ENVIROMENTAL RISK FACTORS OF INFLAMMATORY BOWEL DISEASES

Tibor HLAVATÝ

Department of gastroenterology, University hospital Bratislava, Ruzinovska 6, 82606 Bratislava, Slovakia

Despite major progress in the field of inflammatory bowel diseases (IBD) genetics, it can not explain the dramatic increase in IBD prevalence in recent decades. There are strong lines of evidence that epidemiologic risk factors play an important role. Smoking has been consistently associated with risk of Crohn's disease (CD) and smoking cessation a risk factor for ulcerative colitis (UC), appendectomy diminishes risk of UC. The role of other environmental factors such as diet, oral contraceptives, domestic hygiene, vaccination, breast feeding, physical activity is controversial.

GASTROENTEROLOGY UZBEKISTAN TASHKENT 2012

HISTOPATHOLOGY OF INFLAMMATORY BOWEL DISEASE

Vincente MARCO

Department of Pathology, Hospital Quirón Barcelona, Spain

9th International Symposium of Gastroenterology
31. 5. – 2. 6. 2012
Tashkent, Uzbekistan

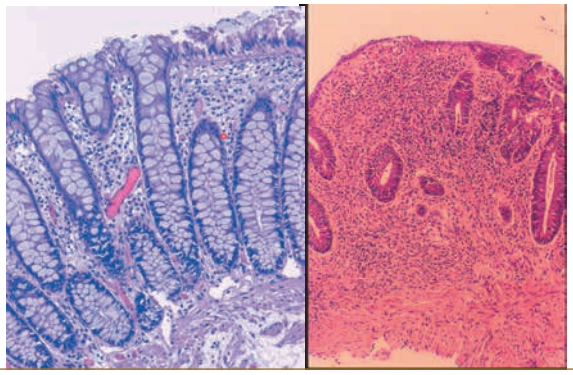
HISTOPATHOLOGY OF INFLAMMATORY BOWEL DISEASE

Dr. Vicente Marco
Department of Pathology
Hospital Quirón Barcelona

HISTOLOGIC FEATURES OF CHRONIC COLITIS

- Increased mononuclear inflammation in the lamina propia.
- Crypt distorsion and atrophy
- Surface villiform change
- Basal plasmocytosis and lymphoid aggregates
- Paneth cell metaplasia (colon distal to hepatic flexure)

NORMAL COLON **CHRONIC COLITIS**

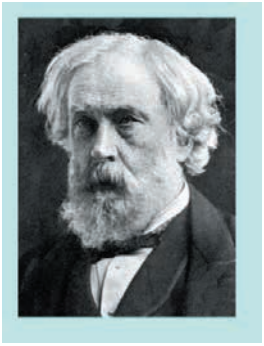


FEATURES OF ULCERATIVE COLITIS (UC) AND CROHN´S COLITIS (CC)

	UC	CC
Gross features		
Isolated right sided colitis	No	Yes
Rectal involvement	Yes	Variable
Distribution	Diffuse	Difusse or focal
Involvement of gut proximal to colon	No Except upper GI	Common
Fistulas	No	Occasional
Creeping serosal fat	No	Common
Thickened bowel wall	No	Yes
Strictures	Rare	Occasional

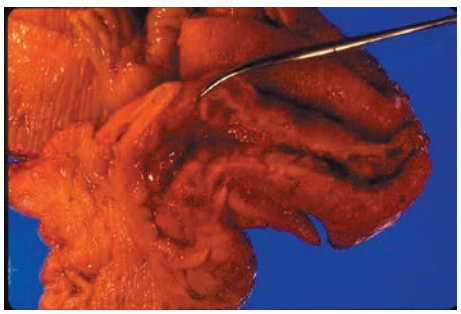
Yantiss RK & Odze RD. Diagnostic difficulties in inflammatory bowel disease pathology. Histopathology 2006;48:116-132

ULCERATIVE COLITIS



Samuel Wilks (1824-1911)

Crohn's Disease, Ileitis



B B Crohn M.D.

Biography
Burrill B. Crohn (1884-1983) was a New Yorker through and through. He was born and raised in New York, attended City College (Class of 1902) and then received his medical degree from Columbia University's College of Physicians and Surgeons (1907). He joined The Mount Sinai Hospital as an intern in pathology and then trained in the Hospitals' house staff program. He served as a volunteer Assistant in pathology and then physiological chemistry from 1911 to 1923, when he was named Chief of Mount Sinai's Gastroenterology Clinic in the Department of Medicine. He joined the in-patient staff in 1926 and ultimately was associated with Mount Sinai for over sixty years. Crohn was President of the American Gastroenterological Association in 1953. Crohn authored four books and over 150 articles, primarily in his chosen specialty of gastroenterology. He is best remembered for his role in the first description of regional ileitis, or Crohn's Disease, along with Mount Sinai surgeons Leon Ginzburg and Gordon Oppenheimer.

Mt Sinai J Med. 2000 May;67(3):263-8.

Regional ileitis: a pathologic and clinical entity. 1932.

Crohn BB, Ginzburg L, Oppenheimer GD.

Mount Sinai Hospital, New York, NY, USA.

Leon Ginzburg M.D.

Biography
Leon Ginzburg was born in New York City in 1898. He attended DeWitt Clinton High School and received bachelor's and medical degrees at Columbia University. He served on the house staff of The Mount Sinai Hospital and became an Adjunct Surgeon in 1926.

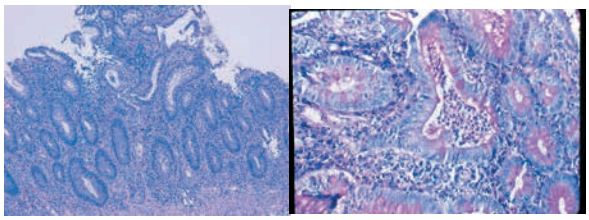
As an Adjunct Surgeon at Mount Sinai, Ginzburg served under the eminent surgeon Dr. A.A. Berg, who charged him and his colleague Dr. Gordon D. Oppenheimer with reviewing surgical specimens in the pathology laboratory. Ginzburg and Oppenheimer developed a particular interest in diseases of the bowel and began a project to describe and categorize their specimens of bowel tumors and strictures. Of the fifty-two specimens they examined, twelve did not fit any previously described pattern of symptoms[1].

FEATURES OF ULCERATIVE COLITIS (UC) AND CROHN´S COLITIS (CC)

	UC	CC
Microscopic features		
Inflammation confined to mucosa and submucosa	Yes	Uncommon
Transmural inflammation	No Except in fulminant colitis	Common
Fissuring ulcers	No Except in fulminant colitis	Yes
Fistulas	No	Yes
Sarcoid-like granulomas	No	Yes
Distribution of inflammation	Diffuse	Focal or diffuse
Vasculitis	No	Yes

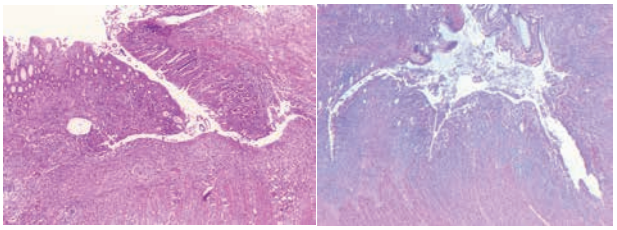
Adapted from D.A. Antonioli. Diagnostic Problems in Biopsy Interpretation of Colorectal Inflammatory Disorders. IAP 2006 Annual Congress

ULCERATIVE COLITIS



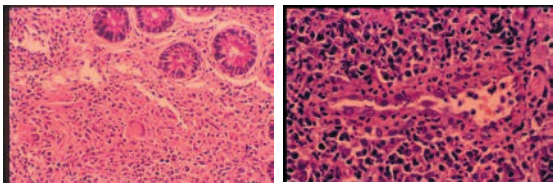
CROHN'S DISEASE

Aftoid Ulcer **Fissure**

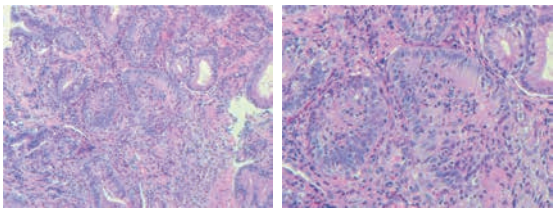


CROHN'S DISEASE

Granuloma **Vasculitis**



FOCALLY ENHANCED GASTRITIS IN IBD



Morphologic variants of Ulcerative Colitis

- Discontinuous or patchy disease
- Absolute or relative rectal sparing
- "Backwash" ileitis
- Extracolonic inflammation
- Aphthous ulcers
- Mural inflammation

Granulomas in Ulcerative Colitis

- Prevalence: 20%
- Most are related to crypt rupture
- Other etiologies:
  - Barium, particulate matter
  - Infections
  - Drugs
  - Other

Features that favor Cronh´s disease

- Chronic active ileitis
- Transmural lymphoid aggregates in areas with intact mucosa
- Deep fissuring ulcers
- Segmental involvement of colon in untreated patients
- Epithelioid granulomas unrelated to ruptured crypts

INDETERMINATE COLITIS

- Definition: Cases of IBD that cannot be classified as UC or CD.
- Prevalence: 5-10% of cases of IBD.
- 60-80% will be reclassified in follow-up, more often as UC than CD.
- Common scenario cases with fulminant colitis, clinically UC, but deep fissuring ulcers and transmural inflammation, suggestive of CD.

DIFFERENTIAL DIAGNOSIS OF IBD AND OTHER FORMS OF COLITIS

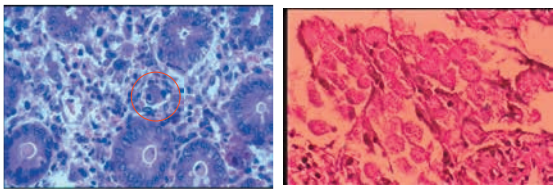
INFECTIOUS DISEASES	
CMV	Crohn´s like. Nuclear inclusions
SALMONELLOSIS	Mimics UC and CD. Acute onset.+Cultures
SHIGELLA SPECIES	Mimics UC and CD. Acute onset.+Cultures
YERSINIA	Mimics CD. Granulomatous inflammation
MYCOBACTERIA	Mimics CD.Necrotizing granulomas. Cultures, PCR+
ACTYNOMYCOSIS	Mimic CD. Granulomatous and neutrophilic inflammation. Gram+ organisms
AMEBIASIS	Mimics UC and CD. Amoebae resemble macrophages. Ingested rbc in AB. AB are Trichrome +

DIFFERENTIAL DIAGNOSIS OF IBD AND OTHER FORMS OF COLITIS

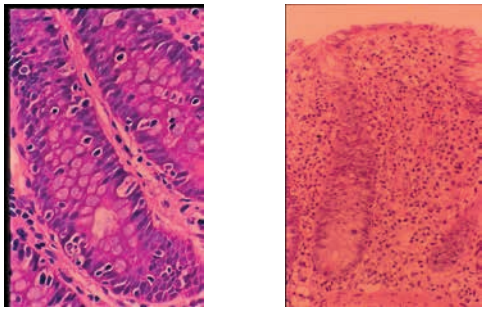
Non infectious diseases	
Diversion colitis Chronic recurrent pouchitis	50-100% of patients with colonic bypass. Ulcers,erosions, nodularity and strictures. Lack of significant architectural distordion. 50% of UC patients with IPAA. CD like inflammation (fissures, fistulas, stenosis)
Diverticular-disease associated colitis	Left colon in region of diverticular disease Rectum spared Cryptitis and granulomas In UC and CD other segments of colon are involved.
NSAID-associated colitis	Colitis and ileitis Aftous ulcers Cryptitis, superficial erosions, increased intraepithelial lymphocytes.
Microscopic colitis with features of IBD	Cryptitis (38%), Paneth metaplasia (14%)

DIFFERENTIAL DIAGNOSIS OF IBD

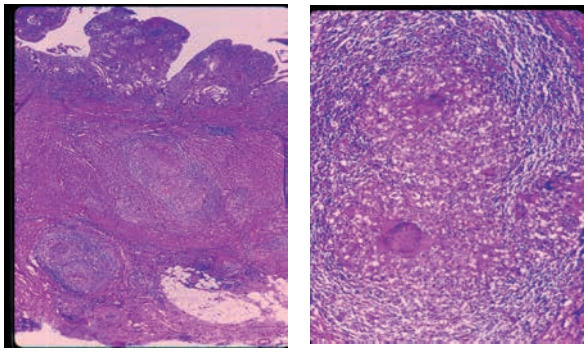
CMV **AMEBIASIS**



DIFFERENTIAL DIAGNOSIS OF IBD SALMONELLOSIS

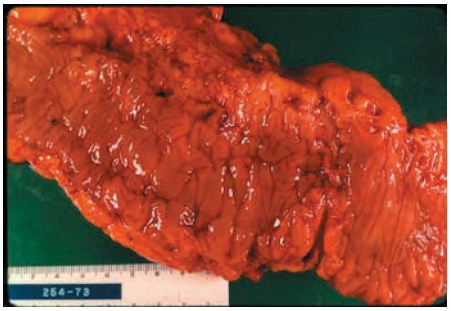


DIFFERENTIAL DIAGNOSIS OF IBD TBC



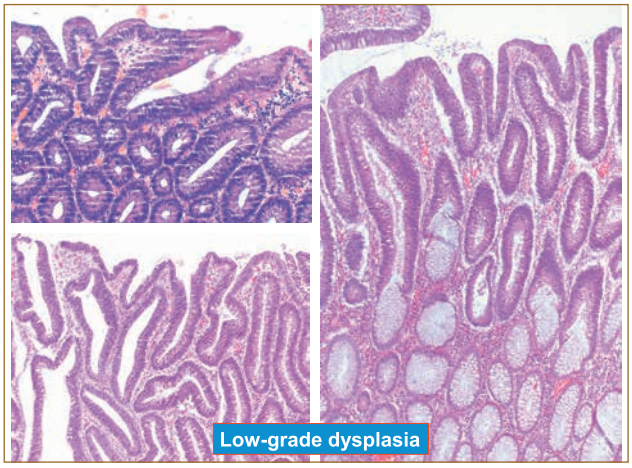
Diverticular Disease-Associated Colitis

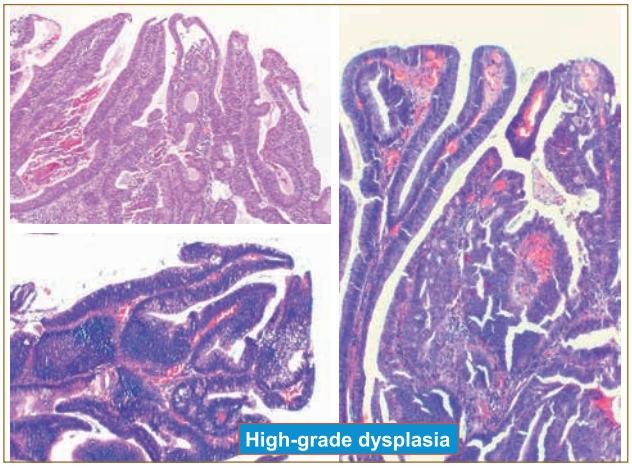
- Chronic colitis in the interdiverticular mucosa
- Disease limited to areas with diverticulosis
- Mucosal colitis (UC-like), rectal sparing
- Pathogenesis uncertain
- Treatment similar to UC
- Rare cases similar to Crohn's, but do not develop Crohn's upon follow-up



