be front line therapy in children with CD, nevertheless, it has been proven that EN is not effective in all patients with CD. The aim of this study was to investigate the risk factors for failing EN in pediatric patients with CD.

Methods: Data of all newly diagnosed CD patients (n = 47) treated in Children’s Hospital Zagreb from 1997 to 2007 were retrospectively analyzed (27 male and 20 female, age range 9–17.8 years). For remission induction, EN was introduced in 30 (63.8% of all treated patients) patients and was given for 5–6 weeks. At the same time mesalamine or azathioprine were introduced with the aim to keep the patient in remission.

Results: In 21 patients (70%) treated with EN, remission was established and last from 4 months to 5 years (mean 17.6 months). We found that all patients (n = 9) who failed EN had ileocolonic disease comparing to EN successful group which majority had ileocecal disease 61.9% (13). As well, 33.33% (3) of patients who failed EN had stricture or stenosis comparing to 9.52% (2) in EN successful group. Patients who failed EN had less perianal disease (22.22%) and upper GI involvement (11.11%) comparing to EN successful group (52.38% and 28.57%, respectively). There was no difference for duration of illness (mean 6 months) and the age at diagnosis (mean 13.8 years) for both groups.

Discussion/Conclusion: Although the number of patients in this study was rather small it seems that patients who had predominantly colonic disease fail on enteral nutrition more often, on the other hand perianal disease and involvement of upper GI tract seems to respond very good to EN.
Clinical course of adult ulcerative colitis (UC): A Markov model analysis of the multinational population-based prospective cohort of the European Collaborative Study of Inflammatory Bowel Disease (EC-IBD)

Selwyn Odes⁴, Hillel Vardi², Michael Friger², Bjorn Moum³, Tomm Bernklev⁴, Dirk Esser⁵, Heidi Waters⁶, Margarita Elkjaer⁷, Reinhold Stockbrugger⁸, Epameinondas Tsianos⁹, Pia Munkholm⁷, Ebbe Langholz¹⁰

1Gastroenterology and Hepatology Department, Soroka Medical Center and Ben Gurion University, Beer Sheva, Israel; ²Epidemiology Department, Ben Gurion University, Beer Sheva, Israel; ³Gastroenterology Unit, Aker University Hospital and Faculty of Medicine, University of Oslo, Trondheim, Norway; ⁴Medical Department, Gastroenterology Unit, Aker University Hospital, Oslo, Norway; ⁵Centocor BV, Leiden, The Netherlands; ⁶Centocor Ortho Biotech Services, Malvern, PA, USA; ⁷Gastroenterology Department, Herlev University Hospital, Copenhagen, Denmark; ⁸Gastroenterology and Hepatology, University Hospital Maastricht, Maastricht, The Netherlands; ⁹Division of Internal Medicine, University of Ioannina, Ioannina, Greece; ¹⁰Gentofte Hospital, Copenhagen, Denmark

Introduction: Forecasting the long-term course of UC is problematic, given its waxing-waning behavior and multiple consequences. We determined clinical outcome by a Markov model, a stochastic process well-suited to outcomes analysis in complex disease.

Methods: EC-IBD incepted European and Israeli patients aged >15 years prospectively during 1991–1993. Patients tracked over 10 years were populated into 7 transition states classified according to therapy, and a death-state. Transition states, in 3-month cycles, were: remission, mild, steroid-responsive, steroid-dependent, steroid-refractory, surgery, post-surgical.

Results: 896 patients (age 41.9 ± 17.0 years, 53% male, 25,093 patient-cycles) spent most of the course as remission or mild states. However, initially 20% and thereafter 10% of patient-cycles were spent in steroid or surgery states. Patients in initial remission/mild state remained there with probability 0.900, and few entered a steroid state or surgery. Steroid-responsive patients transited to less severe states with probability 0.7290. Patients initially in steroid-dependent, steroid-refractory or surgery states had high probabilities of worsening or requiring surgery or dying (Table). Probabilities of transition to further surgery (pouch removal) were 0.0408 and 0.0085 respectively after initial surgery (colectomy) or post-surgical remission.
<table>
<thead>
<tr>
<th>INITIAL STATE</th>
<th>SUBSEQUENT STATE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>steroid-</td>
</tr>
<tr>
<td></td>
<td>responsive</td>
</tr>
<tr>
<td>steroid-responsive</td>
<td>0.1944</td>
</tr>
<tr>
<td>steroid-dependent</td>
<td>0.0000</td>
</tr>
<tr>
<td>steroid-refractory</td>
<td>0.0015</td>
</tr>
<tr>
<td>surgery</td>
<td>0.2551</td>
</tr>
</tbody>
</table>

**Discussion/Conclusion:** While much of the course of UC was mild, an appreciable number of cycles were spent in steroid therapy or surgery, and pouchitis was frequent. Wider use of biologic therapy may alter this course.
Risk factors of the low bone mineral density in patients with inflammatory bowel disease

Alina Pacurari, C. Banciu, Corina Serban, Lelia Susan, I. Romosan
University of Medicine and Pharmacy “V. Babes” Timisoara, IVth Medical Clinic, Timisoara, 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 in the IVth Medical Clinic of the University of Medicine and Pharmacy. 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 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 BMI are predictive factors for low bone density.
Symptoms of functional gastrointestinal disorders (FGID) in patients with inflammatory bowel disease (IBD)

Alina Păcurari¹, C. Banciu¹, Mihaela Floare², Corina Serban¹, I. Romoșan¹
¹University of Medicine and Pharmacy “V. Babeș” Timișoara, IVth Medical Clinic
²“Tibiscus” University Timișoara, Department of Psychology, Timisoara, Romania

Introduction: Psychological comorbidities like anxiety and depression are frequent present in IBD patients there for symptoms of functional gastrointestinal disorders are highly prevalent in those patients. The aim of this study was to determine whether there is any inter-relationship between the presence and number of FGIDs and patients’ quality of life or psychological status.

Methods: The study was carried out on a group of 41 patients diagnosed with IBD (39% had ulcerative colitis, 24.4% Crohn’s disease and 36.6% not differentiated IBD), admitted in the IVth Medical Clinic of the University of Medicine and Pharmacy “V. Babes” Timisoara. The patients were aged between 31–62 years. We applied in all patients a psychological test for personality (E.P.Q.), and a stress test in order to evaluate the psychological status and the quality of life. Disease activity and functional symptoms according to Rome III criteria were also collected.

Results: Of all patients, 70.7% had functional bowel symptoms (Rome III criteria), and 43.9% had other then bowel related functional symptoms. Anxiety was present in 61% of patients and depression was present in just 19.5% of patients. We observed that anxiety was more often present in women then in men and the prevalence was higher in older patients.

Discussion/Conclusion: Functional gastrointestinal disorders are highly prevalent in IBD patients. Patients with no FGID had significantly better physical quality of life than those with functional symptoms.
Neonatal colitis: Be aware of rare causes other than IBD

A. Paerregaard, L. Hansen, U. Engel, V. Wewer
Hvidovre University Hospital Copenhagen, Denmark

Background: Colitis in the neonate may have a variety of causes. Hypohidrotic ectodermal dysplasia (HED) is a rare inherited disorder that may be associated with hypothyroidism and lung disease. Little attention has been paid to its association with neonatal colitis.

Patients: We describe 3 neonates with HED and severe neonatal colitis. They were all of ethnic Danish origin: 1 male (no siblings) and 2 females (sisters, no other siblings). Pregnancies and deliveries were uncomplicated. All infants experienced failure to thrive, bloody stools and endoscopic evidence of moderate-severe pancolitis. Histologic examination of biopsies disclosed acute and chronic inflammation without evidence of inflammatory bowel disease or allergic colitis. Stool examinations for pathogens were negative. All infants required parenteral nutrition and enteral nutrition with hydrolysed formulas and they all gradually recovered over 4–6 months with no later evidence of colonic inflammation at endoscopy. These infants have been followed-up for 3, 10 and 10 years. Incontinentia pigmenti has been diagnosed in all 3, hypothyroidism in 2 and severe lung disease in 1.

Conclusion: Neonatal colitis may occur together with HED as part of an inherited disorder. In such cases the acronym ANOTHER may be used (Alopecia, Nail dystrophy, Ophthalmic complications, Thyroid dysfunction, Hypohydrosis, Enteropathy, and Respiratory tract infections). The intestinal inflammation is not related to inflammatory bowel disease and its prognosis seems to be favorable.
Pancreatic autoantibodies are associated with reactivity to microbial antibodies, penetrating disease behavior, perianal disease and extraintestinal manifestations, but not with NOD2/CARD15 or TLR4 genotype in a Hungarian inflammatory bowel disease cohort

Maria Papp¹, Istvan Altorjay¹, Karoly Palatka¹, Judit Tumpek², Laszlo Lakatos³, Agota Kovacs⁴, Tamas Molnar⁵, Zsolt Barta⁶, Winfried Stocker⁷, Janos Papp⁸, Gabor Veres⁹, the Hungarian IBD Study Group, Peter Laszlo Lakatos²

¹²nd Department of Medicine, University of Debrecen, Debrecen, Hungary; ²Laboratory of Clinical Immunology, University of Debrecen; ³¹st Department of Medicine, Csalnoky F. County Hospital, Veszprem, Hungary; ⁴¹st Department of Medicine, Peterfi Hospital, Budapest, Hungary; ⁵¹st Department of Medicine, University of Szeged, Szeged, Hungary; ⁶³rd Department of Medicine, University of Debrecen; ⁷Euroimmun Medizinische Labordiagnostika AG, Lübeck, Germany; ⁸¹st Department of Medicine, Semmelweis University, Budapest, Hungary; ⁹¹st Department of Pediatrics, Semmelweis University, Budapest, Hungary

Introduction: Pancreatic (PAB) and goblet cell autoantibodies (GAB) are specific for Crohn’s disease (CD) and ulcerative colitis (UC), but the sensitivity alone is low. Conventional antibodies and carbohydrates (glycans) are associated with disease phenotype and may be of diagnostic importance in inflammatory bowel diseases (IBD). Our aim was to determine the accuracy of PAB and GAB autoantibodies as well as to study relevant phenotype-serotype associations.

Methods: A Hungarian study cohort of 1092 subjects; including 689 well-characterized, unrelated IBD patients (CD: 579, m/f: 274/305, duration: 7.9 ± 11.2 yrs; UC: 110, m/f: 53/57, duration: 8.9 ± 9.8 years), 139 celiac patients, 100 healthy and 64 non-IBD gastrointestinal controls were investigated. Sera were assayed for PAB-GAB IgA/IgG, anti-Omp, ASCA and anti-glycans. TLR4 and NOD2/CARD15 was tested by PCR-RFLP. Detailed clinical phenotypes were determined.

Results: The prevalence of PAB was significantly more frequent in CD (41.1%) vs. UC (22.7%), celiac (22.3%), and controls (8% and 4.6%, p < 0.01 for each), while GAB detection was poor in all groups except UC (15.4%). In CD, the combination of PAB and/or anti-glycans/ASCA increased the sensitivity to 72% and 59% for isolated colonic disease. PAB was associated to glycans (OR: 1.74, p = 0.002), ASCA IgG/IgA (OR: 1.75, p = 0.002), Omp (OR: 1.86, p = 0.001) as well as perforating, perianal disease, arthritis, ocular and cutaneous manifestations (p = 0.002–0.032). In contrast, PAB and GAB antibodies were not associated with NOD2/CARD15 or TLR4, response to medical therapy or need for surgery. No associations were found in UC.

Discussion/Conclusion: PAB autoantibodies in combination with ASCA or anti-glycan antibodies increase the sensitivity for detecting CD, especially isolated colonic CD. Antibody response to PAB was associated with complicated disease phenotype and extraintestinal manifestations in this Eastern European IBD cohort.
Mannan-binding lectin levels and deficiency in a large Hungarian cohort of inflammatory bowel disease patients

Maria Papp¹, Istvan Altorjay¹, Karoly Palatka¹, Gyula Farkas¹, Jolan Harsfalvi², Laszlo Lakatos³, Kudnia Farkas⁴, Tamas Molnar⁴, Agota Kovacs⁵, Gabor Veres⁶, Janos Papp⁷, the Hungarian IBD Study Group, Peter Laszlo Lakatos⁷

1²nd Department of Medicine, University of Debrecen, Debrecen, Hungary; ²Clinical Research Center, University of Debrecen; ³¹st Department of Medicine, Csolnoky F. County Hospital, Veszprem, Hungary; ⁴¹st Department of Medicine, University of Szeged, Szeged, Hungary; ⁵¹st Department of Medicine, Peterfi Hospital, Budapest, Hungary; ⁶¹st Department of Pediatrics, Semmelweis University, Budapest, Hungary; ⁷¹st Department of Medicine, Semmelweis University, Budapest, Hungary

Introduction: Mannan-binding lectin (MBL) is a pattern-recognition molecule which is able to recognize carbohydrate sequences present on microbial surface and stimulate the immune system via the lectin pathway of complement activation. Mutations in the MBL gene have been suggested to protect against ulcerative colitis (UC) susceptibility and MBL deficiency was associated with the presence of antibodies against Saccharomyces cerevisiae (ASCA) in Crohn’s disease (CD) and healthy relatives of the patients. We aimed to investigate the association between MBL levels and serological markers as well as to study relevant phenotype-serotype associations in patients with IBD.