Dysplasia in Ulcerative Colitis

- Marker of cancer risk
- Flat or elevated (DALM)
- Dysplasia
  - Incidence at 10 years 5%
  - Incidence at 20 years 20%
- Carcinoma
  - Incidence at 20 years 5-10%
  - Incidence at 30 years 10-20%
  - 1-2%/year after 10 years





Dysplasia in Crohn's Disease

- Risk of colon cancer similar to UC
- Involved (SI and colon) and uninvolved areas
- Dysplasia in 2-16% of patients without carcinoma
- 27% in SI and 73% in colon
- Dysplasia adjacent to Ca in 40-100%

Dysplasia in Ulcerative Colitis

Gross Features

- Flat
- Raised (DALM)

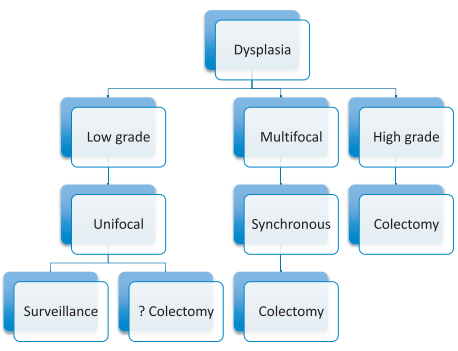
Flat Dysplasia Natural History

(Bernstein et al, Lancet 1994;343:71)

- **1. Low grade**
  - Co-existent carcinoma: 9%
  - Progression to HGD/CA: 30-54%

  (5 year predictive value)
- **2. High grade**
  - Co-existent carcinoma: 40-67%
  - Progression to CA: 40-90%

Management of Dysplasia in IBD



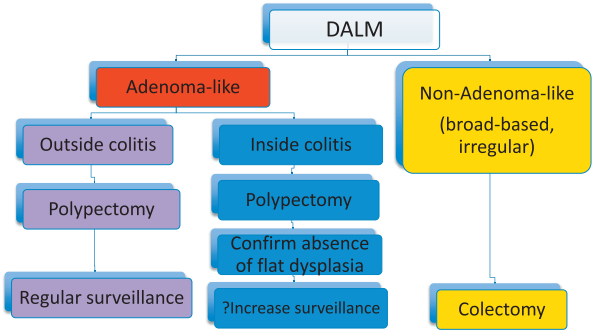
DALM

- Adenoma-like
  - –Sporadic (“adenoma”)
  - –IBD-associated (“Polypoid dysplasia”)
- Non Adenoma-like

DALM

Adenoma Like	**Non Adenoma-Like**
• Sessile/Pedunculated	• Usually sessile
• well circumscribed	• Poorly circumscribed
• smooth surface	• Irregular surface
• visible borders	• indistinct border
• non-ulcerated	• ulceration/necrosis
• no stricture or mucosal tethering	• +stricture/tethering

DALM Management



CONCLUSIONS

- The accurate histopathological diagnosis of IIBD, requires close cooperation between gastroenterologists and pathologists.
- The differential diagnosis includes infectious diseases and and non infectious inflammatory conditions.
- The histological grade of dysplasia, and the endoscopic features of the lesions are important for management.

POST-OPERATIVE MANAGEMENT OF PATIENTS WITH CROHN'S DISEASE

Milan LUKÁŠ

ISCARE Lighthouse and 1st Medical Faculty, Charles University, Prague, Czech Republic

Crohn's disease (CD) is a chronic disabling and destructive disease. Despite use a new therapeutic modalities, including immunosuppressants and biologic agents, more than half of CD patients require surgery within 10 years after diagnosis. Unfortunately, surgical resection is not currative procedure and postoperative recurrence still remains a significant clinical problem.

Ileo-colonoscopy using a Rutgeert's endoscopic score is a gold standard to diagnose early recurrence of CD after operation. It should be done within the first year after resection where treatment decisions may be affected. The role of wireless capsule endoscopy has to be clarified in the next future, but it seems to be potentially promising approach. Transabominal ultrasonography and contrast-enhanced sonography are non-invasive alternative tools for identifying postoperative CD recurrence. Computed tomography enterography (CTE) has a same diagnostic accuracy as ileo-colonoscopy using mucosal enhancement, wall thickness, "comb-signs", anastomotic stenosis and fistulation, but generally is not recommended due to ionising radiation exposure. Magnetic resonance imaging enterography (MRE) is a low invasive diagnostic method emerging as alternative tool for identifying of postoperative CD recurrence. It was proved that MRE finding predicts a clinical postoperative CD recurrence over two postoperative years. Laboratory biomarkers such as fecal calprotectin and(or) lactoferin showed promising results, but at the moment they are not recommended to routinely diagnose of postoperative CD recurrence.

Two recent meta-analysis have shown, that mesalazine is only slight effective for the prevention of postoperative CD recurrence, with NNT (number needed to treat) = 8–12. Meta-analysis reported 30 years ago revealed that sulfasalazine had no benefit in prevention of CD relaps. The same result was published with regard on budesonide efficacy. Antibiotics (metronidazole, ornidazole) were recognized to be more effective than placebo in preventing both clinical end endoscopic CD recurrence but the effect was not sustained beyond 12 months. Thiopurines are modest effective to prevent postoperative clinical and endoscopic CD recurrence with NNT = 8. The clinical problem is a higher rate of adverse events leading to drugs withdrawal. The most promising drugs seems to be anti-TNF agents which dramatically decrease a postoperative CD recurrence in selected patients. It has to be confirmed by larger randomized trials (POCER;PREVENT).

We have only three clinical trials focus on treatment of postoperative CD recurrence. Azathioprine 2.0–2.5 mg/kg was proved to be more effective than mesalazine (4 g daily) in treating endoscopic postoperative recurrence. It was documented that treatment of endoscopic CD recurrence by infliximab was more effective than azathioprine or mesalazine. The complete mucosal healing after one year of therapy was detected in 38 % infliximab group vs 13 % azathioprine group vs 0 % in mesalazine group respectively. In addition, no clinical relaps was observed with infliximab, whilst 38 % and 70 % of patients recurred in the azathioprine and mesalazine groups respectively.

The current approach to patients those underwent intestinal resection surgery due to CD should be based on the stratification of risk of recurrence. The risk factors represent: active smoker; penetrating behavior of CD; perianal lesions; prior intestinal resection; extensive small bowel disease. Patients without risk factors no therapy, or mesalazine might be considered. If one risk factor is present, the thiopurins and antibiotics can be chosen. In patients with two end more risk factors anti-TNF agents therapy is indicated.

FAECAL CALPROTECTIN IN THE DIAGNOSIS OF CHRONIC INFLAMMATORY BOWEL DISEASE

Yuriy STEPANOV

Institute of Gastroenterology of the National Academy of Medical Sciences of Ukraine, Ukraine

Laboratory studies – one of the areas of diagnosis of chronic inflammatory bowel disease. Laboratory studies allow an objective assessment of disease activity, avoid invasive endoscopic procedures. The main laboratory markers of diagnosis of chronic inflammatory bowel disease are the erythrocyte sedimentation rate, C-reactive protein, white blood cells, platelets, calprotectin, lactoferrin. Unfortunately, not all laboratory markers are specific. Meta-analysis in 2010 showed high sensitivity and specificity of fecal calprotectin in the diagnosis of chronic inflammatory bowel disease. Based on own studies noted a direct correlation between the level of fecal calprotectin and severity of Crohn's disease with moderate to severe disease, fecal calprotectin levels in Crohn's disease is largely dependent on the activity of the disease, but not on its prevalence, noted the significant correlation between the endoscopic and histological parameters of activity and the level of fecal calprotectin.

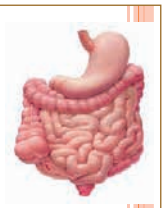
Conclusion: The level of fecal calprotectin in patients chronic inflammatory bowel disease significantly correlated with the activity of inflammation, according to the established endoscopic and histological criteria, which gives reason to use it as a diagnostic marker of active inflammation in the intestine.

GASTROENTEROLOGY UZBEKISTAN TASHKENT 2012

Fecal calprotectin in the diagnosis of chronic inflammatory bowel disease

Prof. Yuriy Stepanov
(Ukraine)

Хронические воспалительные заболевания кишечника: НЯК и болезнь Крона



- От 6 на 100 000 населения (болезнь Крона) до 15 случаев на 100 000 населения (НЯК)
- Пик заболеваемости приходится на возраст 20-40 лет, а также после 60 лет

Направления диагностики хронических воспалительных заболеваний кишечника

- оценка симптоматики
- клиническое обследование
- лабораторные исследования
- рентгенологическое исследование
- эндоскопическое исследование
- гистологическое исследование

Причины интереса исследователей к лабораторным маркерам при ХВЗК

возможность получить объективную оценку активности болезни, т.к. клинические симптомы субъективны

возможность избежать инвазивных эндоскопических вмешательств

Vermeire S., Van Assche G., Rutgeerts P., 2006

Основные лабораторные маркеры ХВЗК

анализ крови
- скорость оседания эритроцитов
- С-реактивный протеин
- лейкоциты
- тромбоциты

анализ кала
- кальпротектин
- лактоферрин

Недостатки существующих серологических маркеров активности ХВЗК

С-реактивный протеин, СОЭ, лейкоциты, тромбоциты могут быть повышены не только при ХВЗК, но и при внекишечных воспалительных заболеваниях.

Это снижает специфичность серологических маркеров в диагностике ХВЗК.

Кальпротектин

Кальпротектин составляет 60% цитоплазменных белков гранулоцитов

Содержание кальпротектина в фекалиях пропорционально нейтрофильной миграции в гастроинтестинальном тракте, что определяет его специфичность для диагностики воспаления кишечника

Кальпротектин

Фекальный кальпротектин – чувствительный маркер для определения воспаления в кишечнике

Фекальный кальпротектин повышается при ХВЗК, хотя он может быть также повышен в некоторых случаях при кишечных инфекциях, новообразованиях, НПВП-энтеропатиях

Кальпротектин

Кальпротектин – кальций-цинк-связанный протеин размером 36 kDa

Фекальный кальпротектин сохраняется в первоначальной концентрации при комнатной температуре около недели

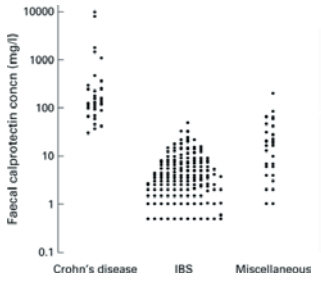
Digestion

Røseth AG, Aadland E, Jahnsen J, Raknerud N. Assessment of disease activity in ulcerative colitis by faecal calprotectin, a novel granulocyte marker protein // Digestion. 1997;58(2):176-80.

Фекальный кальпротектин достоверно повышен при активном НЯК в сравнении с неактивным НЯК и контролем

GUT
An International Journal of Gastroenterology and Hepatology

Tibble J, Teahon K, Thjodleifsson B, Roseth A, Sigthorsson G, Bridger S, Foster R, Sherwood R, Fagerhol M, Bjarnason I. A simple method for assessing intestinal inflammation in Crohn's disease // Gut. 2000 Oct;47(4):506-13.

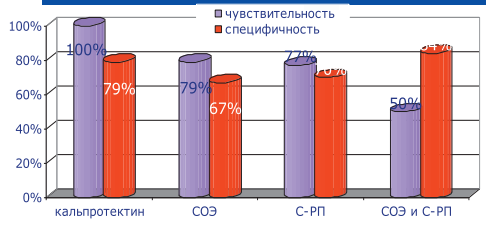


Фекальный кальпротектин достоверно выше при болезни Крона в сравнении с синдромом раздраженного кишечника и другими заболеваниями кишечника

AP&T Alimentary Pharmacology and Therapeutics

Dolwani S, Metzner M, Wassell JJ, Yong A, Hawthorne AB. Diagnostic accuracy of faecal calprotectin estimation in prediction of abnormal small bowel radiology // Aliment Pharmacol Ther. 2004 Sep 15;20(6):615-21.

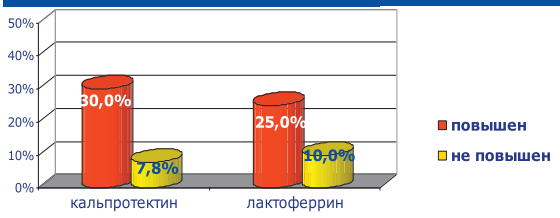
Чувствительность и специфичность кальпротектина выше, чем СОЭ, С-реактивного протеина и комбинации СОЭ+СРП при болезни Крона в сравнении с СРК



INFLAMMATORY BOWEL DISEASES

Gisbert JP, Bermejo F, Pérez-Calle JL, Taxonera C, Vera I, McNicholl AG, Algaba A, López P, López-Palacios N, Calvo M, et al. Fecal calprotectin and lactoferrin for the prediction of inflammatory bowel disease relapse. Inflamm Bowel Dis. 2009;15:1190–1198.

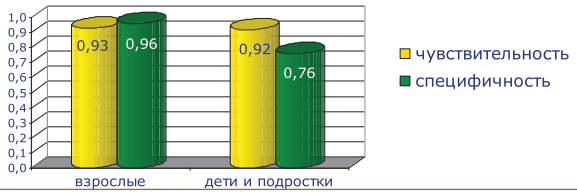
Частота рецидива у больных ХВЗК, находящихся в состоянии ремиссии, в последующие 3 месяца выше при исходно повышенном уровне фекального кальпротектина и лактоферрина



BMJ

van Rheenen PF, Van de Vijver E, Fidler V. Faecal calprotectin for screening of patients with suspected inflammatory bowel disease: diagnostic meta-analysis // BMJ. 2010 Jul 15;341:c3369.

Мета-анализ 2010 года показал высокую чувствительность и специфичность фекального кальпротектина в диагностике ХВЗК (специфичность у детей и подростков меньше, чем у взрослых)



Оценка концентрации фекального кальпротектина у больных с ХВЗК: собственные данные

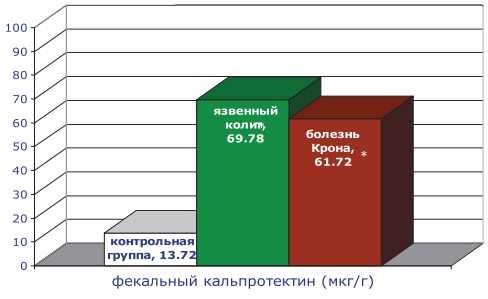
Степанов Ю.М., Федорова Н.С., 2010

В исследование были включены:
- больные с язвенным колитом – 48
- больные с болезнью Крона – 32
- контрольная группа – 31

Кальпротектин определялся иммуноферментным методом (Baulmann, Швейцария)

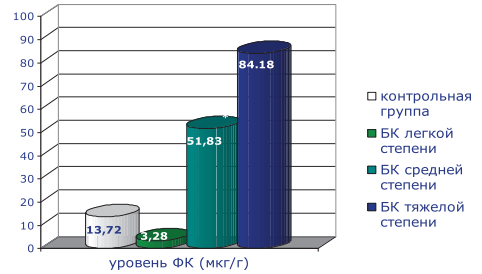
Средняя концентрация фекального кальпротектина, как в группе язвенного колита, так и в группе болезни Крона, достоверно выше, чем в контрольной группе

Степанов Ю.М., Федорова Н.С., 2010



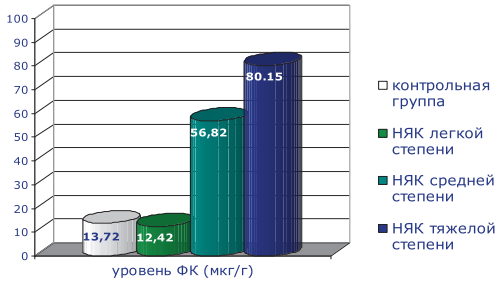
Отмечается прямая зависимость между уровнем фекального кальпротектина и тяжестью течения болезни Крона при средней и тяжелой степени заболевания

Степанов Ю.М., Федорова Н.С., 2010



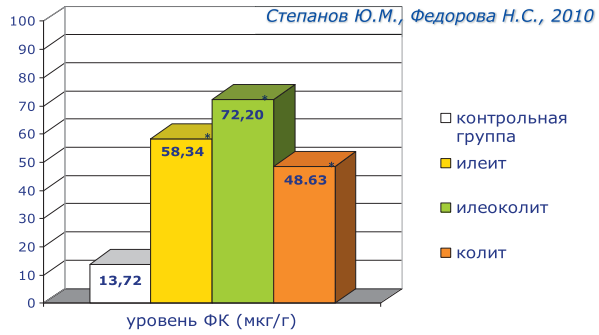
Отмечается прямая зависимость между уровнем фекального кальпротектина и тяжестью течения язвенного колита при средней и тяжелой степени заболевания

Степанов Ю.М., Федорова Н.С., 2010



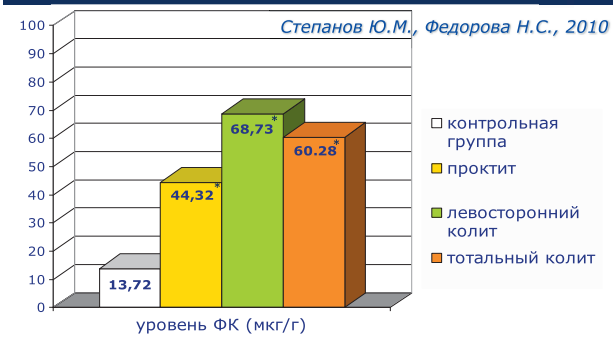
Уровень фекального кальпротектина при болезни Крона в большей степени зависит от активности заболевания, а не от его распространенности

Степанов Ю.М., Федорова Н.С., 2010



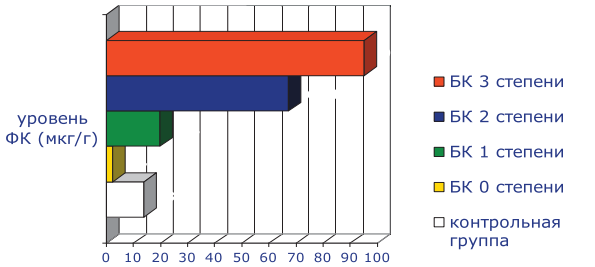
Уровень фекального кальпротектина при язвенном колите в большей степени зависит от активности заболевания, а не от его распространенности

Степанов Ю.М., Федорова Н.С., 2010



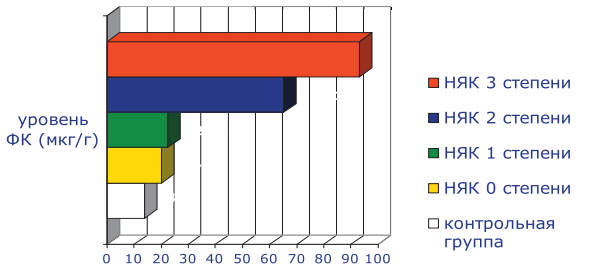
Концентрация фекального кальпротектина у больных болезнью Крона в зависимости от степени эндоскопической и гистологической активности

Степанов Ю.М., Федорова Н.С., 2010



Концентрация фекального кальпротектина у больных язвенным колитом в зависимости от степени эндоскопической и гистологической активности

Степанов Ю.М., Федорова Н.С., 2010



Концентрация фекального кальпротектина у больных ХВЗК в зависимости от степени эндоскопической и гистологической активности

Отмечена существенная корреляция между эндоскопическими и гистологическими параметрами активности и уровнем фекального кальпротектина (r=0,65)

Между показателями фекального кальпротектина у пациентов в активной и неактивной фазе отмечается заметная разница

Выводы

Уровень фекального кальпротектина у больных ХВЗК существенно коррелирует с активностью воспаления, установленной согласно эндоскопических и гистологических критериев, что дает основание использовать его как маркер диагностики активного воспаления в кишечнике

BIOLOGICAL THERAPY OF INFLAMMATORY BOWEL DISEASE – CROHN'S DISEASE AND ULCERATIVE COLITIS

Martin HUORKA

Gastroenterogical and Hepatological Department, V. intern clinic, University Hospital, Comenius University, Slovakia

Therapy for inflammatory bowel disease (IBD) is a rapidly evolving field with the many new biological agents under investigation likely to change therapeutic strategies in the future. The general approach for treating IBD must consider the degree of activity, location, and behavior of the disease, including its course, response to previous medication, side effects of medication and possible presence of extraintestinal manifestations.

The advent of biological therapies (BT) has initiated a new therapeutic area for the treatment of IBD, especially for the patients with corticosteroid-dependent, corticosteroid-refractory or fistulizing disease. New biological agents not only control symptoms but may also alter the natural history of the disease. The main goals of BT include the rapid induction of clinical remission, the maintenance of steroid free clinical remission, the healing of mucosal lesions, improvements in health-related quality of life and a reduction in both the need for surgery and hospital stay.

The current biological drugs include infliximab, adalimubab and certolizumab pegol, which are directed against tumor necrosis factor alfa (TNF alfa) and pro-inflammatory cytokine that plays a central role in the pathogenesis of IBD and natalizumab, an anti-integrin antibody.

Future clinical studies should address efficacy, safety and cost effectiveness of BT for IBD and should provide the necessary information to take maximum advantage of these new therapies.

GASTROENTEROLOGY
UZBEKISTAN TASHKENT 2012

Biological therapy of ulcerative colitis and morbus Crohn

Martin Huorka
Gastroenterogical and Hepatological Department
V. Intern Clinic of Medical Faculty
Comenius University Bratislava

Pathogenesis of IBD and biological therapy (BT)

- In the early 1990s, the pathogenetic mechanisms of IBD were clarified
- Identification of key mediators of inflammation and pharmacologic research was addressed towards specific biologic drugs intefering with this cascade
- Key mediators- proinflammatory cytokines play an important role in amplificitaion of the inflammatory process
- Tumor necrosis factor alfa (TNF) and IL1 are released at the begining of the inflammatory cascade and contribute to recruitment and activation of inflammatory cells, increase mucosal intestinal permeability and stimulate the release of adhesion molecules

Biological therapy (BT) – general characteristic

- Advent of BT- a new therapeutic era especially for pts:
- Corticosteroid- dependent
- Corticosteroid- refractory
- Fistulizing disease
- BT alters the natural history of the disease

BT- tool for...

- Rapid induction of clinical remission
- Maintenance of steroid-free clinical remission
- Mucosal healing
- Reduction in both the need for surgery and hospital day
- Quality of life improvement

(Scribano,ML,New therap.In Crohn´s disease,2010)

Armament of BT

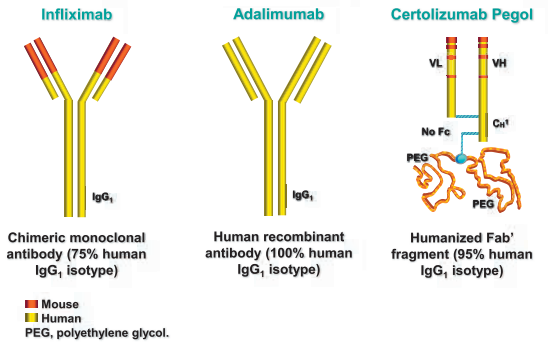
Anti TNF alfa products:

- Infliximab
- Adalimubab
- Certolizumab pegol

Anti-integrin antibody:

- natalizumab

Construct of Anti-TNF-α Biologic Agents



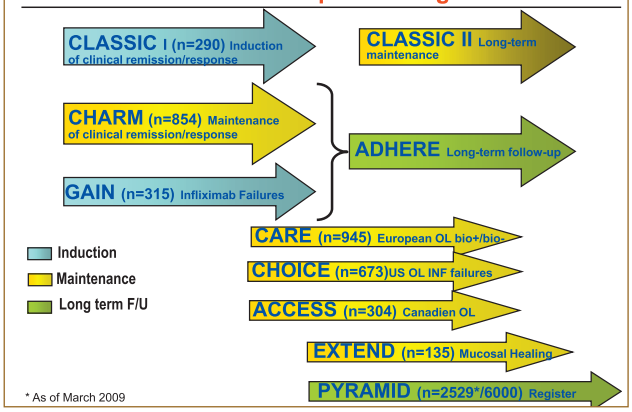
Morbus Crohn

Goals of Therapy for Crohn's Disease

- Induce and maintain remission
- Reduce disease activity leading to symptoms
- Prevent disease complications (e.g., stenoses, abscesses, fistulas)
- Reduce need for surgery
- Improve patient's nutritional status and quality of life

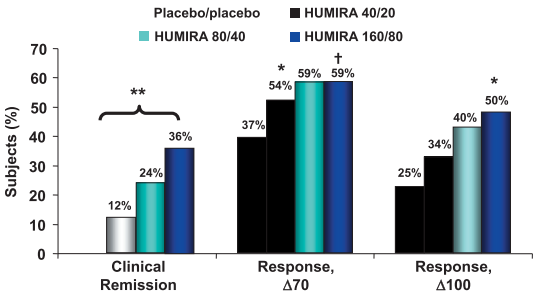
Thompson ABR, et al. *Inflammatory Bowel Diseases.* Edinburgh, UK: Churchill Livingstone; 2003:373-381.

Over 6000 Patients Included in HUMIRA's Broad Crohn's Clinical Development Program



* As of March 2009

CLASSIC I Trial: Results at Week 4

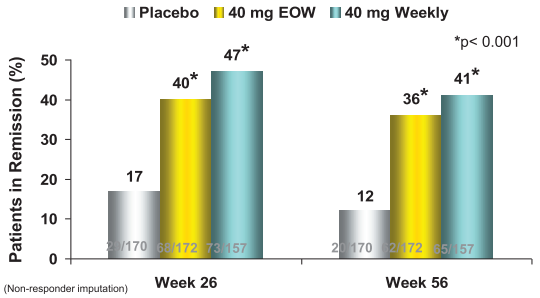


** p=0.004; * p<0.05; ‡ p=0.01; † p=0.007
Clinical remission=CDAI<150
Clinical response Δ70 or Δ100=CDAI decrease from baseline ≥70 or ≥100

Hanauer, S. et al. *Gastroenterology.* 2006;130:323–33

CHARM

Clinical Remission at Weeks 26 and 56 Randomized Responders



NRI (Non-responder imputation)
*p<0.001

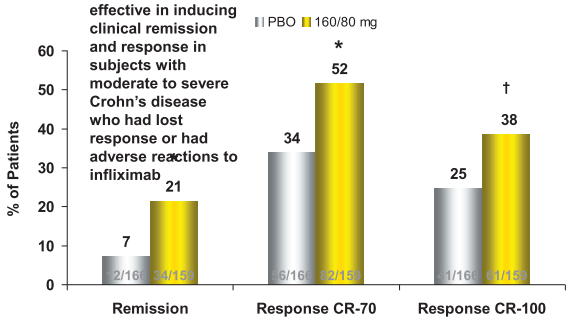
No statistically significant difference between 40 mg EOW and 40 mg weekly dose groups

Colombel JF, et al. *Gastroenterology.* 2007;132 (1):52-65

GAIN

Efficacy Outcomes at Week 4

HUMIRA was effective in inducing clinical remission and response in subjects with moderate to severe Crohn's disease who had lost response or had adverse reactions to infliximab



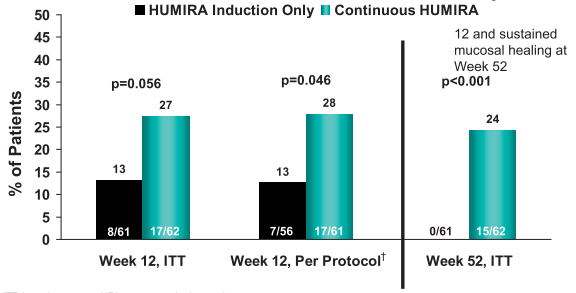
*p<0.001, †p<0.01, both vs placebo

Sandborn WJ, et al. *Ann Intern Med* 2007;146(12):829-38

EXTEND

Complete Mucosal Healing at Weeks 12 and 52: NRI Analysis*

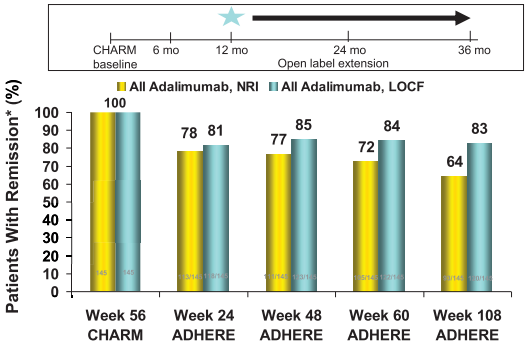
EXTEND demonstrated complete mucosal healing at Week 12 and sustained mucosal healing at Week 52



ITT, intention to treat; NRI, nonresponder imputation.
*NRI for missing ulceration at Weeks 12 and 52 and for missing ulceration and ulceration assessment of switched patients at Week 52. Treatment displayed is original treatment at randomization. Analyzed using Cochran-Mantel-Haenszel (CMH) test.
†Per protocol represents all ITT patients who did not have a significant protocol deviation.