Patients and methods: A Hungarian cohort of 1385 subjects; including 990 well-characterized, unrelated IBD patients (CD: 740, male/female: 337/403; age: 36.7 [SD: 12.7] years; mean duration 8.7 [7.6] yrs; UC: 250, m/f: 122/136; age: 42.9 [14.4] yrs; mean duration 11.2 [9.2] yrs), 296 healthy controls (HC, m/f: 122/174, age 45.1 [15.5] yrs) and 99 non-IBD gastrointestinal controls (GK, m/f: 36/63) were included. Sera were assayed for MBL, antimicrobial antibodies (anti-Omp, ASCA and anti-glycan antibodies) by ELISA and antineutrophil cytoplasmic antibodies (ANCA) by indirect immunofluorescence. TLR4 and NOD2/CARD15 was tested by PCR-RFLP. Detailed clinical phenotypes were determined.

Results: Mean MBL level was not significantly different between IBD (CD: 1298 [SD: 1296] ng/ml; UC: 1109 [1337] ng/ml) and either of the control groups (HC: 1404 [1380] ng/ml; GK: 1250 [1224] ng/ml), as well as the prevalence of absolute MBL deficiency (< 100 ng/ml) was not different (CD: 15.0%, UC: 18.4%, HC: 13.8%, GK: 12.1%). The presence of low MBL level (< 500 ng/ml) was not associated to ASCA IgG/IgA, anti-Omp, anti-glycan antibodies, ANCA, or a combination of these markers in IBD. There was also no association with CRP, CDAI or NOD2/CARD15 status in CD. In contrast, low MBL level or complete deficiency was more common in CD patients without a TLR4 variant (13.0% vs. 5.3%, OR: 2.64, 95% CI: 1.18-5.90). In addition, there was no association with gender, familial disease, smoking status disease duration, location, behavior, perianal disease, extraintestinal manifestations, steroid use/refractory disease, azathioprine or biological use or need for surgery in either CD or UC.
**Conclusion:** In contrast to previous reports we did not find an association between MBL deficiency and serological marker positivity. In addition, MBL was not predictive for clinical phenotype in IBD, but MBL deficiency was associated to TLR4 genotype.
Myocarditis and ulcerative colitis: An infrequent association

Gastroenterology Department, Hospital Infanta Leonor, Madrid, Spain

Introduction: Association between myocarditis and inflammatory bowel disease (IBD) is infrequent.

Clinical case: A 36-year-old male with a severe ulcerative colitis relapse (UC). He had no known allergies, and his home medications mesalamine 2 g twice daily since two months due to a first mild relapsed. At hospital admission was treated with methylprednisolone 60 mg i.v. At fifth day presented a clinical syndrome with chest pain, elevated cardiac enzymes, and depressed left ventricular systolic dysfunction (left ventricular ejection fraction 35%) noted on echocardiogram. On the intensive case unit's admission, mesalamine was discontinued. Without another medication, he experienced rapid improvement of symptoms and a normalization of the troponin levels at fifth day. Fifteen days later, the patient's left ventricular ejection fraction increased at 55% and course of UC improves with disappearance of diarrhoea, rectorraria and fever. Azatioprin 150 mg/day was introduced for prevention of new relapses. Now, one month later, he is without symptoms and he is completing a slow corticosteroid taper.

Discussion: Extraintestinal manifestations are common complications of inflammatory bowel disease (IBD) whereas the association of cardiac disease with IBD is rarely reported. A Danish study in 15,572 patients with IBD, show a incidence rate ratio of 8.3 for Crohn's disease and 2.6 for ulcerative colitis, but the incidence rate was very low (only six had myocarditis -0.03%-). The use of mesalamine is associated with myocarditis in less than ten cases in the literature. According to the Naranjo probability scale, it is probable that this episode of myocarditis was due to mesalamine. There are less than ten cases of this association in the literature and it seems to be a hypersensitivity reaction.

References:


Activated beta1-integrin in normal colonic mucosa and in ulcerative colitis: Immunohistochemical study

A. Portyanko¹, J. Gorgun²
¹Belarusian State Medical University, ²Belarusian Medical Academy of Postgraduate Education, Minsk, Belarus

Introduction: Activated beta1-integrins are typically found in wound regions. HUTS-4 antibody recognizes specific epitopes on the common beta1 subunit of integrins whose expression correlates with the ligand binding activity of these molecules. Since beta1-integrins play an important role in cell migration we hypothesized that the expression of activated beta1-integrin on epithelial and immune cells should be changed in ulcerative colitis (UC).

Methods: Immunohistochemical staining with HUTS-4 antibody of 5 normal and 15 biopsy samples with active UC was performed.

Results: In normal samples positive staining of superficial epithelium was revealed, while there was no staining of lamina propria cells or cryptal epithelium. In 12 cases of UC there were negative regions in superficial epithelium and in 2 cases all superficial cells were negative. Positive staining of cryptal epithelium was found in 6 cases and positive cells in lamina propria – in 11 cases of UC.

Discussion/Conclusion: Activated beta1-integrin is normally present in superficial colonic epithelium. In UC the expression of this molecule is changed. In the majority of studied cases downregulation of activated beta1-integrin in the superficial colonic epithelium was revealed (80%), as well as upregulation in crypts (40%). The presence of inflammatory cells in lamina propria with activated beta1-integrin was found not in all cases (73%). We believe that this heterogeneity of activated beta1-integrin expression in UC could be associated with different prognosis of clinical course. Further investigations are needed to clarify the role of this molecule in UC.
Genitointestinal fistulas in Crohn’s disease. Clinical characteristics and response to therapy

Gema De La Poza¹, Fernando Bermejo², Antonio López San Román¹, Manuel Van Domselaar¹, Alicia Algaba², Javier Die¹, Jesús Alvarez¹
¹Hospital Ramón y Cajal; ²Hospital de Fuenlabrada, Madrid, Spain

Introduction: Genitointestinal fistulas (GIF) in Crohn’s disease (CD) are a difficult problem that probably has not warranted enough attention. Our aim was to analyze the experience of two IBD Units in the management of GIF.

Methods: Patients diagnosed with GIF were identified through the databases of 2 IBD units. Clinical records were reviewed.

Results: Twelve patients with GIF, 3.42% of 350 female Crohn’s patients, were identified. The main type of fistula was recto-vaginal (66.7%). Predominant symptoms were vaginal expulsion of gas (41.7%) and faeces (66.7%). In one case no specific therapy was indicated for the GIF. Antibiotics were given in four cases (100% of temporary responses). Thiopurines were given in 10 cases (10% of complete closures, 30% of transient closures, 50% of partial responses and 10% of non-response). Infliximab was administered in four cases (2 cases of partial response and 2 of non-response). Additionally, one patient received adalimumab, one certolizumab and another one tacrolimus (100% non-response). Three patients (25%) were operated, successfully in all cases (two reinterventions). Despite this variety of therapies, fistulae are still active in 9 cases (75%).

Conclusion: GIF are fortunately rare in women with CD, but condition important anatomical and functional changes. Therapeutic approach is confusing and scarcely effective.
Significance of immunoserological markers in Crohn's disease (CD) according to the age at diagnosis

Carmen Monica Preda, Stela Nicoleta Turchina, M. Manuc, M. Ciocarlan, R. Iacob, Roxana Vadan, M. Diculescu
Center of Gastroenterology and Hepatology Fundeni, Bucharest, Romania

Introduction: Anti- Sacharomices cerevisiae antibodies (ASCA) are a very specific diagnostic marker in CD. pANCA phenotype, which is present in significant proportion among patients with CD, is correlated with the colonic extension. The aim of the study was to investigate the utility ASCA and of pANCA in CD, according to the age at diagnosis.

Methods: A prospective longitudinal study, including all the patients admitted in our Center in 2006/2007 with CD (91 patients). pANCA was determined by indirect immunofluorescence, while ASCA by ELISA method.

Results: ASCA was well correlated with age under 40 years at diagnosis, while ANCA was not.

<table>
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<tr>
<th>AGE AT DIAGNOSIS</th>
<th>ASCA</th>
<th>ANCA</th>
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<tr>
<td></td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>A1 (&lt; 40 years)</td>
<td>10</td>
<td>43</td>
</tr>
<tr>
<td>A2 (≥ 40 years)</td>
<td>1</td>
<td>37</td>
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The phenotype ASCA+ did correlate statistically significant with the colonic forms (L2) or ileocolonic forms (L3), p = 0.05. ASCA+ didn’t correlate with the evolutive pattern of Crohn’s disease, or with its severity. pANCA positive titers were associated with ileocolonic and colonic extension of the disease (p-value – 0.05) and with more severe forms (max. CDAI during evolution). There was no statistically significant association between pANCA titer and: sex, evolutive pattern of Crohn’s disease, or presence of complications.

Conclusions:
- ASCA determination might have a great importance for diagnosis of CD, especially in patients diagnosed < 40 years and those with colonic or ileocolonic extension.
- pANCA is not associated in CD with age at diagnosis, but with a higher severity.
Epidemiological characteristics of inflammatory bowel disease in Albania

Skerdi Prifti¹, Bledar Kraja¹, Marsela Sina¹, Ilir Akshia²
¹University Clinic of Gastrohepatology, University Hospital Centre Mother Teresa, Tirana, Albania
²Service of Statistics, University Hospital Centre Mother Teresa, Tirana, Albania

Introduction: Inflammatory bowel disease (IBD) including ulcerative colitis (UC) and Crohn’s disease (CD) occur with different frequencies around the world. The countries reporting the highest estimates of UC are North America, UK, North Europe and Scandinavia. The diagnosis of IBD can be made at any age with predominance in females. Our aim was to provide epidemiological data of IBD in Albanian patients.

Methods: A total of 110 patients diagnosed and hospitalized in the Department of Gastrohepatology, University Hospital Centre Mother Teresa, Tirana, during 2005–2008, were included in the study. We analyzed age, sex and UC/CD ratio.

Results: Of the total of 110 IBD patients 104 (94.5%) were diagnosed as UC and only 6 (5.5%) were diagnosed as CD. Therefore the UC/CD ratio was over 17/1. The mean age of the IBD patients at the time of diagnosis was 44.6 ± 10.7 years. Patients with CD were significantly younger at the time of diagnosis (27.3 ± 2.1 vs. 45.1 ± 7.8, p < 0.01). Important female predominance was observed in UC patients (female/male ratio was 1.4).

Discussion/Conclusion: Albanian population, similarly with other South East European countries, represents a relatively low incidence of IBD. This is reflected mainly on regard of CD which seems to be very rare in comparison with CU. We found higher prevalence of IBD in females. The age at the time of diagnosis of CU is similar to other European countries, while age of onset of CD is significantly young.
CD83 as a marker of mature dendritic cells increased in Crohn’s disease

Anna Pryczynicz¹, Katarzyna Guzinska-Ustymowicz¹, Jolanta Czyzewska², Dariusz Cepowicz³, Andrzej Kemono²
Department of General Pathomorphology¹, Department of Clinical Laboratory Diagnostics², Department of General Surgery and Gastroenterology³, Medical University of Białystok, Poland

Background/Aim: The aim of this study was to evaluated numbers of mature dendritic cells in Crohn’s disease.

Methods and results: For the study all patients underwent surgical intervention due to failure of medical treatment. 12 patients with Crohn’s disease and 10 patients as a control samples were obtained. At least six files in each tissue were counted for each specimen at a magnification of x400. CD83 expression was found in 90% patients with Crohn’s disease. The increasing of number of dendritic cells (CD83) was observed especially in heavily inflamed tissue. In the control samples CD83 expression we observed in about 10% patients.

Conclusion: Our results demonstrate that Crohn’s disease may lead to increased numbers of mature dendritic cells.

Address for correspondence:

Anna Pryczynicz
Department of General Pathomorphology
Ul.Waszyngtona 13
15-089 Białystok
Poland
E-Mail: apryczynicz@wp.pl
Renal amyloidosis complicating Crohn's disease: Report of three cases

A. Ouaz, L. Kallel, M. Fekih, S. Matri, J. Boubaker, A. Filali
La Rabta Hospital, Tunis, Tunisia

Secondary amyloidosis is caused by the extracellular store of the fragment AA of the circulatory protein in serum amyloid-A. It can complicate diseases such as family mediterranean fever, rheumatoid arthritis or Crohn's disease. Renal amyloidosis is a rare but a serious complication of Crohn's disease. About 70 documented cases of secondary amyloidosis associated with inflammatory bowel disease have been reported. We report three additionnel patients who have developed renal amyloidosis associated with Crohn's disease (CD).

Case 1: Mr GS, 49-year-old is followed since 1990 for an ileo colic CD associated with ankylosing spondylitis. On June 91, the patient was hospitalized for exploration of a biological inflammatory syndrome (VS = 50 mm, fibraemia = 7.9 g/l) while the patient did was asymptomatic regarding the intestine. No etiology for the inflammatory syndrome has been found and during the hospitalization, the patient developed a nephrotic syndrome (proteinuria of 24 hours = 4.7 g/l). He had a renal biopsy that showed a renal amyloidosis. The patient was treated with colchicine, spironolactone and Lasilix®. Since 2001, the patient is in terminal renal failure and hemodialysis sessions.

Case 2: Mr MS, 35 years is followed for Crohn's disease with perineal lesions treated by antibiotics and seton drainage. In August 2007, he developed edema around the eyes, feet face and hands. In Urinary analysis a 24 hour urinary protein measurement showed proteinuria at 7 g. Blood analysis showed Hypoalbuminemia (7 g/l) hypoprotidemia (50 g/l) without renal failure. Hypothyroidism and adrenal insufficiency were also diagnosed. A lip biopsy confirmed the diagnosis of amyloidosis. The patient was treated by Colchicine®, Aldactone®, hydrocortisone, L-thyroxine and azathioprine (for perineal lesions). The evolution was marked by the improvement of the nephrotic syndrome.

Case 3: Mr MA, 31-year-old is followed for ileocolic CD since 1998, associated with ankylosing spondylitis. In July 2002, the patient developed edema of the lower limbs associated with inflammatory syndrome. The biology showed a nephritic syndrome. The kidney biopsy confirmed the diagnosis of secondary renal amyloidosis and the patient was put under colchicine.