Rutgeerts P. et al., *Gastroenterology.* 2009;136(5 Suppl 1):A-116

Sustained Remission Rates for 3 Years



*Proportion of patients in remission at each time point who were randomized to adalimumab, in remission at Week 56 of CHARM, and enrolled in ADHERE (ITT, n=145).

Pannacione et al, P148, presented at ECCO 2009

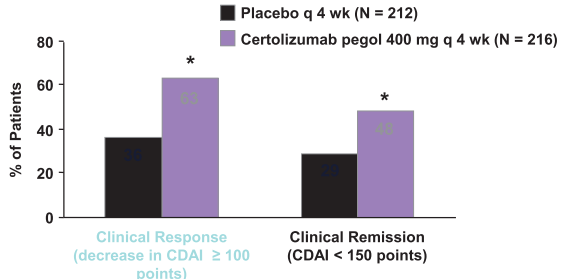
HUMIRA Safety

Safety- Conclusions CHICE, CARE

- Data available in the CD clinical trial database demonstrate that HUMIRA was generally safe and well tolerated in the treatment of patients with moderately to severely active CD
- The most frequently reported serious AE of interest was serious infections; other events were relatively rare
- In CD clinical trials, evidence suggests a decrease in mortality in HUMIRA-treated patients compared with a gender- and age-matched general population
- The safety profile of HUMIRA in this evaluation is comparable to previous reports spanning more than 10 years of clinical observations

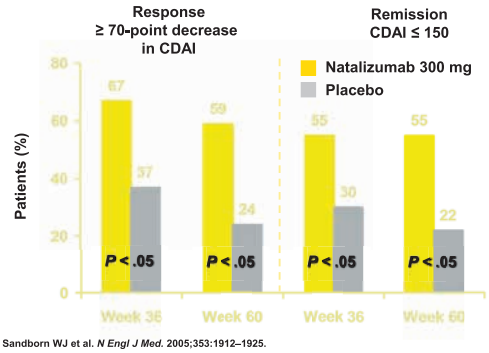
Colombel JF, et al. *Inflamm Bowel Dis.* Published Online May 11, 2009.

PRECiSE 2: Clinical Response and Remission at Week 26 in Patients With CD Randomized Responders (N = 428)



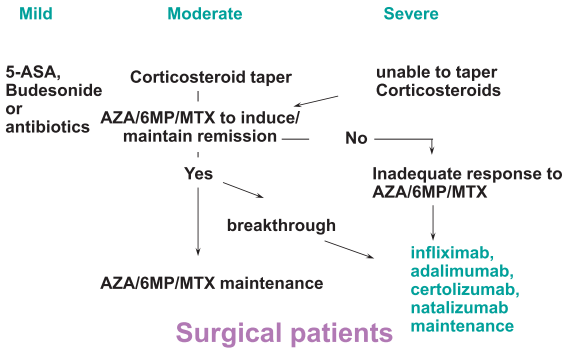
*p < 0.001 vs placebo.
Schreiber S, et al. *Gut.* 2005;54(Suppl VII):A82.

Natalizumab as Maintenance Therapy for Crohn's Disease: *ENACT-2 Trial*



Sandborn WJ et al. *N Engl J Med.* 2005;353:1912–1925.

Crohn's disease - medical management algorithm: *No partial obstruction or abscess detected*



Surgical patients

Summary: HUMIRA in Crohn's Disease

- HUMIRA rapidly induces remission and response in patients with moderately to severely active disease
- HUMIRA is effective as a maintenance therapy
  - Remission and response
  - Steroid discontinuation
  - Healing of draining fistulas
- HUMIRA is effective in a broad patient population
  - Anti-TNF naïve
  - Anti-TNF experienced
- Across clinical studies, HUMIRA was well tolerated, with a safety profile consistent with RA
- Recommended dose:
  - Starting Dose: 160 mg week 0, 80 mg week 2
  - Maintenance Dose: 40 mg EOW beginning week 4

Infliximab and Crohn´s disease

Remicade® Pivotal Trials in Crohn's Disease

Treatment of Crohn's disease:

- Induction treatment: (Targan et al. 1997, *NEJM*)
- Maintenance treatment: ACCENT I (Hanauer et al. 2002, *Lancet*)

Treatment of fistulizing Crohn's:

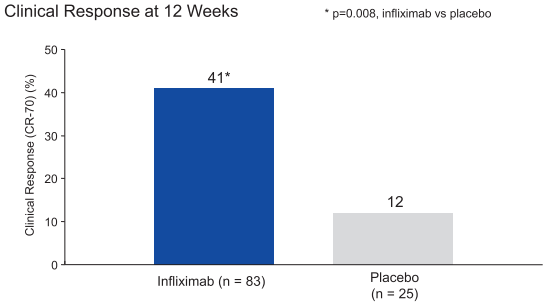
- Induction treatment: (Present et al. 1999, *NEJM*)
- Maintenance treatment: ACCENT II (Sands, 2004, *NEJM*)

Other key trials:

- Pediatric patients with Crohn's disease: REACH (Hyams et al. 2007, *Gastroenterology*)

21

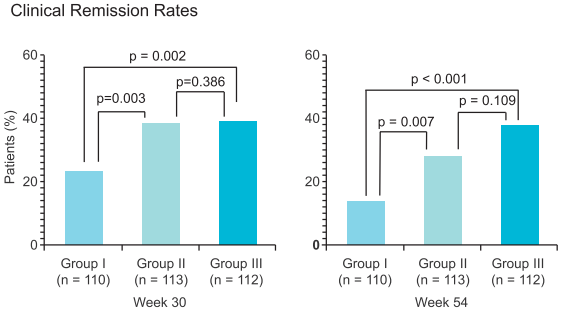
Induction of Clinical Response: Targan et al



Targan et al. *N Engl J Med.*1997;337:1029-35.

22

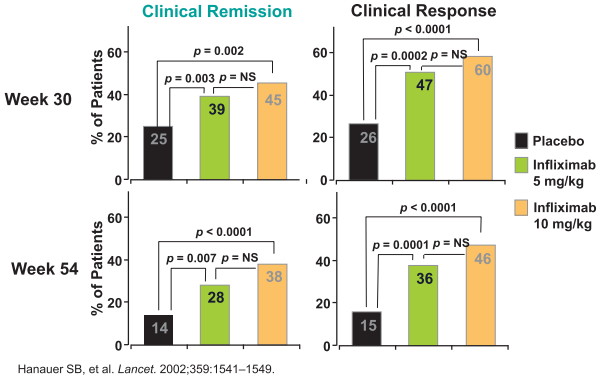
Maintenance Treatment: ACCENT I



Hanauer et al. *Lancet.* 2002;359:1541-9.

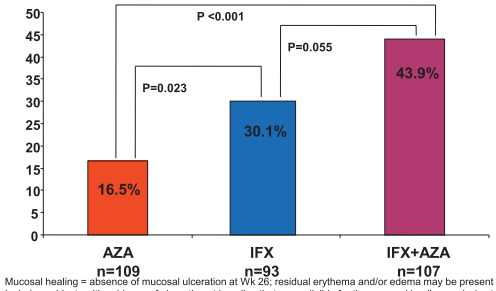
23

ACCENT I: Maintenance Infliximab for CD in Randomized Responders (N = 335)



Hanauer SB, et al. *Lancet.* 2002;359:1541–1549.

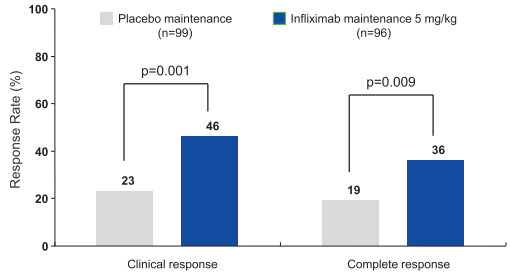
SONIC
Results – Mucosal Healing At Week 26



Mucosal healing = absence of mucosal ulceration at Wk 26; residual erythema and/or edema may be present
Includes subjects with evidence of ulceration at baseline that were eligible for the mucosal healing analysis at Wk 26.

Maintenance Treatment of Fistulizing Crohn's Disease: ACCENT II

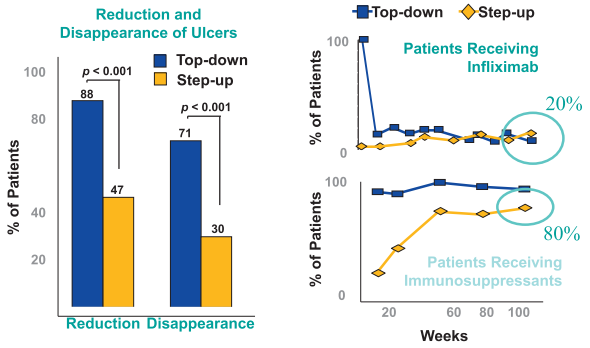
Fistula Response Rate at Week 54



Sands et al. *Engl J Med.* 2004;350:876–85.

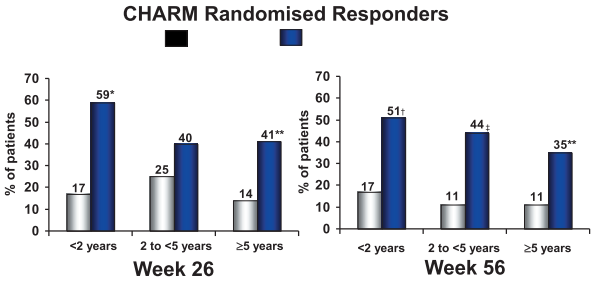
BT- early treatment and step-up vs step-down approach

Top-Down Versus Step-Up Trial
Clinical Results at 2 Years



D'Haens GR, et al. Lancet 2008. 371: 660-7.

Higher percentage of patients in remission observed amongst those who were treated earlier

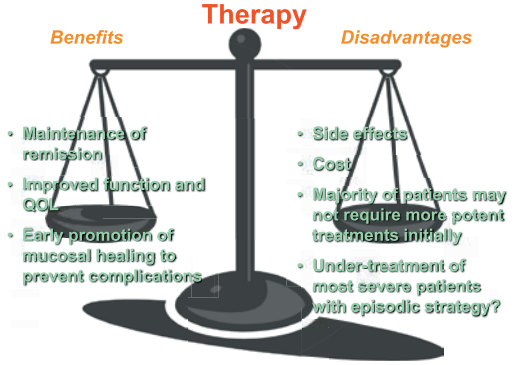


<2 years: PBO n=23 HUMIRA n=39; 2 to <5 years: PBO n=36, HUMIRA n=57; ≥5 years: PBO n=111, HUMIRA n=233

*p=0.002, **p<0.001, †p=0.014, ‡p=0.001 all vs placebo

Schreiber S, et al. *Gastroenterology* 2007;132(4 Suppl 2):A-147.

Weighing the Value of Top-Down Therapy



Lichtenstein GR, et al. *Inflamm Bowel Dis.* 2004;10:S2–S10.
Caprilli R, et al. *Digestive Liver Dis.* 2005;37:973–979.

BT and UC

Double blind, placebo-controlled studies of infliximab for UC

Reference	Outcome	Main result
Järnerot et al 2005	Primary: Colectomy or death within 90 days after infusion	7 (21%) patients in the infliximab group and 14 (67%) in the placebo group had a colectomy (p = 0.017) within 3 months after randomization
Probert et al 2003	Disease activity 6 weeks after the first infusion using the UC scoring system. Two end points utilized to define remission: clinical remission UC scoring system ≤ 2 and sigmoidoscopic remission as a Baron score of 0	Six weeks after initiation of treatment, remission rates were 39% (9/23) in infliximab group vs 30% (6/20) in placebo (p = 0.76) and a Baron score of 0 (26% (6/23) vs 30% (6/20)) respectively (p = 0.96)

Double blind, placebo-controlled studies of infliximab for UC

Reference	Outcome	Main result
Rutgeerts et al ACT 1, 2005	Clinical response was defined as a decrease from baseline in the total Mayo score of at least 3 points with an accompanying decrease in the score for rectal bleeding of at least 1 point or an absolute score for rectal bleeding of 0 or 1. Clinical remission was defined as a total Mayo score of 2 points or lower, with no individual score exceeding 1 point. Mucosal healing was defined as an absolute score for endoscopy of 0 or 1	69% of patients who received 5 mg of infliximab and 61% of those who received 10 mg had a clinical response at week 8 compared with 37% of those who received placebo ($p < 0.001$ for both comparisons with placebo). Mucosal healing at weeks 8, 30, and 54 occurred in significantly more patients in the infliximab groups than in the placebo groups

Double blind, placebo-controlled studies of infliximab for UC

Reference	Outcome	Main result
Rutgeerts et al ACT 2, 2005	Similar to ACT 1	64% and 69% of the patients in the 5 and 10 mg infliximab groups respectively, had a clinical response at week 8 compared with 29% in the placebo ($p < 0.001$ for both comparisons with placebo). Mucosal healing at weeks 8 and 30 occurred in significantly more patients in the infliximab groups than in the placebo groups

Double blind, placebo-controlled studies of infliximab for UC

Reference	Outcome	Main result
Sands et al 2001	The primary endpoint was treatment failure defined as 1) unachieved clinical response as defined by a modified Truelove and Witts severity score, 2) increase in corticosteroid dosage, 3) addition of immunosuppressants, 4) colectomy, or 5) death 2 weeks after infusion.	Four of 8 patients (50%) who received infliximab were considered treatment successes at 2 weeks, compared 0/3 patients who received placebo

Clinical remission

This endpoint was described in only 4 trials

The authors combined the ACT1 and ACT2 trials for the purpose of meta- analysis and reported the other two studies separately because of different outcome measures. Infliximab was effective for the induction of clinical remission at 8 weeks (relative risk [RR] 3.22, 95% CI 2.18–4.16, NNT = 5).