Conclusion: Amyloidosis is a rare complication during Crohn's disease. The association CD – amyloidosis is a major cause of morbidity and mortality. The absence of any predictor of the occurrence of this complication leads us to be vigilant with patients with Crohn's disease especially in the presence of a persistent infection like perineal fistulae.
Are probiotics useful in the treatment of the inflammatory bowel disease (IBD)

Luiza Radu¹, Alina Pacurari¹, B. Pacurari², I. Romoșan¹
¹University of Medicine and Pharmacy “V. Babeș” Timișoara, IVth Medical Clinic
²Technical University, Timișoara, Romania

Introduction: Probiotics are used in the therapy of inflammatory bowel disease. One of the pathogenic hypothesis of the IBD is the imbalance in the normal gut flora and the excessive immune response. Probiotics like, lactobacilli species and bifidobacteria species, play a role thru the manipulation of the microflora of the gut and the stimulation of the immune system. The aim of this study is to evaluate the efficacy of probiotics in the treatment of IBD.

Methods: The study was performed in the IVth Medical Clinic of the University of Medicine and Pharmacy “V. Babes” Timisoara, on a group of 42 patients diagnosed with IBD. We divided the group in two subgroups. The first group received in their diet probiotics, and the second group followed the prescribed diet without probiotics for a 6 months period. All of the patients also received a standard sulphasalazine treatment.

Results: During the 6 months period, in the first group 85.7% of the patients remained in remission, 14.3% of the patients had an acute episode. In the second group, the patients with persistent remission were 57.1%, the rest of them had an acute episode of IBD. No differences between men and women or between UC and CD were observed.

Discussion/Conclusion: The adjuvant treatment with probiotics in IBD seams to be effective in patients with UC and CD.
The effect of inflammatory bowel disease (IBD) during pregnancy on long-term health and illness in children of IBD patients – A multicenter Israeli study

Shimon Reif, Arik Alper, Daniel Rachmilewitz, Iris Dotan
Department of Gastroenterology and Pediatric Gastroenterology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

Background: Several studies describe the effect of IBD during pregnancy on perinatal outcomes. However, limited data exists regarding the long-term effect of maternal IBD on the child's health and development.

Aim: To investigate long-term morbidity or developmental defects in children of IBD mothers.

Methods: Questionnaires containing IBD mothers and child medical details and children's developmental data were filled and compared to matched controls.

Results: A hundred and forty six IBD mothers (93 Crohn's disease, 53 ulcerative colitis) were compared to 70 controls. IBD mothers had 385 children (age 16 ± 10.8 years, 52.8% born after IBD diagnosis) that were compared to 144 children (age 13 ± 9 years) of the control group. Mean mother age: 43 ± 10 vs. 39 ± 8.3 years in IBD vs. controls. Disease duration: 10.8 ± 7.5 years. A third of the patients had IBD exacerbation, mostly (45%) during the first trimester. IBD patients had more spontaneous abortions (0.68 ± 1.2 vs. 0.33 ± 0.6 in controls, p = 0.01). Birth weights were significantly lower in IBD mothers vs. controls' offspring: 3.13 ± 0.6 vs. 3.27 ± 0.45 kg, p = 0.05. Importantly, this trend was found also in adolescence where IBD mothers offspring were significantly shorter and lighter compared to controls' offspring (1.28 ± 0.41 vs. 1.47 ± 0.33 m, 29.3 ± 21 vs. 39 ± 24 kg, p < 0.01). IBD in study group offspring was diagnosed in 3% (p < 0.05 vs. controls) whereas atopic dermatitis was more frequent in controls' offspring (11 vs. 5%, p < 0.05). First-year intercurrent infections were more frequent in study group offspring (p = 0.001 vs. controls). In contrast, wheezy bronchitis was more common in offspring controls (p < 0.05). More learning difficulties and attention deficit disorders (5 vs. 0.8% and 4.6 vs. 0.8%, respectively, p < 0.05), and gross neurologic abnormalities (4.4 vs. 0.7%), but not autism, dyslexia or abdominal pain were detected in the study group offspring.

Conclusions: IBD has significant and diverse short and long-term effects on the health and development of IBD mothers' offspring.
The activation of iron regulatory protein 1 dominates iron homeostasis in inflamed intestinal epithelium

Ram Reifen, Orly Savion, Adi Kammer, Shirly Moshe, Yoram Bujanover, Batia Weiss, Esther Meyron-Holtz
The School of Nutritional Sciences The Hebrew University of Jerusalem, Rehovot, E-Mail: reifen@agri.huji.ac.il; Laboratory for Molecular Nutrition, Faculty of Biotechnology and Food Engineering, Technion, Technion City, Haifa, E-Mail: meyron@tx.technion.ac.il and Pediatric Gastroenterology Shiba Medical Center, Tel-Aviv, Israel

Introduction: In IBD, anemia is a common problem with prevalence ranging between 17% and 50%. It is related with a higher score of disease activity, loss of weight, impaired physical activity and a poor growth in children. The causes are thought to include, a chronic blood loss from the colon and intestine, reduced absorption of iron and, a suppression of erythropoietin production. Iron, which is one of the mainstay therapies of anemia in IBD is highly reactive and has the capacity to accept and donate electrons readily. Since patients with IBD have increased production of oxygen reactive species, there is some concern that oral iron supplementation may exacerbate inflammation and tissue damage by hydroxyl radicals formed from hydrogen peroxide via the Fenton reaction. There is evidence that iron supplementation induces inflammation in animal models of colitis. Also, iron-chelators have been shown to ameliorate oxidative stress and inflammation as shown in colitic rats and colonic biopsies from patients with ulcerative colitis. The recent report of CD patients having elevated blood-hepcidin levels and decreased intestinal transepithelial iron import suggest a contribution of hepcidin to nutritional iron uptake in AI and CD. Elevated hepcidin levels reduce the level of the iron exporter ferroportin, which affects two central locations of the iron cycle: 1. Iron from degraded erythrocytes will be retained in the RE system and will re-enter the blood at a slow pace. 2. Dietary iron imported to the enterocyte may never reach the blood, due to low levels of iron exporter. Intravenous iron administration in combination with erythropoietin has been shown to improve the anemia of CD patients, possibly because this treatment eludes both locations of iron retention. Iron regulatory proteins (IRP) are cytosolic proteins, that modulate the expression of proteins involved in the transport and storage of iron, through binding to their m-RNA templates during iron deficiency. IRP binding generates upregulation of the iron importer transferrin receptor 1 (TfR) and downregulation of the iron storage protein ferritin and possibly the iron exporter ferroportin. At physiologic O₂ conditions IRP2 is the dominant regulator as IRP1 sensing depends on the stability of its iron sulfur cluster and physiologic O₂ concentration is too low for this cluster to act as a sensor.

Methods and results: Both, tissues obtained from CD patients and an in-vitro model of inflammation were used. We compared the IRP1 and IRP2 RNA binding activity from biopsies of CD patients to non-inflamed controls and found IRP1-RNA binding activity elevated in patients. In agreement, levels of ferritin were decreased. We were able to mimic this IRP1 mediated misregulation of iron homeostasis in Caco-2 cells (intestinal epithelial cell-line) by creating an inflammation condition using an NO
donor. We found that inflammation induced IRP-1 activation causes elevated transferrin receptor and decreased ferroportin levels suggesting iron accumulation in the inflamed tissue. This phenomenon was more significant in cells grown at 3% oxygen than 21% oxygen.

**Conclusion**: These results support our model of an inflammation induced imbalance of iron homeostasis, mediated by IRP1 activation. Caco-2 cells are a promising candidate for a cell model for iron homeostasis during inflammation, supplying additional evidence that the preliminary observation in human biopsies of IRP1 activation in CD patients is the mechanism for reactive iron accumulation and acceleration of tissue damage by reactive iron in CD.
Characteristics of the patients with inflammatory bowel diseases in Romania

E.C. Rezi, A. Fraticiu
Department of Gastroenterology, Emergency Clinical County Hospital, Sibiu, Romania

Introduction: The aim of this study was to establish the prevalence and characteristics of the patients with inflammatory bowel diseases (IBD) in our geographical area.

Methods: 911 colonoscopies and rectosigmoidoscopies which were performed during the last 4 years in the Gastroenterological Department from the Clinical County Hospital from Sibiu, Romania.

Results: From the total number of 911 patients, 1.53% patients were diagnosed with IBD (21.42% of them with Crohn’s disease and 78.58% with ulcerative colitis). The medium age of the patients with IBD was 55.92 ± 13.35 years. The gender distribution was 57.14% women and 42.86% men. 42.86% were from rural areas, while 57.14% live in urban areas. 54.54% from the patients with ulcerative colitis had proctosigmoiditis and 45.46% had pancolitis. 3 patients with ulcerative colitis were diagnosed in an active stage (moderate to severe disease). 64.28% of the patients received maintenance therapy with mesalazine (1.5 g/day orally or suppositories). As associated disorders, we have found out that 21.42% of the patients with IBD had skin lesions, one patient presented arthritic complaines and one patient had psychic disorders. 2 patients were obese, three patients were hypertensive and one patient had diabetes mellitus. Only a patient with ulcerative colitis developed high-grade dysplasia.

Discussion/Conclusion: Inflammatory bowel diseases have a low incidence in Romania; ulcerative colitis is three times more frequently than Crohn’s disease. IBD have a higher incidence in women and in urban areas. The risk for IBD related colorectal cancer is low in our area, possibly due to the optimized treatment in the last decade.
Colonoscopy in elder versus younger patients – A retrospective study comparing the risk of developing IBD and colorectal cancer at two different age groups of patients from Sibiu, Romania

E.C. Rezi, A. Fraticiu
Department of Gastroenterology, Emergency Clinical County Hospital, Sibiu, Romania

Introduction: Colonoscopy is currently the best diagnostic modality for evaluating colonic diseases like inflammatory bowel diseases (IBD) and colorectal cancer (CRC) but studies of its use in the very elderly are limited.

Methods: We have retrospectively analyzed all colonoscopies and rectosigmoidoscopies which were performed during the last 4 years in the Gastroenterological Department from the Clinical County Hospital from Sibiu, Romania. The aim of this study was to establish the prevalence of IBD and CRC at elderly people (over 70 years of age) compared with those less than 70 years of age. The results were statistically analyzed using the relative risk (RR).

Results: The medium age for the whole group was 61.31 ± 14.16 years. From the total number of 911 patients, 1.53% patients were diagnosed with IBD (21.42% with Crohn's disease and 78.58% with ulcerative colitis) and at 9.33% there was a colorectal cancer found. The studied lot was divided into 2 groups: a group formed by 318 patients over 70 years, and a group formed by 593 patients which were less than 70 years of age. The gender distribution was equally in both groups. The relative risk of developing a colorectal cancer at the patients older than 70, compared with those less than 70 was 1.73. The relative risk of finding an inflammatory bowel disease at older patients compared with younger ones was 0.5, so this group had a lower risk of IBD.

Discussion/Conclusion: In our area, inflammatory bowel diseases have a low incidence; ulcerative colitis is three times more frequently than Crohn’s disease. The inflammatory bowel disease is two times more likely to appear in the younger patients than in the elder ones. In contrast, the colorectal cancer is almost two times more frequently in elderly patients.
Correlation between ileocolonoscopic and video capsule examination in ankylosing spondylitis

M. Rimbaș1,2, M. Marinescu1,2, S. Caraiola1,4, M. Pârvu3, C. Băicuș4, S. Bucurică1,2, C. Tănăsescu1,4, M.R. Voiosu1,2
1“Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania
2Gastroenterology Department, Colentina Clinical Hospital, Bucharest, Romania
3Rheumatology Department, Colentina Clinical Hospital, Bucharest, Romania
4Department of Internal Medicine, Colentina Clinical Hospital, Bucharest, Romania
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Introduction: An intriguing relationship exists between gut and synovium in patients with spondyloarthopathy.
In ankylosing spondylitis (AS), macroscopic signs of gut inflammation have been found in 29% to 49% of cases, as seen by ileocolonoscopy.
Ileocolonoscopic findings have prognostic importance:
- the presence of gut inflammation is related to a more severe clinical and radiological expression of AS;
- 20% of AS patients with an initial subclinical chronic gut inflammation develop clinical-overt IBD.

Methods: 10 patients with AS (as classified using the modified New York criteria) and no signs of inflammatory gut involvement were investigated using colonoscopy with intubation of the terminal ileum followed by video capsule examination; the presence of macroscopic small bowel inflammatory lesions was recorded.

Results: Of the 10 patients, 7 were found to have macroscopic inflammatory lesions in the small bowel at video capsule examination. Of these, only 2 were found to have macroscopic lesions of the terminal ileum at ileocolonoscopy; the ileoscopy was normal in the other 8 patients.

Discussion/Conclusion: There's a weak correlation between lesions found at ileocolonoscopy and video capsule examination in patients with AS. It is probable that performing only ileocolonoscopy, an inflammatory subclinical involvement of the small bowel is overlooked in more than half of the patients.
Taking into consideration the fact that abnormalities in the gut could have major consequences in the AS patients, and that early treatment of the gut inflammation could prevent disease evolution when the appropriate drugs become available, small bowel video capsule examination could become necessary for the better management of these patients.
Profile of Belgian pediatric Crohn’s disease subjects (2): Snap shot at diagnosis

M. Rogalidou¹, I. Hoffman², T. Mahler¹, S. Staelens¹, S. Van Biervliet³, M. Scaillon⁴, P. Bontems⁴, I. Paquot⁵, F. Bury⁵, S. Collinet⁵, W. Arts⁵, B. Hauser⁷, F. Smets⁸, E. Sokal⁸, P. Alliet⁹, E. Janssens⁹, O. Bauraind¹⁰, I. Etienne¹¹, G. Veereman¹
Pediatric Gastroenterology Departments of ¹Queen Paola Children’s Hospital, Antwerp, ²UZ Gasthuisberg, Leuven, ³UZ Gent, ⁴University Children’s Hospital Queen Fabiola, Brussels, ⁵CHC Clinique de l’Esperance, Liege, ⁶ZOL, Genk, ⁷UZ VUB, Brussels, ⁸UCL St. Luc, Brussels, ⁹Virga Jesse Hospital, Hasselt, ¹⁰Clinique St. Pierre, Ottignies, ¹¹CHR de la Citadelle, Liege, Belgium

Introduction: Recent reports on pediatric IBD patients show that early onset Crohn’s disease (CD) is characterized by a phenotype with extensive, severe and complicated course¹,².