There was no significant difference in the results for the subgroup analysis of 5 mg/kg and 10 mg/kg of infliximab.

The two small studies that reported this outcome showed a trend favoring infliximab but failed to reach statistical significance (Probert et al 2003; Järnerot et al 2005).

Endoscopic remission/mucosal healing

This outcome was described in 4 studies

The two smaller studies did not reach statistical significance.

The two larger studies were grouped for meta-analysis. Infliximab was effective in inducing endoscopic remission and mucosal healing at 8 weeks (RR 1.88, 95% CI 1.54–2.28, NNT = 4) without heterogeneity.

Summary: Anti-TNF-α Therapy in IBD

- **An optimal use of each TNF-α blocker is mandatory**
- **– In case of loss of response, a dose intensification should be attempted either by an increase in dose, a decrease in interval or both**
- **– In case of no response to a dose intensification, the practitioner should seek advice from a specialist referral centre, to discuss a switch to another TNF-α blocker**

Summary: Anti-TNF-α Therapy in IBD

- **Effective therapy for induction and remission of active CD and fistulizing CD (infliximab)**
- **In the current management paradigm, reserved for patients with more severe disease**
- **Mucosal healing with long-term therapy (infliximab)**

- **Safety issues**
  - **Infections**
  - **Reactivation of latent TB**
  - **Possible lymphoma risk**
  - **Hepatosplenic T-cell lymphoma in young patients on infliximab plus concomittant azathioprine (n = 8)**
- **Immunogenicity**
  - **Infliximab: Infusion reactions contributing to loss of response**
  - **Other anti-TNF-α agents: Immunogenicity occurs; significance is uncertain**

CLINICAL AND ENDOSCOPICAL PARALLELS IN LOW DOSE ASPIRIN GASTROPATHY AND REBAMIPIDE EFFICACY IN THE TREATMENT

Yeldos IZATULLAYEV

Institute of Cardiology and Internal Diseases, Almaty, Kazakhstan

Background: Gastropathy represent a disparity of gastric mucosal characterized by sub-epithelial bleeding and erosion. NSAID-gastropathy can be induced by non steroidal anti-inflammatory drugs, including aspirin (aspirin-gastropathy) with or without various endoscopical signs and symptoms.

Aims: To investigate clinical and endoscopical parallels in Low Dose Aspirin Gastropathy and the effectivity of rebamipide in treatment of aspirin-induced gastropathy with endoscopical signs characterized as sub-epithelial petechiae and erosions and clinical symptoms of dyspepsia characterized by epigastric pain, heartburn, nausea, vomit, fullness, and anorexia.

Methods: This study was enrolled from to June 2011 to January 2012 with 45 subjects who were recruited from outpatient and inpatient clinic in Institute of Cardiology and Internal Diseases in Almaty. Endoscopic examination was performed twice in every patients Before and after treatment.

Results: There was no parallels between clinical and endoscopic findings in A-gastropathy. About 43 % of patients with A-gastropathy have no clinical symptoms.
There was an improvement of endoscopical signs and gradation of gastropathy and clinical symptoms after 2 weeks rebamipide treatment.
There was no side effect of administration of rebamipide.

Conclusion: Endoscopy must be a necessary procedure in A-gastropathy diagnostics in patients receive low dose aspirin.
Rebamipide as effective co-medication in aspirin treatment to improve the endoscopical signs and clinic symptoms and in the safe of aspirin induced gastropathy.

GASTROENTEROLOGY
UZBEKISTAN TASHKENT 2012

THE CURRENT STATUS OF LAPAROSCOPIC SURGERY IN PATIENTS WITH CROHN'S DISEASE

Eloy ESPIN

Hospital Valle de Hebron-Universitat Autonoma de Barcelona, Spain

GASTROENTEROLOGY
UZBEKISTAN TASHKENT 2012

CAPSULE ENDOSCOPY AS A DIAGNOSTIC APPROACH IN PATIENTS WITH IBD

Jelena MARTINOV[1], Miodrag KRSTIC[1,2], Aleksandra SOKIC-MILUTINOVIC[1,2], Tomica MILOSAVLJEVIC[1,2], Ivan JOVANOVIC[1,2]

[1] Clinic for Gastroenterology, Clinical Centre of Serbia, Serbia
[2] School of Medicine, University of Belgrade, Serbia

The small bowel (SB) has been defined for a long time as the "black box" of the gastrointestinal system due to its difficult and incomplete examination. Enteroscopy and radiologic studies (small-bowel follow-through, enteroclysis, nuclear bleeding scans and angiography) have a low diagnostic yield and complete endoluminal examination was until recently only possible with intra-operative endoscopy. The introduction of capsule endoscopy (CE) in 2000. present a significant advance in the imaging of the SB and dramatically changed the management and surveillance in patients with suspected SB lesions. Over the past decade many indications have been approved for the use of CE.

In last few years many prospective studies have been published on the role of the CE in detecting SB lesions in patients with suspected or known Crohn's disease (CD). Results of these studies have been shown the superiority of the CE in comparasion with other diagnostic modalities (even CT and MR enteroclysis). CE is superior in detecting mucosal lesions, whereas CT and MR enteroclysis are better in detecting transmural and extraintestinal manifestations of CD. Among patients with established CD, CE may be used to determine the extent and severity of the SB involvement, post-operative recurrence, post-therapy mucosal healing and wheather active SB lesions exists in the clinical setting of functional bowel disorder. In patients with unclassified colitis, CE is useful in distinguish between ulcerative colitis (UC) and CD. The role of CE in UC is limited, some authors advocate CE before colectomy for refractory cases, in patients with unexplained anemia or abdominal symptoms, in order to exclude CD.

CE is well tolerated, complications are rare and include capsule retention at strictures. The new "patency capsule" is available and can diminish that problem, especially in patients with symptoms suggesting SB obstruction.

GASTROENTEROLOGY UZBEKISTAN TASHKENT 2012

POSITIONING AND OPTIMIZING CONVENTIONAL THERAPY IN ULCERATIVE COLITIS

Martin BORTLÍK

IBD Clinical and Research Center ISCARE and 1st Medical Faculty, Charles University, Prague, Czech Republic

Despite the fact that high attention is currently paid to biologicals and other new molecules, conventional drugs still represents a cornerstone of medical therapy in patients with ulcerative colitis (UC). Many data indicates that effectiveness of medical treatment is closely associated with patient's adherence, which can be increased by several means. Patients should be appropriately informed about benefits and risks of therapeutic options, and discussion between attending doctor and the patients should be a permanent process. Physicians have nowadays enough data supporting a decrease of number of daily doses of mesalazine, continuing topical (rectal) therapy even during maintenance phase, or commencing immunosuppressive therapy also in patients with UC. Patients with proctitis or left-sided colitis often benefit from combined topical plus oral administration of mesalazine, which should be given in appropriate doses. Although infliximab has been found effective in treatment of patients with severe, steroid-refractory UC, there is still a place also for cyclosporine A, especially in patients who are naïve to thiopurines. Some data also indicates that cyclosporine may be more efficious in patients with most severe or fulminant attacks of UC. Patients with UC, especially those treated with immunosuppressively acting drugs, may suffer from infectious complications such as cytomegalovirus or *Clostridium difficile* infection. Correct and timely diagnosis of such complications leads to proper therapy, which may prevent these patients from administration of more aggressive (and thus more risky) medical therapy (eg. biologicals). Finally, gastroenterologists should still keep in mind that UC may be cured by surgical therapy, although this can be associated with other potential problems for the patient.

GASTROENTEROLOGY UZBEKISTAN TASHKENT 2012

THE ROLE OF COLONOSCOPY IN THE DIAGNOSIS AND SURVEILLANCE OF IBD

Jaroslaw REGULA

Department of Gastroenterology, Medical Centre for Postgraduate Education and Institute of Oncology, Warsaw, Poland

Colonoscopy plays crucial role in the management of patients with inflammatory bowel disease. It's obvious role in the diagnosis, differential diagnosis, endoscopic activity assessment, localization of diseased areas, therapy of strictures and surveillance to avoid cancer development has been known for a long time. Recently additional role helps in obtaining proofs of so called "deep remission" following biological therapy. Evaluation of IBD patients requires knowledge of available classifications for both ulcerative colitis and Crohn's disease. Ileoscopy is currently an imperative of colonoscopic evaluation. During treatment – the mucosal healing should be assessed as exactly as possible; endoscopy has also become necessary in the postoperative period in Crohn's disease patients to help further management decisions. Oncologic surveillance is currently well defined with availability of therapeutic options.

GASTROENTEROLOGY UZBEKISTAN TASHKENT 2012

ILEAL POUCH-ANAL ANASTOMOSIS IN ULCERATIVE COLITIS PATIENTS: SHORT AND LONG TERM RESULTS

Antonio GONZALEZ

Hospital Vall d'Hebron, Spain

STUDY OF INTESTINAL MICROFLORA IN PATIENTS WITH FATTY LIVER DISEASE

A. L. ALAVI, M. M. KARIMOV, G. N. SOBIROVA

Republican Specialized Scientific Practical Medical Center of Therapy and Medical Rehabilitation, Tashkent, Uzbekistan

Aims: Study of intestinal biocoenosis in patients with fatty liver disease (FLD).

Methods: 31 patients with FLD (steatosis and nonalcoholic steatohepatitis (NASH)) in age 18–57 (mean 41,3 ± 5,4 years), 19 female and 12 male, were included in investigation. Clinical and biochemical examination, microbiological investigation of intestinal biocoenosis were done. The structure of symbiosis was detected with constancy index of different taxons. All taxons divided into permanent (C < 50 %), additional (25 % < C < 50 %) and random (C < 25 %).

Results: In all patients with FLD we observed abdominal painful syndrome and flatulence of difference intensity, which makes up 2,3 ± 0,25 и 2,2 ± 0,2 points respectively. In 19 patients (61,3 %) pains associated with constipation, and in 12 ones (38,7 %) – with diarrhea. We revealed disbacteriosis of 2 degree in 14 patients (45,2 %) and 3 degree in 7 patients (22,5 %).
Dominant type of microflora of patients with FDL are facultative – anaerobic bifidobacteria and lactobacteria (C = 85,4 % и 77,4 % respectively), obligate-anaerobic bacteroides (C = 63,5 %), anaerobic Escherichia Coli with high index constancy (C = 90,5 %) against healthy people – bifidobacteria and lactobacteria (C = 100,0 %, C = 100,0 %, respectively), Escherichia Coli (C = 100,0 %) and bacteroides (C = 65,0 %). Besides that we noticed conditional pathogenic microorganisms enterococcus (C = 57,6 %), fungi Candida (C = 55,5 %) only in patients with NASH. The intensity of dysbiosis in patients with NASH was more significant than ones with steatosis.

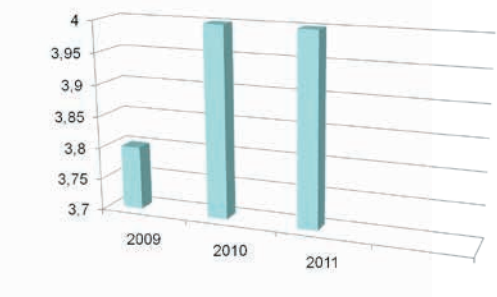
Conclusion: In patients with NASH we revealed considerable changes of intestinal microflora, which can cause of endotoxicosis.

GASTROENTEROLOGY UZBEKISTAN TASHKENT 2012

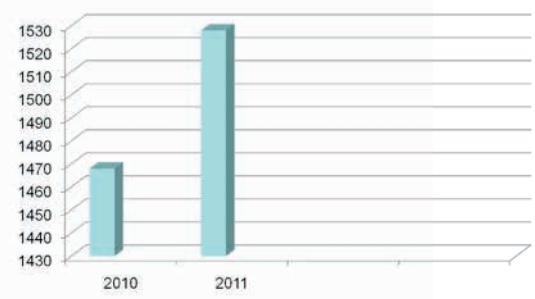
M. M. KARIMOV (UZB)

IBD as a risk factor for colorectal carcinoma

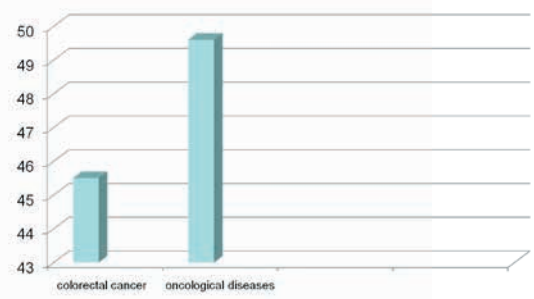
Frequency of a colorectal cancer in Uzbekistan (on 100000 population)



The primary detection of colorectal cancer in Uzbekistan



Five-year survival rate of patients with colorectal cancer (canceroncological diseases)



Rome criteria III

- In recent years, histological findings showed that the differences between the "functional" and "organic" changes have become blurred

Douglas Drossman

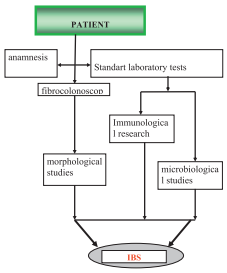
The functional gastrointestinal disordes and the Rome III process. Gastroenterology. 2006. 130 (5).1459-65.