Methods: The IBD working group of Bespghan recently established a registry of Belgian pediatric CD. We report data on the first 100 patients at the time of diagnosis.

Results: Mean age at diagnosis was 11.7 ± 2.7 yrs corresponding with mean bone age 11.6 ± 3.3 yrs. The mean z-score for height was -1.1 ± 1.3. PCDAI was retrieved from 58 charts: 3 scored less than 10, 18 had mild to moderate disease (10-30) and 37 rated severe (> 30). The PCDAI at diagnosis was correlated negatively with birth weight, (p = 0.0473) and birth height (p = 0.0407) not with age at presentation or symptom duration. Diagnosis was based on endoscopy and histology in 87.7% (in accordance with Porto criteria³), 97% had (ileo)colonoscopy, 68.7% OGD, 1% sigmoidoscopy. Imaging studies: 61.6% of patients had abdominal US, 25.3% small bowel enteroclysis, 14.1% CT and 9.1% MRI. White cell scan was used in 2% and small bowel capsule in none. Based on endoscopic exploration the most frequently involved intestinal area was the ileocolon (52%). Histological diagnosis was possible in 72.7% patients undergoing OGD.

Discussion/Conclusion: In conclusion: At diagnosis children presented with extensive involvement of the GI tract but the small bowel remains mostly unexplored. The severity of disease at presentation may be related to intrauterine growth. Data collection on disease progression and therapy is being conducted.

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References:


Profile of Belgian pediatric Crohn’s disease subjects (1): Demography and background of the first 100 patients

M. Rogalidou1, I. Hoffman2, T. Mahler1, S. Staelens1, S. Van Biervliet3, M. Scaillon4, P. Bontems4, I. Paquot5, F. Bury5, S. Colinet5, W. Arts6, B. Hauser7, F. Smets8, E. Sokal8, P. Alliet8, E. Janssens9, O. Bauraind10, I. Etienne11, G. Veereman1

Pediatric Gastroenterology Departments of 1Queen Paola Children’s Hospital, Antwerp, 2UZ Gasthuisberg, Leuven, 3UZ Gent, 4University Children’s Hospital Queen Fabiola, Brussels, 5CHC Clinique de l’Esperance, Liege, 6ZOL, Genk, 7UZ VUB, Brussels, 8UCL St. Luc, Brussels, 9Virga Jesse Hospital, Hasselt, 10Clinique St. Pierre, Ottignies, 11CHR de la Citadelle, Liege, Belgium

Introduction: Epidemiological observations seek to identify factors and parameters that may influence the evolution and prognosis of CD.

Methods: The IBD working group of Bespghan recently established a registry of Belgian pediatric CD with ulterior goal to study demographical data, treatment and disease course over 5 years.

Results: We report on the background and history of the first 100 inclusions. The group counts 60 boys and 40 girls, 92 are Caucasian. Birth history reveals that 85% were delivered by vaginal route, mean gestational age was 38.4 wks ± 2.3, and 19 patients were premature. The mean birth weight was 3.3 kg ± 0.6 and height 49.8 cm ± 3.0. Data on neonatal feeding are available from 77 infants: 67.6% were breastfed for a mean duration of 11.4 wks. The majority (60%) of formula used was cow’s milk based. There was a suspicion of food allergy in 20.9% infants (33.3% to cow’s milk). In their prior history 18.5% needed dietary restrictions and 38.5% underwent surgery. Family history was positive for IBD (CD and Ulcerative colitis) in 52.3% and a 1st degree relative in 15.4% or a 2nd degree relative in 27.7% with CD. Family history for autoimmune diseases (exc diabetes & hepatitis) was positive in 49.2%.

Discussion/Conclusion: In conclusion: in the Belgian pediatric CD population prior disease history appears unremarkable. Positive family history for IBD & autoimmune diseases is common. Further study will compare phenotypes with disease course and factors that may influence severity and prognosis.

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Methotrexate for pediatric IBD: Induction and maintenance of remission in a regional cohort study

P. Rogers¹, A. Tybulewicz¹, D. Hoole¹, J. Satsangi², P.M. Gillett¹, D.C. Wilson³
¹Paediatric Gastroenterology, Royal Hospital for Sick Children, Edinburgh, United Kingdom
²Adult Gastroenterology, Western General Hospital, Edinburgh, United Kingdom
³Child, Life and Health, University of Edinburgh, Edinburgh, United Kingdom

Background and aim: There is limited data on the use of Methotrexate (MTX) for induction and maintenance of remission in children with Crohn's Disease (CD). We reviewed our experience of induction and maintenance of remission.

Methods: A cohort study of 244 patients diagnosed with early-onset (< 18 years of age) IBD and managed in a UK regional centre 1/8/97–31/12/07 and treated with MTX (16 week induction course of s/c MTX (15 mg/m²) followed by the equivalent oral dose). PCDAI was used to measure disease activity during treatment; PCDAI ≤ 15 indicated remission and a score > 30 indicated severe disease.

Results: 122 with CD were treated with AZA/6-MP; 53 children received a MTX induction course. These 53 patients had received MTX at 14.0 yrs (6.8–17.9) years. The median PCDAI at commencement was 35 (IQR 20–37.5). 41 (78%) patients entered remission at 11 (3–16) weeks. 2 of 41 had recalcitrant OFG, so 39 with luminal CD had a median (range) duration of follow-up of 85 (26–310) weeks. 20 (51%) maintained long-term remission with no relapse; 7 (18%) had a single relapse of which 6 (15%) re-entered remission, and 12 (31%) had > 1 relapses. The median (range) time to first relapse was 39 (20–181) weeks. On MTX treatment, 24 (46%) had nausea/vomiting, 18 (34%) had raised ALT, 1 had shingles and none had bone marrow toxicity.

Conclusions: MTX appears to be effective in inducing (78%) and maintaining (51%) remission in patients who have failed to remit on AZA, and, appears to be well tolerated and safe.
Early atherosclerosis in inflammatory bowel disease patients

Corina Serban¹, Lelia Susan¹, Alina Pacurari¹, C. Banciu¹, Versavia Ancusa², Germaine Savoiu¹, Ioan Romosan¹
¹UMF, Timisoara, Romania
²UPT, Timisoara, Romania

Introduction: Patients with inflammatory bowel disease (IBD) have an increased risk of thrombotic complications. Arterial and venous system may be involved. Moreover, mesenteric microvascular thrombosis has been hypothesised as a contributing factor in the pathogenesis of IBD. The main objective of this study was to evaluate the presence of atherosclerosis in a group of 78 IBD patients without the classical cardiovascular risk factors comparative with a group of 70 control subjects.

Methods: Patients aged > 45 years, with a history of cardiovascular disease and known risk factors for atherosclerosis were excluded from the study. All the patients underwent complete clinical and paraclinical exams. We measured inflammatory markers (erythrocyte sedimentation rate, fibrinogen, C-reactive protein) in all subjects. Intima-media thickness (IMT) was measured by carotid ultrasonography proximal to the carotid bifurcation over both right and left common carotid arteries.

Results: Inflammatory markers (erythrocyte sedimentation rate, fibrinogen, C-reactive protein) were significantly elevated in IBD patients compared with controls. Common carotid artery intima-media thickness was significantly higher in inflammatory bowel disease patients (0.65 ± 0.15 mm) compared with controls (0.51 ± 0.06 mm).

Discussion/Conclusion: The vasculature plays a central role in human IBD and may contribute to pathogenesis through thrombotic, ischemic, or inflammatory mechanisms. The patients with IBD may have an increased risk of early atherosclerosis that healthy control, a finding that requires further study. Inflammatory markers can be indicators of disease severity or activity of IBD.
A study of colorectal cancer in inflammatory bowel disease

Corina Serban¹, Madalin Munteanu², Lelia Susan¹, C. Banciu¹, Alina Pacurari¹, Raluca Dumache¹, Germaine Savoiu¹, Ioan Romosan¹
¹UMF, Timisoara, Romania
²Clinical County Hospital, Timisoara, Romania

Introduction: Inflammatory bowel disease (IBD) characterized by conditions such as ulcerative colitis and Chron's disease, increases the risk of developing colorectal cancer (ulcerative colitis increases risk more than Chron's disease). The main objective of this study was to analyze colorectal cancer in IBD in a group of patients hospitalised between January 2004 and January 2008 in Medical Clinic CF Timisoara.

Methods: We investigated 152 patients with IBD (40 women and 112 men, aged between 45 ± 30 years). The diagnosis of IBD was based on the combination of clinical, endoscopic and histologic findings.

Results: Mean age at the time of diagnosis of cancer was 46 years. 5 patients had documented IBD for less than eight years before their cancer diagnosis. 40% of these patients had the colonoscopy to investigate changes in IBD symptoms or signs and the other 50% underwent endoscopy as routine surveillance. For 10% of the patients, operated for worsening symptoms, the carcinoma was detected in the pathological specimen. Most of the patients did not have a preoperative diagnosis of dyplasia. The tumors were: mucinous (23%), multicentric (17%) and 60% were located distal to the splenic flexure.

Discussion/Conclusion: The key risk factors that can contribute to colorectal cancer in people with IBD include: having IBD for 10 years or longer; having IBD involving the whole colon (pancolitis); having primary sclerosing cholangitis; and having a family history of colorectal cancer. For patients with IBD, the main way to detect colorectal cancer is through regular colonoscopies every year or two.
Arachidonic acid increases ulcerative colitis risk – A prospective cohort study in EPIC-Denmark using biomarker data

P.S.A. de Silva*, A. Olsen¹, A. Tjonneland², K. Overvad³, E. Berg Schmidt⁴, A.R. Hart⁵
¹Department of Gastroenterology, Norfolk and Norwich University Hospital, Norwich, United Kingdom, ²Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, ³Departments of Cardiology and Clinical Epidemiology, Aarhus University Hospital, ⁴Department of Cardiology, Aalborg Hospital, Aalborg, Denmark, ⁵School of Medicine, University of East Anglia, Norwich, United Kingdom

Introduction: Arachidonic acid (AA), an n-6 polyunsaturated fatty acid, is a component of the phospholipid bilayer of colonocyte membranes and is metabolized to pro-inflammatory eicosanoids PGE2 and LTB4. The latter are found in increased concentrations in the mucosa of patients with ulcerative colitis (UC). We aimed to measure for the first time, in a prospective cohort investigation, if increased AA concentration in adipose tissue biopsies increases risk of developing incident UC.

Methods: 57,053 men and women, aged 50–64 years, were recruited in the EPIC-Denmark Study (European Prospective Investigation into Cancer) between 1993–1997. Adipose tissue biopsies were taken at recruitment and AA fatty acid constituents measured. The cohort was monitored up to June 2004 to identify individuals who developed UC. Each case had 4 age and gender matched controls, and AA levels divided into quartiles. Unconditional logistic regression was used to calculate univariate odds ratios for AA levels and multivariate analysis performed adjusted for cigarette smoking and marine n-3 PUFAs in adipose tissue.

Results: 34 subjects (15 w, 19 m) developed incident physician confirmed UC. Median age at diagnosis 58.8 years, (53.3–71.1 years). Median time between recruitment and diagnosis 3.7 years (1.7–7.1 years). The highest adipose concentration of AA was associated with an odds ratio for UC of 12.3 (95% CI 2.6–57.8, p = 0.002) with a statistically significant trend across quartiles (OR for trend = 1.9, 95% CI 1.3–2.8, p = 0.001). Adjustment for co-variates did not affect the magnitude of the findings.

Discussion/Conclusion: Initially well participants, who have higher adipose tissue concentrations of AA, which represent dietary intake, have a significantly higher risk of developing UC compared to those with lower levels. This supports previous data from dietary questionnaire-based studies showing n-6 PUFAs may be involved in UC etiology. Lowering dietary intake of AA may prevent the UC development.
Mucosal healing and complete regression of transmural inflammation with doubling the third infliximab induction dose in refractory Crohn colitis

Małgorzata Sładek, Agnieszka Świat, Izabela Herman-Sucharska*, Stanisław Pieczarkowski, Zofia Grzenda-Adamek, Krzysztof Fyderek
Department of Pediatrics, Gastroenterology and Nutrition, Jagiellonian University School of Medicine, *Medical Diagnostic Center – Voxal, Krakow, Poland

Introduction: The recommended infliximab (IFX) initial dosage in Crohn disease (CD) is 5 mg/kg body weight in an induction regiment at 0, 2, and 6 weeks. Primary non-response to IFX can be determinate after the second dose and patients not responding to the initial two infusions should be discontinued from further IFX therapy. IFX dose intensification is currently recommended only for the lost of the response to maintenance therapy.

Methods: We report the case of 15-years-old girl with fulminant steroid refractory Crohn colitis who was successfully treated with the third induction IFX dose increased up to 10 mg/kg body weight. An otherwise healthy 15-year-old girl presented with abdominal pain and intense bloody diarrhea for one week was diagnosed according to Porto criteria with moderate Crohn disease (A1, L2 + L4, B1). Pediatric Crohn Disease Activity Index (PCDAI) was 35. Because of the lack of the response to metyprednisolon (2 mg/kg) and worsening disease activity (PCDAI 51) IFX was introduced at recommended schedule. After the second IFX dose, despite clinical response intense blood lost persisted. On control colonoscopy severe mucosal lesions was found and transmural colon inflammation was present on MRI scan. Then, the third induction dose was increased up to 10 mg/kg body weight.

Results: Doubling the third IFX induction dose resulted in the rapid mucosal healing and complete regression of transmural inflammation and clinical remission (PCDAI < 10), thereby avoiding colectomy.

Discussion/Conclusion: This is the first report of the successful IFX induction dose intensification in CD and the first report of the IFX induction dose intensification in refractory Crohn colitis. Modification of the induction remission strategy by doubling the third dose may be considered in case of not full response, before concerning patient as primary no responder.
A two-year longitudinal study of the anemia associated with inflammatory bowel disease

Lelia Susan¹, Corina Serban¹, C. Banciu¹, Alina Pacurari¹, V. Ancusa², Smaranda Gotia¹, Ioan Romosan¹
¹UMF Timisoara, Romania
²UPT Timisoara, Romania

Introduction: Anemia affects many patients with inflammatory bowel disease (IBD). A lot of factors contribute to anemia in patients with IBD, including blood loss, inadequate intake/absorption and the underlying inflammatory disease process. The aim of this study was to analyze the association between anemia and IBD in patients with IBD, from Clinical Medical CF Timisoara in a two years period.

Methods: From October 2006 to October 2008, we investigated 78 IBD patients, aged between 45 ± 15 years. By all, 48 of the patients (61.53%) were diagnosed with ulcerative colitis (UC) and 30 of them with Crohn’s disease (38.46%). All the patients underwent complete clinical and paraclinical tests. The values of Ht, the number of reticulocytes, the Hb erytrocytes indices, transferring saturation (TS), the total capacity of iron bounding (CTLF) and the ferritin were determined in all patients.

Results: 24 patients with ulcerative colitis (50%) and 8 patients with Crohn’s disease (26.66%) had anemia (Hb lower than 13.5 g/dl in men and lower than 11.5 g/dl in women). The mean Hb value was 8.1 ± 1.4 and the mean value of Ht was 26 ± 3.3 in the patients with anemia. The number of reticulocytes and the values of CTLF, ferritin, TS were decreased in patients with anemia and IBD.

Discussion/Conclusion: Our study suggested that there is a relationship between anemia, disease severity and quality of life in patients with IBD. The therapy with erythropoietin is useful in treating the anemia associated with Crohn’s disease and ulcerative colitis.
Predictive value of serologic markers in inflammatory bowel disease

Lelia Susan¹, Corina Serban¹, C. Banciu¹, Alina Pacurari¹, V. Ancusa², Germaine Savoiu¹, Ioan Romosan¹
¹UMF Timisoara, Romania
²UPT Timisoara, Romania

Introduction: Perinuclear antineutrophil cytoplasmic antibodies (pANCA) and anti-Saccharomyces cerevisiae antibodies (ASCA) are proposed to be specific markers for ulcerative colitis (UC) and Crohn’s disease (CD). Their prevalence in patients with inflammatory bowel disease (IBD), however, it is unclear. We studied the prevalence of these serologic markers in a group of IBD patients.

Methods: 126 patients with IBD (UC, n = 88 and CD, n = 38) hospitalised between October 2005 until October 2008 in Clinical Medical CF Timisoara participated in this study. All the patients underwent complete clinical, paraclinical, haematological, imagistic and histological exams.

Results: 10 of the patients with CD (26.31%) were ASCA-positive and 27 of UC patients were pANCA-positive (30.68%). Positive ASCA was more frequent in CD patients with stricturing or penetrating complications than in those with inflammatory behavior at diagnosis. Moreover, the presence of ASCA was associated with an at least twice higher risk of evolving more severe disease behavior during follow-up. In UC, pANCA expression was related to female gender and the use of azathioprine and in CD, to colon-limited disease and age ≥ 45 years at diagnosis.

Discussion/Conclusion: The prevalence of ASCA in CD and pANCA in UC appears markedly lower than in referral-based populations. Even with the low prevalence, our study gives further support to the role of ASCA and pANCA as markers for inflammatory bowel disease.
Fertility and outcomes of pregnancies fathered by male patients exposed to thiopurines

Carlos Teruel¹, Antonio López San Román¹, Carlos Taxonera², Alicia Algaba³, Javier Gisbert¹, José Pérez Calle⁵, María Martín Arranz⁶, Manuel Van Domselaar¹, Jesús Estellés², Fernando Bermejo³, Pablo Linares⁴, Pilar López Serrano⁵
¹Hospital Ramón y Cajal; ²Hospital Clínico San Carlos; ³Hospital de Fuenlabrada; ⁴Hospital de la Princesa; ⁵Fundación Hospital Alcorcón; ⁶Hospital La Paz, Madrid, Spain

Introduction: Immunomodulators are widely used as maintenance treatment of inflammatory bowel disease (IBD). Data regarding their safety in the course of pregnancy when fathers are exposed at the time of conception are limited. Our aim was to evaluate outcomes of pregnancies in which fathers had been taking mercaptopurine or azathioprine at the time of conception.

Methods: A series of male patients followed in IBD clinics in the Community of Madrid, Spain, was studied. Any exposure to thiopurines during the 3 months preceding conception was considered. Controls consisted of pregnancies fathered by men with IBD who had never taken thiopurines or had abandoned them more than 3 months before conception.

Results: There were 44 pregnancies in the group exposed to thiopurines (mercaptopurine 8, azathioprine 36) and 74 in the control group. There were no significant differences regarding negative pregnancy outcomes (preterm delivery, abortion, low weight at birth, malformations) and no infant malignancies were registered. The proportion of patients who needed more than a year to achieve a pregnancy was also similar, although higher in the thiopurine exposed group.

Conclusion: Our data suggest that paternal exposure to thiopurines does not influence pregnancy outcomes or male fertility.
Experience of infliximab therapy for refractory ulcerative colitis in a district general hospital

I. Tetlay, D. Sadigh, D. Hughes, R. Turner, J. O’Brien, G. Bray, M. McStay
Southend University Hospital, High Wycombe, UK

Introduction: Tumour necrosis factor-α (TNF-α) is an important cytokine involved in the pathogenesis of inflammatory bowel disease. The benefits of monoclonal antibody to TNF-α, infliximab, in Crohn’s disease are established. We investigated its efficacy in ulcerative colitis (UC).

Methods: Since 2005, 23 patients (aged 14–83 years) with UC refractory to treatment with standard combination therapy have been treated with infliximab in Southend Hospital. The patients’ notes were reviewed.

Results: Of 23 patients, 16/23 (70%) had moderately active, and 7/23 (30%) had severely active UC requiring intravenous steroids.
In patients with moderately active UC: 6/16 (36%) remain in remission on 8-weekly maintenance infusions (5 mg/kg) [median follow-up 24 months (range 7–28)]; 3/16 (19%) achieved remission on induction therapy and remain in remission on azathioprine/6 mercaptopurine [median follow-up 24 months (range 12–26)]; 6/16 (38%) achieved remission with induction therapy but relapsed after a median time of 6 months (range 3–16) requiring colectomy; 1/16 (6%) had secondary loss of response after 18 months of maintenance infusion requiring colectomy.
In patients with severely active UC: 3/7 (43%) achieved remission after induction therapy and remain in remission on azathioprine/6 mercaptopurine [median follow-up 24 months (range 6–24)]; 2/7 (29%) achieved remission with induction therapy but subsequently relapsed (mean duration 12 months) requiring colectomy; 2/7 (29%) of patients had no response to infliximab and underwent colectomy.
No side-effects were reported. The 2 patients with severe UC who did not respond to infliximab died from post-surgical complications within 30 days.

Discussion/Conclusion: Our experience suggests acceptable response rates, colectomy rates and side-effect profile of treatment with infliximab for moderate and severe UC.
Ulcerative colitis in young patients – Epidemiological and clinical course in North-Eastern Romania county

Elena Toader¹, Liliana Croitoru², Oana Arhip³, Rodica Mihăilă⁴
¹“Gr.T. Popa” University of Medicine and Pharmacy Iași, Institute of Gastroenterology and Hepatology Iași, Romania
²District Hospital, Suceava, Romania
³District Hospital, Botosani, Romania
⁴District Hospital, Barlad, Romania

Background: Ulcerative colitis (UC) represents a distinct entity of Inflammatory Bowel Disease (IBD) with unknown etiology which affects young people. UC is a ubiquitous disease with an incidence rate that varies greatly worldwide.

Introduction: The aim of the present study was to evaluate the frequency and clinical course of UC in young patients from North-Eastern (NE) Romania county.

Methods: There were identified 746 UC cases according the diagnosis criteria for UC during 1988–2007. In 485 cases (65%) the onset of the disease was made in the young patients (< 50 years).

Results: UC incidence in the young patients from NE Romania county during 1988–2007 was 2.04/10⁵ inhabitants. Extraintestinal manifestations were noted in 13% patients and family history of UC was found in 1.4% of cases. In our region p-ANCA were found in 18% patients with UC. Extension of disease as proctitis were found in 25.3% of cases, left-sided colitis in 22.6% cases and pancolitis in 22.6% cases. Severity of the first attacks evaluated according to Truelove and Witts criteria was mild in 38.2% cases, moderate in 40.7% cases and severe in 21.1% cases.

Discussion/Conclusion: The low incidence of UC in NE Romania (2.04/10⁵ inhabitants) with high frequency in young patients confirms the epidemiological trend of the disease in this part of Europe. Socio-demographic characteristics, clinical features, disease extent and clinical course of UC are the same in low- as well as high-incidence area.
Perinuclear anti-neutrophil cytoplasmic antibodies in patients with inflammatory bowel disease and their first degree in North-Eastern Romania areas

Elena Toader¹, Cecilia Durnea²
¹“Gr.T. Popa” University of Medicine and Pharmacy, Institute of Gastroenterology and Hepatology, Iași, Romania
²Institute of Public Health, Immunology Department, Iasi, Romania

Background: Perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) are more common in patients with ulcerative colitis (UC) than in patients with Crohn’s disease (CD), but its prevalence depends on the population being studied and the method employed for its detection.

Introduction: The aim of the present study is to determinate the prevalence of p-ANCA in inflammatory bowel disease (IBD) patients and their first degree in NE Romania area

Methods: In this study, we investigated the prevalence of p-ANCA as detected by ELISA, in the sera of 66 patients with IBD (44 with UC and 22 with CD) and 22 first degree relatives. We also correlated the presence of this antibody with disease activity and extent, extraintestinal complications and therapy. 26 healthy individuals comprised the control group.

Results: p-ANCA was detected in 19% of the patients with IBD. 12 of 44 patients with UC were positive for p-ANCA and only one of 22 patients with CD was p-ANCA positive. Of the 12 p-ANCA positive UC patients 2 cases were found to have proctosigmoiditis, 6 cases had left-sided colitis and 4 cases had pancolitis. There was no correlation between the presence of this antibody and any of the studied clinical variables. No person of the first degree and control group presented positive test.

Discussion/Conclusion: The prevalence of p-ANCA in NE Romania patients with IBD (19%) is lower than that in the Western population. The negativity of p-ANCA in all first degree relatives of NE Romania IBD patients should be further elucidated.
Extraintestinal manifestations in pediatric patients with inflammatory bowel disease

Hospital Gregorio Marañón, Madrid, Spain

Introduction: The objective of our study was to describe the frequency of development of extraintestinal manifestations (EIM) in pediatric patients with inflammatory bowel disease (IBD) in our hospital in last 20 years.

Methods: Retrospective descriptive study including 50 patients followed in pediatric gastroenterology service with IBD (18 ulcerative colitis [UC], 32 Crohn’s disease [CD]) and the presentation of EIM.

Results: EIM appeared in 30% (15 children) of followed patients. There were differences comparing EIM between UC and CD: 16% of patients with UC present EIM and 37% of children with CD. We found the next EIM in our patients: Articular manifestations 33%: artralgias (n = 4: UC 2/CD 3), sacroileitis (n = 1: CD). Dermatologic manifestations 13%: erythema nodosum (n = 2: 1 UC/1 CD). Ophthalmologic manifestations 13%: uveitis (n = 2: CD). Hepatobiliary/pancreatic manifestations 13%: sclerosing cholangitis (n = 1: CD); autoimmune pancreatitis (n = 1: CD). Endocrinologic manifestations 13%: hyperparatiroidism (n = 1: UC), hypotiroidism (n = 1: CD). Other manifestations 13%: idiopathic thrombocytopenic purpura (ITP) (n = 1: CD), Wolff-Parkinson-White: (n = 1: CD).

Discussion/Conclusion: Articular disease was the most prevalent of extraintestinal manifestations of IBD. Systemic manifestations are more frequent in patients with Crohn’s disease than in those with the diagnosis of ulcerative colitis in children.
Cytokine profile in autoimmune liver disease-inflammatory bowel diseases (overlap-syndrome)

E.A. Torres, O. S. Shifrin, V.B. Zolotatevsky, V.T. Ivashkin
Department of Propaedeutics of Internal Diseases, Gastroenterology and Hepatology, Moscow Medical Academy I.M. Sechenov, Moscow, Russia

Cytokine serum profile in autoimmune liver diseases and chronic inflammatory colonopathies may help clarify overlap-syndrome pathogenesis.

**Objectives:** To determine the serum level of principal pro- (IL-12, TNFα и INFγ) and anti-inflammatory (IL-4, IL-10) cytokines in autoimmune liver disease (primary biliary cirrhosis) and inflammatory bowel disease (ulcerative colitis)-overlap-syndrome.