- Rome criteria controversial and imperfect, caused a lot of discussions. Patients can now be quieted that they are legitimate violations, and not imaginary feelings under normal results of diagnostic researches

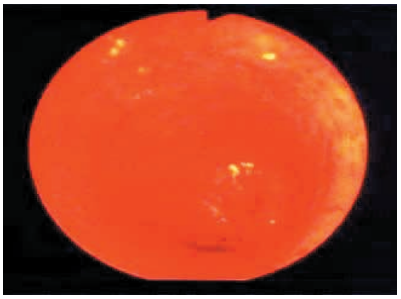
W. Grant Thomson

The road to Rome. Gastroenterology. 2006. 130(5). 1466-79

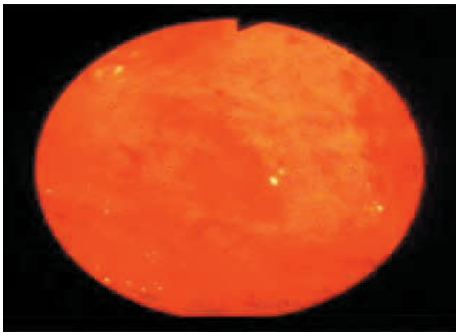
The algorithm of examination of the patient



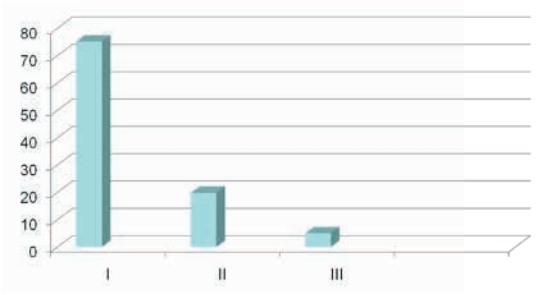
Endoscopic picture rectosigmoid section of the intestines. On the background of expressed hyperemia there are only single point of bleeding



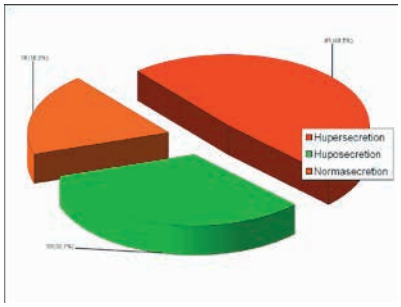
Endoscopic picture sigmoid section of the large intestine. Mucous membrane bowel pale pink, vascular figure strengthened.



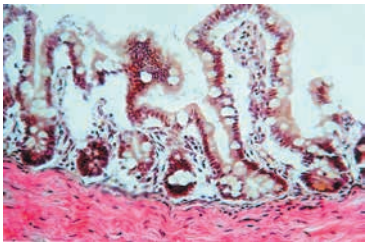
The degree of severity of inflammation in the mucous membrane of the large intestine



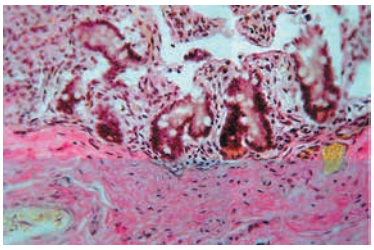
The distribution of patients depending on the secretory activity of the mucous membrane of the large intestine



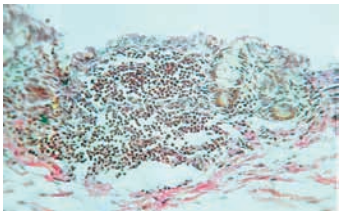
Hyper secretion form of morphological changes. Painting hematoxylin - eosin staining. X: OK. 10, of. 20.



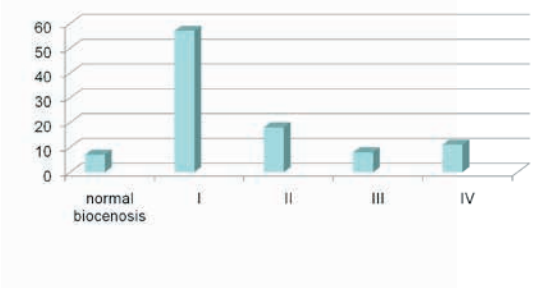
Hyposecretion form of morphological changes. Microphotography Painting hematoxylin - eosin staining. X: OK. 10, of. 20.



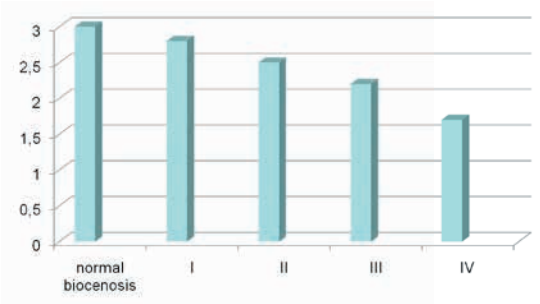
Normal secretion form of morphological changes. Microphotography. Painting hematoxylin - eosin staining. X: OK. 10, of. 20.



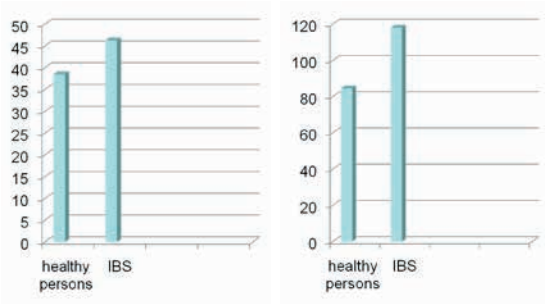
The degree of dysbacteriosis in patients with IBS



Content of s Ig A in biopsies of the large intestine in patients with IBS (g/l)



The contents of TNF and IL-6 in patients with IBS



MICROSCOPIC COLITIS – ONE OR TWO DISEASES?

Magdalena R. CHRUSCIELEWSKA-KILISZEK

Department of Gastroenterology and Hepatology, Medical Center for Postgraduate Education Department of Gastroenterology, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland

Microscopic colitis is classified as mild inflammatory bowel disease. There are two subtypes of microscopic colitis: lymphocytic and collagenous. The epidemiology is underestimated due to clinical similarity to functional diarrhea without histopathological verification of the diagnosis. Microscopic abnormalities in colonic mucosa with normal endoscopic and radiologic examination of the colon are typical for that entity. The incidence – regarding different data – is estimated to be 10 to 20 % of cases with refractory diarrhea. The clinical course is similar in both subtypes of the disease; the histopathological criteria of a diagnosis are different. The pathognomonic feature in collagenous colitis is thickened subepithelial collagenous band; in lymphocytic colitis – the increased number of intraepithelial lymphocytes.

The first-line treatment are antidiarrheal drugs (e.g.: loperamid, immodium), 5-aminocalicylates derivatives, cholestyramine or bismuth salts. The steroidotherapy (budesonid) is a good choice in severe cases; in steroid resistant cases – immunosuppressant drugs are used (azatioprine or 6-mercaptopurine). The risk of gastrointestinal neoplasia in these patients doesn't seem to be increased in comparison with general population.

Microscopic colitis – one or two diseases ?

M. R. Chruscielewska-Kiliszek M.D., Ph.D.

Department of Gastroenterology, Medical Centre for Postgraduate Education, Institute of Oncology, Warsaw, Poland

Diagnosis of microscopic colitis (MC)

- two subtypes of the same disease:
  - collagenous colitis (CC)
  - lymphocytic colitis (LC)
- two separate clinical entities with similar clinical course

Schiller LR, Lancet 2000

Epidemiology of CC

- increasing number of cases (USA)
- all cases of MC 103/100 000
- CC - 39,3/100 000
- F : M = 20:1

Pardi DS. et al., Gut 2007

Epidemiology – CC and MC

- smoking – a risk factor of CC development (…10 years earlier than in no smokers)
- current and past cigarette smoking significantly increase risk for MC.
- in MC: lower risk of colorectal cancer (and colorectal adenomas)
- osteopenia (up to 60% pts with MC)

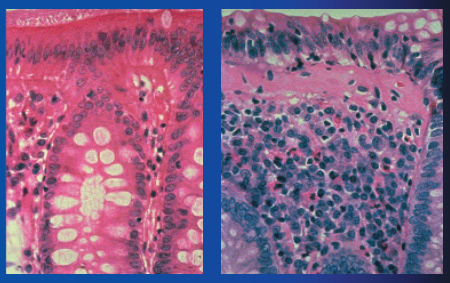
Vigren et al., Scand J Gastroenterol 2011
Yen et al., Dig Dis Sci 2012, Yen et al., Inflamm Bowel Dis 2011
Lorinczy et al., BMC Gastroenterol 2011

Collagenous colitis

- chronic, watery diarrhea
- normal endoscopic and radiological view
- histopathological parameters:
  - SECT - (SubEpithelial Collagen Table)> 10 µm
  - inflammatory infiltration of lamina propria
  - intraepithelial lymphocytosis (IEL)

Lindstrom CG, Pathol Eur 1976
Read NW et al., Gastroenetrology 1980

Normal mucosa Collagenous colitis



Pathogenesis of diarrhea in CC and LC

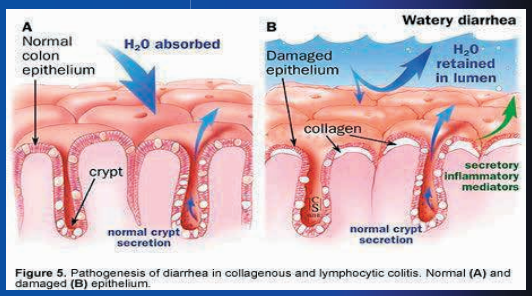


Figure 5. Pathogenesis of diarrhea in collagenous and lymphocytic colitis. Normal (A) and damaged (B) epithelium.

http://www.hopkins-gi.org/subspecialties/collagenous/causes.htm

Etiology

- autoimmune disorder
- inflammmatory - bacterial toxins?
- abnormal synthesis/metabolism of collagen?
- NSAID
- bile acids malabsorption

Nyhlin N et al., Aliment Pharmacol Thnerapeut 2006

Clinical course

- chronic watery non-bloody diarrhoea
- abdominal colic pain
- 40% pts: decrease in BMI, sudden onset of symptoms
- 40% pts: concurrent autoimmune diseases
- absent malabsorption symptoms

Pardi DS., Mayo Clin Proc 2003

CC and celiac disease

- AGA – up to 17% pts with MC
- 4% pts with celiac disease refractory to gluten-free diet: MC
- 2% pts with CC – celiac disease
- risk of MC in pts with celiac disease – 45x greater than in general population

Fine KD et al., Gastroenterology 1997
Green PH et al., Clin Gastroenterol Hepatol 2009

Colonoscopy?

- in biopsy – higher concentration of collagenous deposits in right colon
- colonoscopy with multiple biopsy of normal mucosa, mainly right sided

Carpenter HA et al., Dig Dis Sci 1992
Narabayashi K etb al., Digestion 2012

FSS ?

- FSS, multiple left-sided biopsy
- when result of FSS negative with strong clinical suspicion of CC – colonoscopy

Bjornbak et al., Aliment Pharmacol Ther 2011
Pardi DS., Am J Gastroenterol 2002

Lymphocytic colitis

typical features (70%)

- chronic diarrhea
- normal endoscopic view
- increased IEL, normal SECT

atypical features (30%)

- fulfilled histopathological criteria
- no clinical and endosopic criteria of typical LC

Wang et al. Am J Sur Path 1999

Epidemiology of LC

- increasing number of cases (USA)
- lymphocytic colitis (LC) – 63,7/100 000
- LC - F = M

Pardi DS. et al., Gut 2007

Etiology

...like in CC and:

- ticlopidine
- lansoprazole (!)
- ranitidine
- cymetidine
- simwastatin
- acarbose
- carbamazepine
- SSRI
- beta blockers
- bisfosfonians

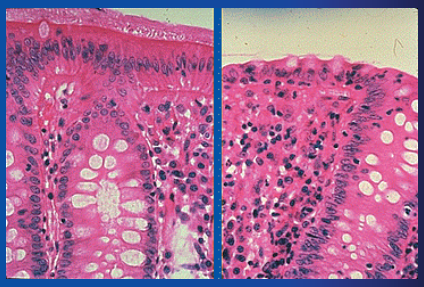
Beaugerie L et al., Aliment Pharmacol Ther 2005

Histopathology

- IEL: (CD3+ i CD 8+) > 20/100 epithelial cells
- normal SECT (<10 µm)
- normal crypts
- EOS + plasma cell infiltration in lamina propria

Olesen et al., Gut 2003

Normal mucosa **Lymphocytic colitis**



Clinical course

- in typical type – similar to CC
- in atypical type – constipation(!), mucosal erosions/ulcerations, positive stool cultures, haematochezia
- complete remission in LC 60-95% during 3-4 years of follow up

Pardi DS. et al., Am J Gastroenetrol 2002

LC and celiac disease

1. 20-30% pts with celiac disease (CD) are diagnosed with LC
2. „Lymphocytic enterocolitis" – intraepithelial lymphocytosis as a marker of refractory to gluten-free diet celiac disease
3. >> colonoscopy – when CD treatment (-) (women)

   >> EGD – when LC treatment (-)

1. Walber et al. Human Patol. 1990
2. Du Bois JAMA, 1989
3. Simondi et al..Rev Esp Enferm Dig, 2010
4. Stewart et al. Aliment Pharmacol Ther 2011

FSS

- left-sided biopsy sufficient for LC diagnosis

Bjornbak C et al., Aliment Pharmacol Ther 2011

Rare subtypes of MC

- „giant cell colitis"
- NOS=no otherwise specified
- MC with reactive granulomatosis
- others ..

Chang F et al., Adv Anat Pathol 2005

MC vs IBD

- distinct diseases
- disease coexistence described
- different sequence of diagnosis
- difficulties in histopathological differential diagnosis (DD)

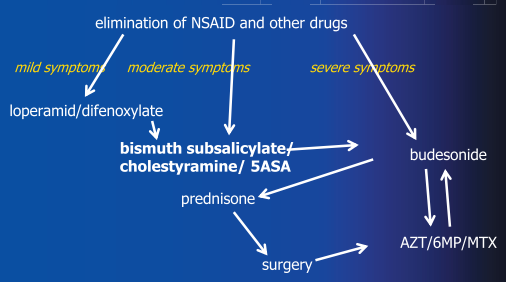
Differential Diagnosis

- Crohn's disease
- ulcerative colitis
- ischemic colitis
- chronic radiation proctitis
- SLE
- eosinophilic colitis
- IBS
- GEP-NET
- amyloidosis

(CC and LC – morphological variants of Crohn's disease?)