**Methods:** Main group consisted of 20 patients with the mean age of 55.25 ± 11.8 years. Overlap-syndrome in this group was diagnosed based on the clinical signs and symptoms as well as laboratory results. In 15 of these 20 patients morphology study was performed and results confirming the overlap-syndrome were received. Control group consisted of 10 nearly healthy individuals, main group – of 20 patients, 10 out of them suffer primary biliary cirrhosis (group 1), and the rest (10 patients) – primary biliary cirrhosis + ulcerative colitis (group 2).

**Results:** IL-4 (7.78 ± 1.79 pg/ml) and IL-10 (83.96 ± 25.75 pg/ml) level showed no significant difference between overlap-syndrome group and the control group (p = 0.56, p = 0.49) and group 1 (p = 0.81, p = 0.93). IL-12 (180.51 ± 62.3 pg/ml), TNFα (22.5 ± 4.3 pg/ml) and IFNγ (251.5 ± 214.6 pg/ml) level in the group 2 was significantly higher than in control group (p = 0.01, p = 0.002, p = 0.015). In the group 1 IL-12 level was lower (p = 0.002) than in the group with overlap-syndrome, and TNFα и IFNγ level didn’t show significant difference with the this group (p = 0.36, p = 0.38).

**Discussion/Conclusion:** Increased secretion of pro-inflammatory cytokines (IL-12, TNFα, IFNγ) in overlap-syndrome is likely to be accounted for by the immune cell (T-lymphocytes, monocytes/macrophages) activation.
Endoscopic diagnosis versus histopathologic diagnosis in inflammatory bowel disease (IBD)

Stela Nicoleta Turchina, Carmen Monica Preda, G. Becheanu, Mona Dumbrava, C. Gheorghe, M. Diculescu
Center of Gastroenterology and Hepatology Fundeni, Bucharest, Romania

Introduction: We consider that the endoscopy is the most important diagnostic tool in IBD. The aim was to correlate the endoscopic description with histopathology.

Material and methods: We performed a retrospective study, including 170 patients with active IBD (endoscopic diagnosis), examined during 2000–2003 in our Department. There were 3 groups of patients: Group CD: 65 patients with an endoscopic description suggestive of Crohn’s disease. Group UC: 99 cases with an endoscopy suggestive of ulcerative colitis. Group IC: 6 patients with non-specific description (indeterminate colitis). All patients included performed colonoscopy, with multiple mucosal biopsies.

Results: on the description of an expert histopathologist, we found 6 categories of biopsies: suggestive of UC, suggestive of CD, non-specific (chronic active inflammatory infiltrate without any specificity), suggestive of acute microbial colitis (AMC), other diagnosis (other), normal. This description was applied to the 3 patients groups: see table.

<table>
<thead>
<tr>
<th>Patients group</th>
<th>UC</th>
<th>CD</th>
<th>Non-specific</th>
<th>AMC</th>
<th>Other</th>
<th>Normal</th>
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<tbody>
<tr>
<td>CD</td>
<td>5</td>
<td>12</td>
<td>38</td>
<td>6</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>UC</td>
<td>68</td>
<td>0</td>
<td>23</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>IC</td>
<td>3</td>
<td>0</td>
<td>3</td>
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Conclusions:
- in patients with endoscopy suggestive of CD, biopsy findings are most often non-specific (58.5%), while in 7.7% suggests UC and in 9.23% AMC.
- in patients with endoscopic ulcerative colitis, the biopsy is concordant with the endoscopy in 68.7%, only 23.2% have non-specific findings.
- cases with endoscopic indeterminate colitis have bioptic findings of UC in 50%, while in 50% are non-specific.
- mucosal biopsies seem more important for differential diagnosis, rather than for positive diagnosis.
A prospective multicenter study of outcomes and predictors of response in severe pediatric ulcerative colitis

SickKids Hospital, University of Toronto, Canada (coordinating site)

Aim: In the first prospective study of hospitalized children with severe UC, we aimed to assess short and long-term outcomes and identify clinical and biological predictors of non-response to intravenous corticosteroids (IVCS).

Methods: 128 children (47% males; 12.9 ± 3.9 years) admitted for severe UC (85% extensive; 52% new onset; disease duration 14 months [IQR 4–32]) were enrolled from 10 pediatric IBD centers. Patients were managed according to the local practice. Clinical data and the Pediatric UC Activity Index (PUCAI) were recorded on days 1, 3, 5, at discharge and initiation of additional therapy. Radiographic and laboratory variables, including day-3 fecal calprotectin, lactoferrin and S100A12 were ascertained. Predictors of response were analyzed using univariate and multivariate analyses, survival analysis and diagnostic utility approach. Follow-up data were prospectively obtained 1-year after hospital discharge.

Results: 37 (29%; 95% CI 22–37%) children failed IVCS and received, within 12 ± 7 days, cyclosporine (n = 1, 3%), colectomy (n = 3, 8%) or infliximab (n = 33, 89%). Of the latter, 25 (76%) responded and 8 (24%) proceeded to colectomy, bringing cumulative colectomy rate by discharge to 9%. Several predictors were associated with IVCS failure, but the best multivariable model included rectal bleeding (OR 2.3 [1.2–4.1]), abdominal pain (OR 1.8 [1.1–3.3]) and number of nocturnal stools (OR 1.6 [1.2–2.2]) at the 3rd day of treatment. The PUCAI most strongly predicted response when compared with Travis (Oxford), Seo and the Fulminant Colitis Index, ESR, albumin and CRP (AUC of ROC curve 0.82 [95% CI 0.72–0.92]; p < 0.001; vs. all others with AUC < 0.77). The 3 fecal inflammatory markers were very high in all 128 patients but were not useful in predicting response to medical therapy (AUC 0.65 [0.5–0.81]. Aiming for sensitivity on day 3, PUCAI > 45 screened for patients likely to fail IVCS (NPV = 94%, PPV = 43%; p < 0.001). Aiming for specificity on day 5, PUCAI score > 70 optimally guided implementation of 2nd line therapy (PPV = 100%, NPV = 87%; p < 0.001). The day 3 PUCAI score, predicted response up to 1 year post discharge (p < 0.001; log rank test of time to 2nd line therapy). In 1 year follow-up, 10 of the 91 primary IVCS responders received infliximab or colectomy and 7/25 infliximab-responders underwent colectomy (cumulative 1 year colectomy rate 18%).

Conclusions: The PUCAI, calculated on days 3 and 5 of steroid therapy, can identify patients requiring 2nd line therapy. Infliximab therapy is successful in inducing remission in steroid-refractory UC. Remission, once achieved with or without infliximab, can usually be sustained to 1 year.
Epidemiological risk factors for childhood onset inflammatory bowel disease in Scotland: A case-control study

J. Van Limbergen\textsuperscript{1,2,5}, H. Spiers\textsuperscript{1,5}, R. Farhadi\textsuperscript{1,5}, M.L. Wilson\textsuperscript{5}, R.K. Russell\textsuperscript{3}, G. Mahdi\textsuperscript{4}, J. Satsangi\textsuperscript{2}, D.C. Wilson\textsuperscript{1,5}

\textsuperscript{1}Paediatric Gastroenterology & Nutrition, Royal Hospital for Sick Children, Edinburgh; \textsuperscript{2}GI Unit, Molecular Medicine Centre, Western General Hospital, University of Edinburgh; \textsuperscript{3}Paediatric Gastroenterology, Yorkhill Hospital, Glasgow; \textsuperscript{4}Paediatric Gastroenterology, Royal Aberdeen Children’s Hospital, Aberdeen; \textsuperscript{5}Child Life and Health, University of Edinburgh, UK

Introduction: Inflammatory bowel disease (IBD)-incidence is increasing among children in Scotland. We investigated the influence of several environmental factors in IBD pathogenesis.

Methods: 126 paediatric IBD cases (diagnosed < 17 years of age; median age at diagnosis 9.8 years [Q1–Q3: 7.5–11.7]) were matched with one control subject by age, sex and geographical location (socio-economic status). Children with IBD and their parents were interviewed face-to-face to obtain data on breastfeeding, immunisation history, surgical and medical history and family history (FH). Control data was obtained via postal questionnaire. Unifactorial analyses ($\chi^2$) and multifactorial analysis (binary logistic regression) were performed.

Results: FH of IBD was associated with IBD (OR 3.34; 95% [1.70–6.56], $p = 0.0003$). History of asthma, eczema and food allergy (OR 2.48 [1.28–4.78], $p = 0.005$, OR 2.83 [1.50–5.36], $p = 0.001$ and OR 2.98 [1.04–8.54], $p = 0.03$, respectively) show association with paediatric IBD and CD. There were no differences between cases and controls regarding breastfeeding (52% vs. 55%, $p = 0.71$). Multivariate analysis implicated FH of IBD, bowel cancer and history of asthma and eczema ($p < 0.001$, 0.033, 0.045 and 0.015, respectively). In contrast with unifactorial analysis, no association of IBD with parental smoking during pregnancy, at birth and currently was found in the multifactorial analysis, irrespective of FH of IBD.

Discussion/Conclusion: We have shown an association between atopy and paediatric IBD but none with breastfeeding practices. FH of IBD/bowel cancer is associated with IBD. Our epidemiological data are noteworthy in the context of the increasing number of genetic associations related to common inflammatory pathways identified in IBD and cancer.
Childhood-onset versus adult-onset inflammatory bowel disease: Phenotype

Johan Van Limbergen1,2,6, Richard K. Russell3, Hazel E. Drummond1, Marian C. Aldhous1, Nicola K. Round1,2, Elaine R. Nimmo1, Peter M. Gillett2, Paraic McGrogan3, Lawrence T. Weaver4, W. Michael Bisset5, Gamal Mahdi5, Ian D. Arnott1, Jack Satsangi1, David C. Wilson2,6

1Gastrointestinal Unit, Molecular Medicine Centre, Western General Hospital, University of Edinburgh, Edinburgh, United Kingdom
2Department of Paediatric Gastroenterology and Nutrition, Royal Hospital for Sick Children, Edinburgh, United Kingdom
3Department of Paediatric Gastroenterology, Yorkhill Hospital, Glasgow, United Kingdom
4Department of Child Health, University of Glasgow, Glasgow, United Kingdom
5Department of Paediatric Gastroenterology, Royal Aberdeen Children’s Hospital, Aberdeen, United Kingdom
6Child Life and Health, University of Edinburgh, Edinburgh, United Kingdom

Introduction: Childhood-onset inflammatory bowel disease (IBD) might be etiologically different from adult-onset IBD. We analyzed disease phenotype/progression of childhood-onset disease and compared them with adult-onset IBD.

Methods: Anatomical location and behavior were assessed in 416 patients with childhood-onset (276 CD/99 UC/41 IBDU diagnosed before 17th birthday) and 1297 patients with adult-onset (596 CD/701 UC) IBD using the Montreal classification.

Results: At diagnosis in children, Crohn’s disease (CD) involved small bowel and colon in 51%, colon in 36%, and ileum in 6%; the upper GI tract was also affected in 51%. In 39%, the anatomical extent increased within 2 years. Behavioral characteristics progressed: 24% developed structuring/penetrating complications within 4 years (versus 9% at diagnosis; p < 0.0001, OR 3.32 [1.86–5.92]).

Compared with adults, childhood-onset disease was characterized by a ‘panenteric’ phenotype (ileocolonic plus upper GI) (43% versus 3%; p < 0.0001, OR 23.36 [13.45–40.59]) with less isolated ileal (2% versus 31%; p < 0.0001, OR 0.06 [0.03–0.12]) or colonic disease (15% versus 36%; p < 0.0001, OR 0.31 [0.21–0.46]).

Ulcerative colitis (UC) was extensive in 82% of the children at diagnosis, versus 48% of adults (p < 0.0001, OR 5.08 [2.73–9.45]); 46% of the children progressed to develop extensive colitis during follow-up.

46% of children with CD and 35% with UC required immunomodulatory therapy within 12 months of diagnosis. The median time to first surgery was longer in childhood-onset than adult-onset patients with CD (13.7 versus 7.8 years, p < 0.001); the reverse was true for UC.

Discussion/Conclusion: Childhood-onset IBD is characterized by extensive intestinal involvement and rapid early progression.
Characteristics of new pediatric IBD patients enrolled in the Hungarian Pediatric IBD Registry (HUPIR)

G. Veres\(^1\), P. Lakatos\(^2\), M. Papp\(^3\), Hungarian Pediatric IBD Registry (HUPIR) Group
\(^1\)Ist Department of Paediatrics, Budapest, Hungary
\(^2\)Ist Department of Medicine, Budapest, Hungary
\(^3\)Department of Gastroenterology, Debrecen, Hungary

**Background and aims:** On behalf of the Hungarian Pediatric Gastroenterology Society prospective registry of pediatric inflammatory bowel disease (IBD) was launched from the 1st of January 2007 with the cooperation of 27 institutes (clinics, hospitals, outpatient departments) ensuring the coverage of the whole country. The survey data has been forwarded online to the center of the European Pediatric IBD Registry (Rotterdam). In recent epidemiological studies from Europe and North America the reported incidence of childhood Crohn disease (CD) is 3–4 cases per 100,000 per year, and of ulcerative colitis (UC) 2–3 cases per 100,000 per year. So far the incidence of pediatric IBD in Hungary is unknown.

**Methods:** The participating institutes are requested to fill out a questionnaire (78 parameters) about every newly diagnosed IBD patients younger than 18 years. The questionnaire is about epidemiological and anthropometrical data, main symptoms, diagnostic procedures (endoscopy, CT, MRI), and the detailed results of histological and imaging procedures.

**Results:** Between 01.01.2007 and 30.10.2008 233 newly diagnosed cases of IBD were prospectively identified: 145 cases of CD, 72 cases of UC and 16 cases of indeterminate colitis. As a result the incidence of childhood IBD was 6.13 cases per 100,000, with the incidence of CD being 4.07 cases per 100,000 per year, the incidence of UC 1.67 cases per 100,000 per year and the incidence of indeterminate colitis 0.40 cases per 100,000 per year. The mean age at diagnosis was 13 years (range: 1.5–18 year). There was a male preponderance in CD, in contrast, sex ratio in UC patients were equal. Positive family history of IBD was registered in 7.8% of patients and 9.2% of patients with CD were reported to have a fistula. Ileoscopy rate was only 48% technical problem was the most common reason for the lack of ileal intubation. Oesophago-gastro-duodenoscopy was performed in 50% of all cases. In 35% were MRI or CT scan made for the detailed verification of the disease.

**Conclusions:** The incidences reported in the first 22 months of HUPIR are similar to the European and North American data. The dominance of CD proved to be also consistent with other studies. Almost 10% of the patients with CD had fistula. Ileal intubation and oesophago-gastro-duodenoscopy were performed in the half of the cases, and this rate should be improved in the future.
Response to medical treatment in patients with Crohn’s disease: The role of NOD2/CARD15 mutations, disease phenotype and age of diagnosis

B. Weiss¹, O. Lebowitz¹, H. Fider², I. Maza³, A. Levine⁴, R. Shaoul⁵, S. Reif⁶, Y. Bujanover¹, A. Karban³

¹Division of Pediatric Gastroenterology and Nutrition, Safra Children’s Hospital, Sheba Medical Center, Tel-Hashomer, and Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel
²Department of Gastroenterology, Sheba Medical Center, Tel-Hashomer, and Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel
³Department of Gastroenterology, Rambam Medical Center, and Rappaport Faculty of Medicine, Technion, Haifa, Israel
⁴Division of Pediatric Gastroenterology and Nutrition, Wolfson Medical Center, Holon, and Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel
⁵Division of Pediatric Gastroenterology and Nutrition, Bnei-Zion Medical Center, and Rappaport Faculty of Medicine, Technion, Haifa, Israel
⁶Division of Pediatric Gastroenterology and Nutrition, Dana Children’s Hospital, Souraski Medical Center, and Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

Introduction: Medical therapeutic options of Crohn's disease are diverse, however, it is unclear which factors affect the outcome of the medical treatment, and why different patients respond differently to the same treatment. To examine the effects of disease characteristics and NOD2/CARD15 gene mutations on the outcome of the medical treatment with steroids, immunomodulators and infliximab.

Methods: A retrospective analysis of 199 medical records of Crohn’s disease patients, children and adults, from several medical institutions in Israel. Patients were treated with steroids, immunomodulators (6-mercaptopurine or azathioprine) or infliximab. Each of the participants has a previous evaluation for the presence of one of three mutations in the NOD2/CARD15 gene (G908R, R702W, fs1007). Demographic, genotype and phenotype details were reviewed. Remission or response to medical therapy was assessed using the Harvey-Bradshaw score.

Results: CD-associated NOD2/CARD15 mutations were not related to the rate of steroids dependency, or clinical response to AZA/6-MP and infliximab. Steroid dependency was associated with colonic involvement: 33/127 (26%) patients with colonic disease were steroid dependent, compared with 7/72 (9.7%) patients with isolated small bowel disease (ISB), (p = 0.009). ISB was mildly associated with a better remission/response to AZA/6-MP treatment. Disease behavior and age of diagnosis were not related to response to therapy.

Discussion/Conclusion: Response to treatment with systemic steroids, AZA/6-MP and infliximab are not related to NOD2/CARD15 mutations, age of diagnosis and disease behavior. Patients with colonic disease have higher rates of steroid dependency.
Role of the antioxidative enzyme Prdx6 in inflammatory bowel disease (IBD)

Jonas Zeitz, Isabelle Frey-Wagner, Esther Kresin, Michael Fried, Gerhard Rogler
Division of Gastroenterology and Hepatology, University Hospital, Zurich, Switzerland, E-Mail: jonas.zeitz@usz.ch

Background: Inflamed tissue of patients suffering from IBD shows high infiltration of macrophages and neutrophils. Oxidative burst of these cells exerts oxidative stress and contributes to tissue damage and subsequently increased epithelial permeability. The antioxidative enzyme Peroxiredoxin 6 (Prdx6) has been shown to be highly expressed in the intestinal epithelium and in macrophages.

Methods: Acute or chronic colitis was induced by administration of 2% dextran sodium sulfate (DSS) with the drinking water in Prdx6 knockout mice and transgenic mice overexpressing Prdx6. Oxidative tissue damage was determined by Western blot of derivatized protein carbonyl units. Cytokine secretion by mesenterial lymphocytes (ML) was determined in a multiplex immunoassay.

Results: Prdx6 protein expression was decreased by acute and chronic colitis in wildtype and in Prdx6 overexpressing animals. Prdx6 knockout animals displayed lower histological scores in acute as well as in chronic DSS colitis. Prdx6 overexpressing animals showed a higher histological score in the proximal colon after induction of chronic DSS colitis. In the chronic colitis model increased secretion of proinflammatory (TNF-α, IL-6) as well as antiinflammatory (IL-10, IL-2, IL-4, IL-5) cytokines by ML could be observed in Prdx6 knockout animals in comparison to wildtype animals whereas lower levels of these cytokines were secreted by ML isolated from Prdx6 overexpressing animals.

Conclusion: Our data suggest that effective defense against bacterial translocation by reactive oxygen species might ameliorate the course of DSS-colitis as Prdx6 knockout animals, in which less neutralization of ROS occurs, displayed lower histological scores in acute as well as in chronic colitis.
Author Index to Poster Abstracts
(Name - Poster Number)