Aqel B et al., Dig Dis Sci 2003
Pokorny CS et al., J Clin Gastroenterol 2001

Therapeuthic approach



Yen,Pardi, Aliment Pharmacol Therap 2011

Budesonid in MC

- induction of remission (LC and CC)
- clinical and histological remission control (CC)

Stewart et al., Clin Gastroenterol Hepatol 2011

Treatment

- Cochrane Database 2011

MC:

1/.budesonide (9-6-3 mg/24h)

2/.bismuth subsalicylate (3x3 tablets a 282 mg /24h)

3/.mesalazine (3x800 mg/24h) +/- cholestyramine (4 g/24h)

(Boswellia serrata 3x400 mg, probiotics, prednisolone 50 mg)

Summary

- „an umbrella term" for LC and CC – MC:

„….should perhaps be considered one clinical entity and include lymphocytic colitis, collagenous colitis, and incomplete findings of microscopic colitis".

- „CC and LC may coexist and interchange"

Bjonbak et al., Aliment Pharmacol Ther 2011; 34: 1225–1234

„Take home message"

MC:

- relatively common cause of chronic diarrhea
- often mild symptoms
- no evidence for oncological potential
- biopsy should be taken during FSS or colonoscopy
- good response of budesonide

EFFICIENCY OF COMBINATION THERAPY OF BARRETT'S ESOPHAGUS AND EROSIVE ESOPHAGITIS WITH AN APPLICATION OF PROTON PUMP INHIBITOR AND URSODEOXYCHOLIC ACID

Vladislav V. TSUKANOV

Federal State Budgetary Institution "Scientific research institute of medical problems of the North" Siberian branch under the Russian Academy of Medical Sciences, Krasnoyarsk, Russian Federation

Aim. To carry out research of efficiency combination therapy of proton pump inhibitor + ursodeoxycholic acid (Ursosan) with efficiency of proton pump inhibitor monotherapy in case of patients with Barrett's esophagus and erosive esophagitis.

Methods. We performed prospective (5 years), open, randomized study for comparison of efficiency combination therapy of proton pump inhibitor + ursodeoxycholic acid (Ursosan) with efficiency of proton pump inhibitor monotherapy in case of patients with Barrett's esophagus and esophagitis in patients over 60 years of age. The method of "closed envelope" patients were divided into two groups. Group A including 31 patients (15 men, 16 women, middle age 67.2 years) and group B – 31 patients (17 men, 14 women, middle age 66.6 years). Patients of group A taking PPIs (omeprazole) 40 mg/day. Patients of group B received a combination of omeprazole 40 mg/day and UDCA (Ursosan) an average dose of 10 mg/kg/day. Group A included 21 patients with cholelithiasis, group B – 22 patients with cholelithiasis. The diagnosis of Barrett's esophagus verified by histological examination of biopsy samples from the lower third of the esophagus. Degree of esophagitis intensity has been defined according to Los Angeles Classification [Lundel L.R., et al., 1999].

Clinical examination of patients has been carried out 3 times a year, ultrasound investigation of liver – once a year, endoscopic examination – once a year, diagnostics of morphological changes in esophagus mucous has been conducted prior to beginning of the examination, in 3 years and in 5 years from beginning of the examination. 24-hour pH monitoring of esophagus and impedancemetry have not been used in the work.

Results. After 5 years of treatment in group A determination of the frequency of Barrett's esophagus decreased from 100 % to 93.5 % ($p = 0.15$), while in group B – from 100 % to 67.7 % ($p < 0.001$). In this case the final results of the treatment groups differed in the surveyed also significantly ($p = 0.01$). Frequency of heartburn after 5 years of therapy in group A decreased from 77.4 % to 35.5 % ($p = 0.001$), in group B – with 80 % to 13.3 % ($p < 0.001$). The frequency of diagnosis of erosive esophagitis decreased after 5 years of therapy from 80.6 % to 51.6 % in group A ($p = 0.016$) and from 86.7 % to 16.7 % in group B ($p < 0.001$).

Conclusion. Combination of PPI with UDCA in the treatment of Barrett's esophagus and erosive esophagitis is more effective than monotherapy with PPIs.

GASTROENTEROLOGY
UZBEKISTAN TASHKENT 2012

Efficiency of Barrett esophagus treatment is low

- Wang K.K., Sampliner R.E. Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett esophagus // Am. J. Gastroenterol. – 2008. – V.103, N3, P.788-797.
- Sharma P. et al. Management of nondysplastic Barrett's esophagus: where are we now // Am. J. Gastroenterol. – 2009. – V.104, N4. – P.805-808.
- AGA Technical review on the management of Barrett's esophagus // Gastroenterology. – 2011. – V.140, N3. – P.e18-e52.

Treatment of Barrett esophagus

Metaanalyse basing on Cochrane

Rees J.R. et al., Cochrane Database Syst. Rev., 2010, Jan, Vol. 20, N1, P.CD004060.

16 works – 1,074 patients have been selected.

Radio frequency ablation ranks first in reference to endoscopic treatment of Barrett esophagus.

Association of Barrett esophagus with choledocholithiasis and dysmotility of gallbladder

Izbeki F. et al.,
Dig. Dis. Sci., 2008, Vol.53, N8, P.2268-2275.

707 patients have been examined, 203 of which had Barrett esophagus.

Prevalence rate of choledocholithiasis referred to patients with Barrett esophagus - 34 %, and persons without Barrett esophagus - 20 %, p=0.01.

Association of Barrett esophagus with choledocholithiasis and dysmotility of gallbladder

Izbeki F. et al.
Dig. Dis. Sci., 2008, Vol.53, N8, P.2268-2275.

Persons with Barrett esophagus have complex dysmotility of gastro-intestinal tract, which includes abnormalities of gallbladder, and this makes these patients be more prone to choledocholithiasis.

Dysfunction of gallbladder contributes to progression of Barrett esophagus and adenocarcinoma of esophagus

Nassr A.O. et al.,
J. Gastrointest. Surg., 2011, Vol.15, N6, P.908-914.

Three groups of patients have been examined, all groups are without choledocholithiasis.

Group 1: (p = 15) - control.

The 2nd group (p = 15) - patients with a segment of Barrett esophagus of more than 3 sm in length.

Group 3: (p = 15) - patients with adenocarcinoma of esophagus.

Gallbladder function has been examined by means of ultrasound investigation.

Dysfunction of gallbladder contributes to progression of Barrett esophagus and adenocarcinoma of esophagus

Nassr A.O. et al.,
J. Gastrointest. Surg., 2011, Vol.15, N6, P.908-914.

Gallbladder function is being progressively affected in case of Barrett esophagus and adenocarcinoma of esophagus. Dysfunction of gallbladder increases duodenogastric reflux, by affecting the bottom part of the esophagus with aggressive chemical agents.

New functions of bile acids

Hylemon P.B. et al., J. Lipid Res., 2009, Vol. 50, N6, P.1509-1520.

"Nowadays, it is absolutely evident that bile acids are hormones, which may activate signaling pathways, have potential control over cell proliferation and inflammatory processes in liver and gastro-intestinal tract"

Bile acids regulate apoptosis in liver and gastro-intestinal tract

Amaral J.D. et al., J. Lipid Res., 2009, Vol. 50, N7, P.1721-1734.

Hydrophobic bile acids induce apoptosis by means of stimulation of caspase and Bcl-2, cause direct affect of mitochondria, inducing oxidative stress.

Hydrophobic bile acids are Bcl-2 antagonists, protect from mitochondrial dysfunction and apoptosis.

Methods

There has been carried out prospective **(within 5 years)** open-label randomized study for efficiency comparison regarding complex therapy of proton pump inhibitor + ursodeoxycholic acid (Ursosan) with efficiency of proton pump inhibitor monotherapy in case of patients with choledocholithiasis and Barrett esophagus over 60 years of age.

Methods

Patients with Barrett esophagus and choledocholithiasis have been randomized according to several groups: **group "A"** including 31 patients (15 men, 16 women, middle age 67.2 years) and **group "B"** (17 men, 14 women, middle age 66.6 years).
Group "A" included 21 patients with choledocholithiasis,
Group "B" – 22 patients with choledocholithiasis.

Methods

Patients from **group "A"** took proton pump inhibitor (omeprazole) with a dosage of 20 mg x 2 times a day. Patients from **group "B"** took a combination of omeprazole 20 mg x 2 times a day and ursodeoxycholic acid preparation (Ursosan) with an average dose of 10 mg/kg/a day during the whole period of observation.

Methods

Clinical examination of patients has been carried out 3 times a year,

Ultrasound investigation of liver – once a year, endoscopic examination – once a year,

Diagnostics of morphological changes in esophagus mucous has been conducted prior to beginning of the examination, in 3 years and in 5 years from beginning of the examination.

24-hour pH monitoring of esophagus and impedancemetry have not been used in the work.

Methods

Degree of esophagitis intensity has been defined according to Los Angeles Classification [Lundel L.R.,et al., 1999].

Methods

According to the current recommendations (Wang K.K., Sampliner R.E. // Am. J. Gastroenterol. – 2008. – V.103, N3, P.788-797), Barrett esophagus shall be understood to mean intestinal metaplasia in esophagus mucous membrane. Diagnosis verification has been carried out only basing on histologic examination.

Methods

Taking biopsy material has been carried out according to 4 quadrant method, starting in gastro-oesophageal junction and proximally every 1-2 sm to proximal edge of the Barrett mucous, as well as from any abnormal segment (Tytgat, G.N.J. et al., 1994).

Influence of bile acids on progression of Barrett esophagus

Experimental and clinical examinations show the role of bile acids in progression of serious esophagitis and Barrett esophagus [Kazumori H. et al., Nihon Shokakibyo Gakkai Zasshi, 2007; Jenkins G. et al., Mutagenesis, 2008; Dvorak K. et al., Am. J. Gastroenterol., 2009].

New mechanism of Barrett's esophagus development

Goldman A. et al. (Gut, 2010, V.59, N12, P.1606-1616, Dec.)

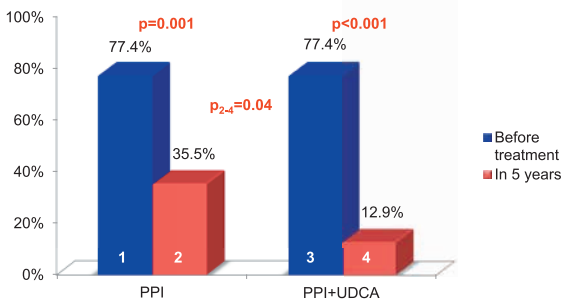
Hydrophobic bile acids increase production of free radicals, that may be significant for progression of Barrett esophagus.

Ursodeoxycholic acid in treatment of Barrett esophagus

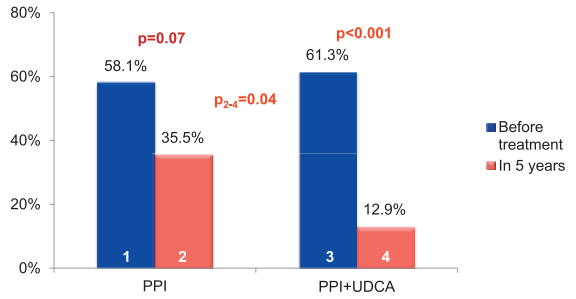
10-minute exposure of ursodeoxycholic acid on Barrett esophagus cells without dysplasia in acid medium reduces DNA affection, cytotoxicity, and production of reactive oxygen species, exercising cytoprotective and antioxidant effect

[Goldman A. et al., Dis. Esophagus, 2010, Vol.23, N2, P.83-93.].

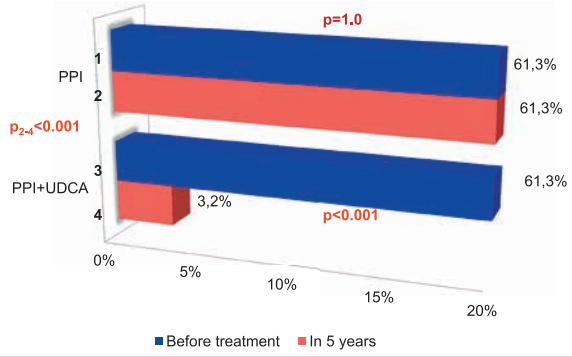
Dynamics of weekly heartburn in 5 years of proton pump inhibitor therapy vs. proton pump inhibitor + ursodeoxycholic acid (Ursosan)



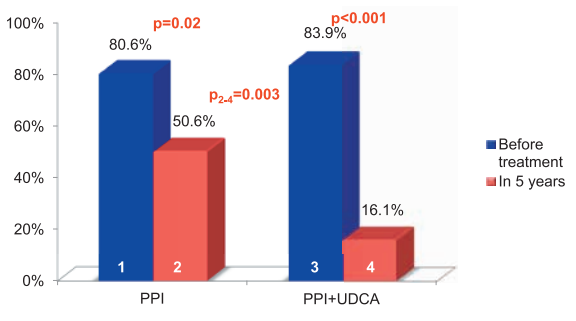
Dynamics of weekly regurgitation in 5 years of proton pump inhibitor therapy vs. proton pump inhibitor + ursodeoxycholic acid



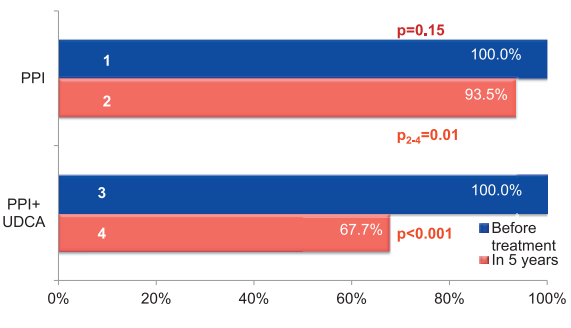
Dynamics of constipation in 5 years of proton pump inhibitor therapy vs. proton pump inhibitor + ursodeoxycholic acid



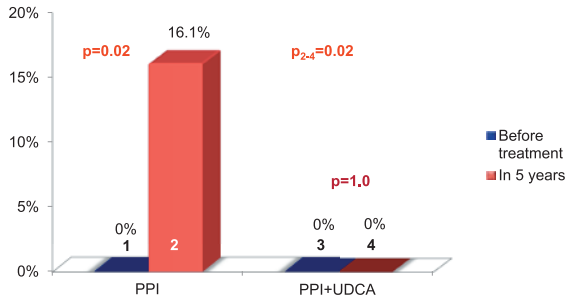
Dynamics of erosive esophagitis in 5 years of proton pump inhibitor therapy vs. proton pump inhibitor + ursodeoxycholic acid



Dynamics of Barrett esophagus in 5 years of proton pump inhibitor therapy vs. proton pump inhibitor + ursodeoxycholic acid



Dynamics of dysplasia of esophagus in 5 years of proton pump inhibitor therapy vs. proton pump inhibitor + ursodeoxycholic acid



Conclusion

1. There are obvious interrelations between abnormality of gallbladder and esophagus diseases.

Conclusion

2. As a result of the 5-year research, there has been detected higher efficiency of combination of proton pump inhibitor + ursodeoxycholic acid **(Ursosan)** in comparison with proton pump inhibitor monotherapy for treatment of epigastric burning, esophagitis, and Barrett esophagus.