Abdovic, S. 29, 43 Bidmon- 12
Adán Merino, L. 25, 42 Fliegenschnee, B.
Akshia, I. 54 Biervliet, S. van 63, 64
Alberdi, J.M. 50 Bigvava, T. 35
Aldeguer, M. 50 Bisset, M. 81
Aldhous, M.C. 81 Bock, J.-U. 33
Algaba, A. 1, 9, 10, 11, 52, 72 Bonetns, P. 63, 64
Alilliet, P. 63, 64 Boubaker, J. 22, 36, 37, 56
Alper, A. 58 Bray, G. 73
Altorjay, I. 48, 49 Broide, E. 14
Alvarez, J. 52 Bucurica, S. 62
Alvarez Calatayud, G. 5, 76 Bujanover, Y. 59, 83
Ancusa, V.M. 66, 70, 71 Bury, F. 63, 64
Appleby, V.J. 2
Arakhhamia, T. 35 Camuesco, D. 17, 24
Arhip, O. 74 Caniklioglu, A. 7
Armott, I. 81 Caraiola, S. 62
Arribas, B. 17, 24 Carneros, J.A. 9, 10, 11
Arts, W. 63, 64 Carrión, G. 50
Atanasssova, A. 3 Cepowicz, D. 55
Avram, G. 23, 30 Chavoushian, A. 15
Chkhartishvili, E. 34, 35
Baghdasaryan, A. 32 Chouliaras, G. 16
Baicus, C. 62 Ciocarlan, M. 53
Bailon, E. 17, 24 Claudel, T. 32
Ballauff, A. 40 Colinet, S. 63, 64
Banciu, C. 4, 45, 46, 66, 67, 70, 71 Comalada, M. 17, 24
Barredo Valderrama, 5, 76 Comito, D. 18, 21
E. Concha, A. 17
Craciun, C. 23, 30
Barreiro, A. 50 Crandall, W. 79
Barta, Z. 48 Crespo Medina, M. 5, 76
Bartosova, L. 8 Crini, M. 16
Baskol, G. 6, 7 Croitoru, L. 74
Baskol, M. 6, 7 Cucuruz, M. 27
Batovsky, M. 8 Czyzewska, J. 55
Bauraind, O. 63, 64
Baurecht, H. 40 Day, A.S. 79
Becheanu, G. 78 De Pousa, I. 1
Ben Mustapha, N. 36 Díaz, A. 50
Berg Schmidt, E. 68 Diculescu, M. 53, 78
Bermejo, F. 1, 9, 10, 11, 52, 72 Die, J. 52
Bernal, T. 44 Dogruel, F. 6, 7
<table>
<thead>
<tr>
<th>Name</th>
<th>Numbers</th>
<th>Name</th>
<th>Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Domínguez, I.</td>
<td>1</td>
<td>Grzenda-Adamek, Z.</td>
<td>69</td>
</tr>
<tr>
<td>Domselaar, M. Van</td>
<td>10, 19, 52, 72</td>
<td>Guerra, I.</td>
<td>9, 11</td>
</tr>
<tr>
<td>Dotan, I.</td>
<td>14, 58</td>
<td>Gumhold, J.</td>
<td>32</td>
</tr>
<tr>
<td>Draganov, V.</td>
<td>20</td>
<td>Gursoy, S.</td>
<td>6, 7</td>
</tr>
<tr>
<td>Drummond, H.E.</td>
<td>81</td>
<td>Guzinská-</td>
<td>55</td>
</tr>
<tr>
<td>Dumache, R.</td>
<td>67</td>
<td>Ustymowicz, K.</td>
<td></td>
</tr>
<tr>
<td>Dumbrava, M.</td>
<td>78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Durnea, C.</td>
<td>75</td>
<td>Hansen, J.B.</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hansen, L.F.</td>
<td>47</td>
</tr>
<tr>
<td>Eberstein, A.</td>
<td>33</td>
<td>Harsfalvi, J.</td>
<td>49</td>
</tr>
<tr>
<td>Ehrmann, J.</td>
<td>39</td>
<td>Hart, A.R.</td>
<td>28, 68</td>
</tr>
<tr>
<td>Elkjaer, M.E.</td>
<td>44</td>
<td>Hauser, B.</td>
<td>63, 64</td>
</tr>
<tr>
<td>Engel, U.</td>
<td>47</td>
<td>Healey, J.</td>
<td>2</td>
</tr>
<tr>
<td>Eruli, S.</td>
<td>41</td>
<td>Herman-Sucharska, I.</td>
<td>69</td>
</tr>
<tr>
<td>Esser, D.</td>
<td>44</td>
<td>Hernandez, M.</td>
<td>5, 76</td>
</tr>
<tr>
<td>Estellés, J.</td>
<td>72</td>
<td>Hoffman, I.</td>
<td>63, 64</td>
</tr>
<tr>
<td>Etienne, I.</td>
<td>63, 64</td>
<td>Hojsak, I.</td>
<td>29, 43</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hoole, D.</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Huber, W.-D.</td>
<td>12</td>
</tr>
<tr>
<td>Fallingborg, J.</td>
<td>13</td>
<td>Hughes, D.</td>
<td>73</td>
</tr>
<tr>
<td>Famiani, A.</td>
<td>18, 21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farhadi, R.</td>
<td>80</td>
<td>Huidobro Fernández,</td>
<td>5, 76</td>
</tr>
<tr>
<td>Farkas, G.</td>
<td>49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farkas, K.</td>
<td>49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feki, M.M.</td>
<td>37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fekih, M.</td>
<td>22, 36, 37, 56</td>
<td>Iacob, R.</td>
<td>53</td>
</tr>
<tr>
<td>Fider, H.</td>
<td>83</td>
<td>Ilias, T.</td>
<td>23, 30</td>
</tr>
<tr>
<td>Filali, A.</td>
<td>22, 36, 37, 56</td>
<td>Ivashkin, V.T.</td>
<td>77</td>
</tr>
<tr>
<td>Floare, M.</td>
<td>46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fratiliu, A.</td>
<td>60, 61</td>
<td>Jacobsen, C.</td>
<td>31</td>
</tr>
<tr>
<td>Fratila, O.</td>
<td>23, 30</td>
<td>Jadresin, O.</td>
<td>29, 43</td>
</tr>
<tr>
<td>Frey-Wagner, I.</td>
<td>84</td>
<td>Jahlke, V.</td>
<td>32</td>
</tr>
<tr>
<td>Fried, M.</td>
<td>84</td>
<td>Jaklin-Kekez, A.</td>
<td>29, 43</td>
</tr>
<tr>
<td>Fries, W.</td>
<td>21</td>
<td>Janssens, E.</td>
<td>63, 64</td>
</tr>
<tr>
<td>Friger, M.</td>
<td>44</td>
<td>Jongen, J.</td>
<td>33</td>
</tr>
<tr>
<td>Froílán Torres, C.</td>
<td>25, 42</td>
<td>Jorjoliani, L.</td>
<td>34, 35, 38</td>
</tr>
<tr>
<td>Fuchsbichler, A.</td>
<td>32</td>
<td>Jurik, A.</td>
<td>40</td>
</tr>
<tr>
<td>Fydek, K.</td>
<td>69</td>
<td>Kaabachi, N.</td>
<td>37</td>
</tr>
<tr>
<td>Gallizzi, R.</td>
<td>18</td>
<td>Kadian, H.</td>
<td>15</td>
</tr>
<tr>
<td>Galvez, J.</td>
<td>17, 24</td>
<td>Kahlke, V.</td>
<td>33</td>
</tr>
<tr>
<td>García-Durán, F.</td>
<td>9, 11</td>
<td>Kallel, L.</td>
<td>22, 36, 37, 56</td>
</tr>
<tr>
<td>García-Garzón, S.</td>
<td>9, 11</td>
<td>Kammer, A.</td>
<td>59</td>
</tr>
<tr>
<td>Garrido, E.</td>
<td>10, 19</td>
<td>Kappler, R.</td>
<td>40</td>
</tr>
<tr>
<td>Gheorghe, C.</td>
<td>78</td>
<td>Karban, A.</td>
<td>83</td>
</tr>
<tr>
<td>Gillett, P.M.</td>
<td>65, 81</td>
<td>Karoui, S.</td>
<td>36, 37</td>
</tr>
<tr>
<td>Gisbert, J.P.</td>
<td>1, 10, 72</td>
<td>Karseladze, E.</td>
<td>38</td>
</tr>
<tr>
<td>Gómez Senent, S.</td>
<td>25, 42</td>
<td>Karseladze, R.</td>
<td>34, 35, 38</td>
</tr>
<tr>
<td>Gorgun, J.V.</td>
<td>51</td>
<td>Kattamis, A.</td>
<td>16</td>
</tr>
<tr>
<td>Gotia, L.S.</td>
<td>26, 27</td>
<td>Kemon, A.</td>
<td>55</td>
</tr>
<tr>
<td>Gotia, S.R.</td>
<td>26, 27, 70</td>
<td>Klar, A.</td>
<td>14</td>
</tr>
<tr>
<td>Griffiths, A.M.</td>
<td>79</td>
<td>Kolacek, S.</td>
<td>29, 43</td>
</tr>
<tr>
<td>Name</td>
<td>Page(s)</td>
<td>Name</td>
<td>Page(s)</td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------</td>
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<td>---------</td>
</tr>
<tr>
<td>Koletzko, S.</td>
<td>40</td>
<td>Moun, B.</td>
<td>44</td>
</tr>
<tr>
<td>Koncny, M.</td>
<td>39</td>
<td>Munkholm, P.</td>
<td>31, 44</td>
</tr>
<tr>
<td>Kotzev, I.A.</td>
<td>3</td>
<td>Munteanu, M.</td>
<td>67</td>
</tr>
<tr>
<td>Kovacs, A.</td>
<td>48, 49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kraja, B.</td>
<td>54</td>
<td>Nieto, A.</td>
<td>17</td>
</tr>
<tr>
<td>Kresin, E.</td>
<td>84</td>
<td>Nijaa, N.</td>
<td>36, 37</td>
</tr>
<tr>
<td>Lacher, M.</td>
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<td>Nos, P.</td>
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<td>Lagona, E.</td>
<td>16</td>
<td>Nouira, K.</td>
<td>22</td>
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<tr>
<td>Lakatos, L.</td>
<td>48, 49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lakatos, P.L.</td>
<td>48, 49, 82</td>
<td>O´Brien, J.</td>
<td>73</td>
</tr>
<tr>
<td>Langholz, E.</td>
<td>44</td>
<td>Odes, H.S.</td>
<td>44</td>
</tr>
<tr>
<td>Langner, C.</td>
<td>32</td>
<td>Olsen, A.</td>
<td>68</td>
</tr>
<tr>
<td>Leach, S.T.</td>
<td>79</td>
<td>Otley, A.R.</td>
<td>79</td>
</tr>
<tr>
<td>Lebowitz, O.</td>
<td>83</td>
<td>Ouerdiane, S.</td>
<td>22</td>
</tr>
<tr>
<td>Leleiko, N.</td>
<td>79</td>
<td>Overvad, K.</td>
<td>68</td>
</tr>
<tr>
<td>Lerner, A.</td>
<td>14, 41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levine, A.</td>
<td>14, 83</td>
<td>Pacurari, A.</td>
<td>45, 46, 57, 66,</td>
</tr>
<tr>
<td>Limbergen van, J.</td>
<td>80, 81</td>
<td>Pacurari, B.</td>
<td>57</td>
</tr>
<tr>
<td>Linarens, P.</td>
<td>1, 72</td>
<td>Paerregaard, A.</td>
<td>31, 47</td>
</tr>
<tr>
<td>Lohse, P.</td>
<td>40</td>
<td>Palamidou, F.</td>
<td>16</td>
</tr>
<tr>
<td>López San</td>
<td>9, 10, 19, 52, 72</td>
<td>Palatka, K.</td>
<td>48, 49</td>
</tr>
<tr>
<td>Roman, A.</td>
<td>72</td>
<td>Panayiotou, J.</td>
<td>16</td>
</tr>
<tr>
<td>López Serrano, P.</td>
<td>72</td>
<td>Papp, J.</td>
<td>48, 49</td>
</tr>
<tr>
<td>Lozano, M.</td>
<td>50</td>
<td>Paquot, I.</td>
<td>63, 64</td>
</tr>
<tr>
<td>Mack, D.</td>
<td>79</td>
<td>Parvu, M.</td>
<td>62</td>
</tr>
<tr>
<td>Mahdi, G.</td>
<td>80, 81</td>
<td>Patterson, D.</td>
<td>2</td>
</tr>
<tr>
<td>Mahler, T.</td>
<td>63, 64</td>
<td>Peleikis, H.</td>
<td>33</td>
</tr>
<tr>
<td>Mamula, P.</td>
<td>79</td>
<td>Penchev, P.</td>
<td>15, 20</td>
</tr>
<tr>
<td>Manevkska, B.</td>
<td>3</td>
<td>Peran, L.</td>
<td>17</td>
</tr>
<tr>
<td>Marian, L.</td>
<td>4</td>
<td>Pérez Calle, J.</td>
<td>72</td>
</tr>
<tr>
<td>Marinescu, M.</td>
<td>62</td>
<td>Perl, D.</td>
<td>41</td>
</tr>
<tr>
<td>Markowitz, J.F.</td>
<td>79</td>
<td>Pichler, J.</td>
<td>12</td>
</tr>
<tr>
<td>Martín, S.</td>
<td>50</td>
<td>Pieczarkowski, S.</td>
<td>69</td>
</tr>
<tr>
<td>Martín Arranz, E.</td>
<td>25, 42</td>
<td>Piqueras, B.</td>
<td>9, 10, 11</td>
</tr>
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<td>Martín Arranz, M.D.</td>
<td>25, 42, 72</td>
<td>Ponferrada, A.</td>
<td>50</td>
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<tr>
<td>Matri, S.</td>
<td>22, 36, 37, 56</td>
<td>Portyanko, A.</td>
<td>51</td>
</tr>
<tr>
<td>Maza, I.</td>
<td>83</td>
<td>Poza, G. de la</td>
<td>52</td>
</tr>
<tr>
<td>McGrogan, P.</td>
<td>81</td>
<td>Preda, C.</td>
<td>53, 78</td>
</tr>
<tr>
<td>McGStay, M.</td>
<td>73</td>
<td>Prifti, S.</td>
<td>54</td>
</tr>
<tr>
<td>Meyron-Holtz, E.</td>
<td>59</td>
<td>Prochazka, V.</td>
<td>39</td>
</tr>
<tr>
<td>Mihaila, R.</td>
<td>23, 30</td>
<td>Pyczynicz, A.</td>
<td>55</td>
</tr>
<tr>
<td>Mihaila, R.</td>
<td>74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Misak, Z.</td>
<td>29, 43</td>
<td>Quaz, A.</td>
<td>56</td>
</tr>
<tr>
<td>Moalem, S.</td>
<td>41</td>
<td></td>
<td></td>
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<tr>
<td>Molnar, T.</td>
<td>48, 49</td>
<td>Rachmilewitz, D.</td>
<td>58</td>
</tr>
<tr>
<td>Morales, J.L.</td>
<td>5, 76</td>
<td>Radu, L.</td>
<td>57</td>
</tr>
<tr>
<td>Moreea, S.</td>
<td>2</td>
<td>Raffa, V.</td>
<td>18, 21</td>
</tr>
<tr>
<td>Moshe, S.</td>
<td>59</td>
<td>Raubal, B.</td>
<td>12</td>
</tr>
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<td>Name</td>
<td>Page(s)</td>
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<td>Real, Y.</td>
<td>50</td>
<td>Stockbrügger, R.W.</td>
<td>44</td>
</tr>
<tr>
<td>Reif, S.</td>
<td>58, 83</td>
<td>Stocker, W.</td>
<td>48</td>
</tr>
<tr>
<td>Reifen, R.</td>
<td>59</td>
<td>Stoinov, S.</td>
<td>15</td>
</tr>
<tr>
<td>Rezi, E.C.</td>
<td>60, 61</td>
<td>Susan, L.M.</td>
<td>26, 45, 66, 67, 70, 71</td>
</tr>
<tr>
<td>Rimbas, M.</td>
<td>62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rodriguez, J.L.</td>
<td>1, 9, 11</td>
<td>Swiat, A.</td>
<td>69</td>
</tr>
<tr>
<td>Rodríguez-Cabezas, M.E.</td>
<td>17, 24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rodriíguez-Gandía, M.</td>
<td>10</td>
<td>Taneascu, C.</td>
<td>62</td>
</tr>
<tr>
<td>Rogalidou, M.</td>
<td>63, 64</td>
<td>Tankova, L.</td>
<td>20</td>
</tr>
<tr>
<td>Rogers, P.</td>
<td>65</td>
<td>Taxonera, C.</td>
<td>72</td>
</tr>
<tr>
<td>Rogler, G.</td>
<td>84</td>
<td>Teglbjaerg, P.S.</td>
<td>13</td>
</tr>
<tr>
<td>Roma-Giannikou, E.</td>
<td>16</td>
<td>Télay, I.</td>
<td>73</td>
</tr>
<tr>
<td>Romano, C.</td>
<td>18, 21</td>
<td>Toader, E.</td>
<td>74, 75</td>
</tr>
<tr>
<td>Romosan, I.</td>
<td>4, 45, 46, 57, 66, 67, 70, 71</td>
<td>Tolin Hernani, M.</td>
<td>5, 76</td>
</tr>
<tr>
<td>Rossi, P.</td>
<td>18, 21</td>
<td>Tomás, E.</td>
<td>9, 11</td>
</tr>
<tr>
<td>Round, N.</td>
<td>81</td>
<td>Tonkonogy, S.</td>
<td>41</td>
</tr>
<tr>
<td>Russell, R.I.</td>
<td>80, 81</td>
<td>Torres, E.A.</td>
<td>77</td>
</tr>
<tr>
<td>Sachar, D.B.</td>
<td>41</td>
<td>Trauner, M.</td>
<td>32</td>
</tr>
<tr>
<td>Sadigh, D.</td>
<td>73</td>
<td>Tsianos, E.</td>
<td>44</td>
</tr>
<tr>
<td>Saginadze, L.</td>
<td>34, 35, 38</td>
<td>Tskhakaia, M.</td>
<td>34</td>
</tr>
<tr>
<td>Sánchez Prudencio, S.</td>
<td>9, 11</td>
<td>Tumpek, J.</td>
<td>48</td>
</tr>
<tr>
<td>Sánchez Sánchez, C.</td>
<td>5, 76</td>
<td>Turchina, S.N.</td>
<td>53, 78</td>
</tr>
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<td>Sartor, R.B.</td>
<td>41</td>
<td>Turner, D.</td>
<td>79</td>
</tr>
<tr>
<td>Satsangi, J.</td>
<td>65, 80, 81</td>
<td>Turner, R.</td>
<td>73</td>
</tr>
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<td>Savion, O.</td>
<td>59</td>
<td>Tybulewicz, A.</td>
<td>65</td>
</tr>
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<td>Savoiu, G.</td>
<td>66, 67, 71</td>
<td>Ustrilla, P.</td>
<td>24</td>
</tr>
<tr>
<td>Scaillon, M.</td>
<td>63, 64</td>
<td>Uusoue, K.</td>
<td>79</td>
</tr>
<tr>
<td>Schröpf, S.</td>
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<td>Utrilla, P.</td>
<td>24</td>
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<td>40</td>
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<td>79</td>
</tr>
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<td>Segura Cabral, J.M.</td>
<td>25, 42</td>
<td>Van Limbergen, J.</td>
<td>80, 81</td>
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<td>45, 46, 66, 67, 70, 71</td>
<td>Vardi, H.</td>
<td>44</td>
</tr>
<tr>
<td>Shaoul, R.</td>
<td>83</td>
<td>Veereman-Wauters, G.</td>
<td>63, 64</td>
</tr>
<tr>
<td>Shifrin, O.</td>
<td>77</td>
<td>Velikova, C.</td>
<td>20</td>
</tr>
<tr>
<td>Silbert, D.</td>
<td>32</td>
<td>Verdes, D.</td>
<td>26</td>
</tr>
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<td>68</td>
<td>Veres, G.</td>
<td>48, 49, 82</td>
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<tr>
<td>Silverberg, M.</td>
<td>79</td>
<td>Villa, J.C.</td>
<td>9, 11</td>
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<td>Simedrea, I.</td>
<td>4</td>
<td>Voiosu, R.</td>
<td>62</td>
</tr>
<tr>
<td>Sina, M</td>
<td>54</td>
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<td></td>
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<tr>
<td>Sladek, M.</td>
<td>69</td>
<td>Walters, T.D.</td>
<td>79</td>
</tr>
<tr>
<td>Smets, F.</td>
<td>63, 64</td>
<td>Waters, H.</td>
<td>44</td>
</tr>
<tr>
<td>Sokal, E.</td>
<td>63, 64</td>
<td>Weaver, L.T.</td>
<td>81</td>
</tr>
<tr>
<td>Southern, P.</td>
<td>2</td>
<td>Weiss, B.</td>
<td>14, 59, 83</td>
</tr>
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<td>Spassova, Z.</td>
<td>15</td>
<td>Wewer, V.</td>
<td>31, 47</td>
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<td>Spiers, H.</td>
<td>80</td>
<td>Wilschanski, M.</td>
<td>14</td>
</tr>
<tr>
<td>Staelens, S.</td>
<td>63, 64</td>
<td>Wilson, D.C.</td>
<td>65, 80, 81</td>
</tr>
</tbody>
</table>
Wilson, M.L. 80

Yerushalmi, B. 14
Yurci, A. 6, 7

Zarzuelo, A. 17, 24
Zeitz, J. 84
Zolotarevsky, V.B. 77
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