3. Possible positive influence of ursodeoxycholic acid **(Ursosan)** on progression of esophagus abnormality may be associated with impact on gastro-intestinal tract motility and direct protective effect on the esophagus mucous.

THE ROLE OF AUTOIMMUNITY IN GASTROENTEROLOGY

Jan KREJSEK

Charles University in Prague, Faculty of Medicine, Hradec Králové, Czech Republic
krejsek@fnhk.cz

Autoimmunity is a very complex phenomenon comprising both the physiological and pathophysiological immune reactivity. Based on the classical paradigma, autoimmune immunopathological reaction is induced in genetically predisposed individuals exposed to precipitating harm factors, e.g. of infectious origin, but in clinical situation largely of unknown origin. The central role in this classical view is given to autoreactive T cells which are not deleted during intrathymic induction of self tolerance. However, this concept which is firmly proved by numerous *in vitro* and *in vivo* experiments, is poorly reiterated in the clinical presentation of autoimmune diseases in humans.

There is a substantial shift in our understanding of the function of immune system nowadays. Specific immunity "self, non-self" recognition is enriched by the overwhelming evidences that the fundamental activities of the immune system are based on innate immunity which is able to discriminate between "safe" and "danger". In short, "danger" is all signals which either directly or indirectly disturb homeostasis, whereas "safe" signals are not influencing homeostasis. Danger signals of both exogenous origin (e.g. microbial PAMPs) or endogenous danger associated molecular patterns (DAMPs) are recognized by the limited set of evolutionary highly conserved surface or intracellular molecules designated as pattern recognition receptors (PRRs). Danger pattern recognition is followed by the assembly of signaling complexes, such as signalisomes and (or) inflammasomes, which are in the end responsible for proinflammatory activities. Danger molecules are internalized by the innate immunity cells, most effectively by dendritic cells. Subsequently these molecules are processed and presented in the context of HLA molecules to specific T cells.

There is the loss of the firm borderline between autoimmunity and immunopathology. Rather, it seems apparent now that the formerly autoimmune diseases involving gut are associated with the presence of DAMP which are induced by numerous variables including abnormal patterns of cell death, such as necrosis, pyroptosis or autophagy; oxidative stress; accumulation of structurally impaired molecules and (or) organells or persisted presence of intracellularly localized microbial PAMPs. In the end of this process is the fail in the homeostatic regulations, including abnormal activities of regulatory subsets of T cells; e.g. Treg, TH17 and abnormities in both innate and mucosal immunity in patients suffering from immunopathological diseases of gut.

GASTROENTEROLOGY
UZBEKISTAN TASHKENT 2012

FOOD ALLERGY

Javier SANTOS

Hospital Vall d'Hebron, Spain

EOSINOPHILIC OESOPHAGITIS

Ondřej URBAN

Vítkovice Hospital, Czech Republic

Eosinophilic Esophagitis (EoE)

O.Urban, M.Kliment, P.Fojtík, P. Falt , M. Hanousek
Vitkovice Hospital, Czech Republic

Definiton and Prevalence

1.Clinical symptoms of esophageal dysfunction

2.>15 Eos / hpf in esophagel biopsy

3. Absence of GERD (lack of response to high-dose PPI or normal pH monitoring)

Prevalence 4,5/10 000 Olten County, Switzerland *

Furuta , et al. Gastroenterology 2007
AGA institute /NASPGHAN consensus recommendation 2007
*Noel, et al. N Engl J Med 2005 **

EoE: History

1978: Description in adult patient

Landers RT, et al. Gastroenterology 1978

1993: 12 pts

Attwood S, et al. Dig Dis Sci 1993

2003: 30 pts , FU ~ 7 yrs

Straumann A, et al. Gastroenterology 2003

2006: 74 pts

Gonsalves N, et al. Gastrointest Endosc 2006

EoE: Etiology

- Alergen exposure through respiratory or alimentary tracts (52% prevalence of atopic disorders in adults with EoE)
- Eosinophilia 30%, increased IgE 55%[1]
- 72% sensitivity to aeroalergens, 82 % specific IgE to foods[2]
- Th-2 type immune response (expression of IL-4, IL-5, IL-5, and mast cells in biopsies)
- 1% ot the genom dysregulated in patients with EE (eotaxin-3 gene)[3]

1. Fox V, et al. Gastrointest Endosc 2002
2. Katzka R et al. Clin Gastro Hep 2008
3. Blanchard et al. J Clin Invest 2006

EoE: Clinical Features in Adults

Age (yrs)	37 (14-81)
Male	72-77%
Mean duration (years)	5 (0-38)
Atopic history	52-74%
Food alergy history	19%
Dysphagia	82-93%
Food Impaction	62-76%
Heartburn	24-29%
Chest pain	8%

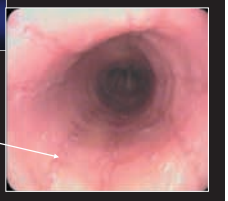
Sgouros S, et al. Eur J Gastroenterol Hepatol 2006
Toto, DDW 2010

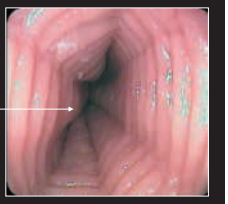
EoE: Endoscopic Hallmarks

Evident in 90% of adult cases

Longitudinal furrows	80%
Mucosal rings	64%
Small caliber esophagus	28%
Exudates	16%
Strictures	12%

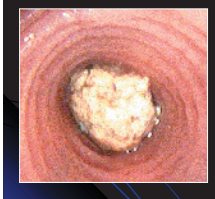
„ Corrugated esophagus “

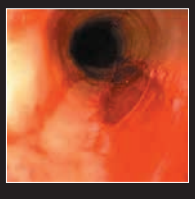




Remedios M, et al. Gastrointest Endosc 2006

Endoscopic Hallmarks of EoE





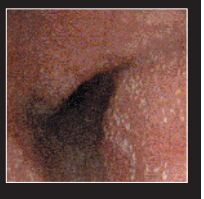


Table 1. Clinical Features of Eosinophilic Esophagitis in Children and Adults

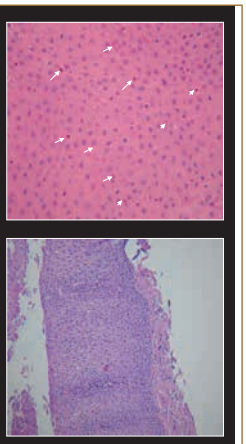
Study	N	Age (range)	Male (%)	Allergy (%)	% Patients with peripheral eosinophilia	Endoscopic Findings
Adult						
UC 2006	12	40 (22-64)	83	50	NR	Rings 17%, Rings+Furrows 33%, Rings and Furrows 25%
Australia 2003	31	37 (17-70)	77	45	36	Furrows+Furrows 87%
Mayo 2003	21	40 (26-55)	67	29	5	Rings 71%, Furrows 14%
Secteranic 2005	30	41 (19-70)	73	29	50	Furrows 53%, Rings 20%, Stricture 20%, Normal 10%
Milwaukee, 2004	29	33 (19-62)	72	48	NR	Rings 79%, Furrows 10%, Small caliber 7%, Exudates 14%, Normal 14%
Chicago 2005	34	35 (14-75)	76	50	9	Rings 38%, Furrows 24%, Strictures 6%, Exudates 15%, Normal 18%, Other 18%
Australia 2006	28	41 (17-67)	50	77	3	Furrows 57%, Rings 32%, Small caliber 21%, Exudates 15%, Stricture 12%

Gonsalves N, et al. Gastroenterol Hepatol 2006;1:10-15

EoE: Histology

≥ 15 intraepithelial Eos/ hpf

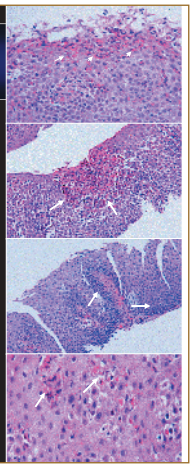
Entitiy	Eos/hpf
EoE	≥ 15
Indeterminate	6-14
GERD	< 5



Sgouros S, et al. Eur J Gastroenterol Hepatol 2006;18:211-217

EoE: Other Histological Features

- Eosinophilic absces (≥ 4 Eo)
- Eosinophil degranulation
- Other inflammatory cells (lymfocytes mastocytes)
- Basal layer expansion / >30% epith.
- Papillary elongation / >70% epith.
- Subepithelial fibrosis



EoE: 5 Biopsies Better than 1

1 biopsy = senzitivity 55%
5 biopsií = senzitivity 100%

Take biopsy in each young patient with unexplained dysphagia, food impaction or refractory heartburn despite normal endoscopy

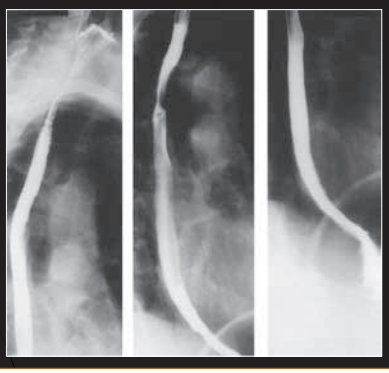
Gonsalves N, et al. Gastrointest Endosc 2006

Differential Diagnosis for Esophageal Eosinophilia

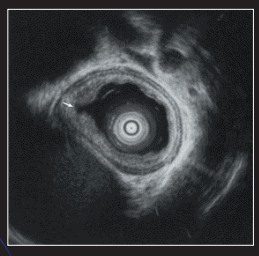
GERD
Eosinophilic gastroenteritis
Hypereosinophilic syndrome
Drug hypersensitivity
Infectious esophagitis
Connective tissue disoreders
Achalasia
Neoplasia
Immunosuppression

EoE: RTG

„ Small caliber “ esophagus

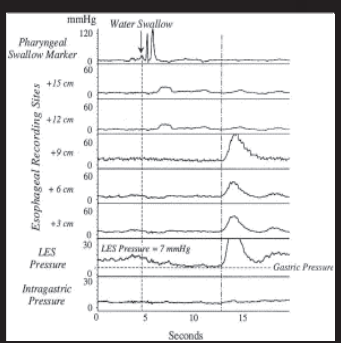


EoE: EUS



EoE: Manometic Features

Non-specific dysmotility
↓LES pressure
Simultaneous contractions



Stevoff C, et al. Gastrointest Endosc 2001

EoE: Time to Diagnosis

Study	n	~ month to dg	
Potter et al 2004	55	66	(0-420)
Croese et al 2002	31	54	(0-180)
Gonsalves et al 2006	74	82	

Gonsalves N, et al. Gastrointest Endsc 2006;64:313-19

Reasons Behind Delayed Dg

55 patients with EoE:

- No biopsy during first upper endoscopy 25/55 (45%)
- Histology misinterpretation 12/55 (22%)
- Absence of eosinophils number determination 6/55 (11%)

Sanjeevi A, et al. Gastroenterology 2005;128(4)Suppl 2:41

GERD vs. EoE

	GERD	EoE
Dominant sy	Heartburn	Dysphagia
Food impaction	Uncommon	Common
Gender	M=F	Male predom
Atopic history	Normal	70%
Endoscopy	NERD	Furrows
	Erosions	Rings
	Barrett´s	Exudate
Histology	< 7 Eos / hpf	>15 Eos / hpf

- *Hirano, AGA postgr course, DDW 2010*

Contribution of GERD to Pathogenesis of EoE ?

1. Eosinophilic viability increased by acidic pH
   (Kottyan, Blood, 2009)
2. Acid reflux induces release of mast cell mediators
   (Paterson, Am J Physiol 1998)
3. PPI therapy may have antiinflamatory effects beyond acid suppression
   (Cheng, DDW, 2010)

Coexistance of GERD and EoE

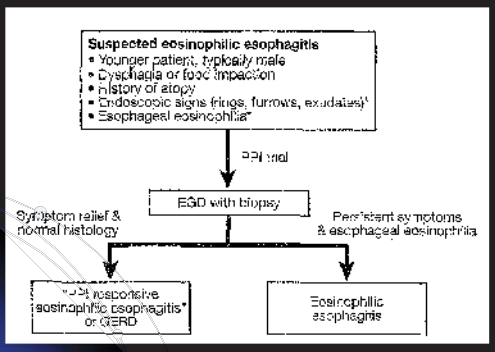
Pediatric EoE
Abnormal pH testing in 25-50%[1]

Adult EoE
Erosive esophagitis or abnormal pH testing in 29-42% [2]

75% pts with esophageal eosinofilia respond to 8 wk course of PPI (↓ < 5 Eos / hpf) [3]

1. *Gupta, J.Pediatrics 2009*
2. *Remedios, Gastrointest Endosc 2006*
3. *Molina-Infante, Clin Gastroenterol Hepatol 2011*

Suggested Approach to Adult Patient with EoE



Hirano, Clinical Gastroenterol Hepatol 2011

Medical Therapy

Systemic corticosteroids
Pediatric study: MP 1 mg/kg/d BID

Medical Therapy

Systemic corticosteroids
Pediatric study: MP 1 mg/kg/d

Topical corticosteroids (Budesonid)
36 adult pts.; 1mg BID 15 days = remission
Straumann et al., Gastroenterology 2008, 134(4)A104

Medical Therapy

Systemic corticosteroids
Pediatric study: MP 1,5 mg/kg/d = clinical and histol.remission
Not recomended

Topical corticosteroids (Budesonid)
36 adult pts.; 1mg BID 15 days
Straumann et al., Gastroenterology 2008, 134(4)A104

Montelukast
10-100 mg/d 4 months
Attwood S., et al. Gut 2003;52:181-185

Medical Therapy

Systemic corticosteroids
Pediatric study: MP 1,5 mg/kg/d = clinical & histol.remission

Topical cortikosteroids (Budesonid)
36 adult pts.; 1mg BID 15 days = remission
Straumann et al., Gastroenterology 2008, 134(4)A104

Montelukast
8 pts. 10-100 mg/d 14 month
Attwood S., et al. Gut 2003;52:181-185

Mepolizumab
(Anti IL-5 monoclonal Ab)
Garrett J., et al. J Allergy Clin Immunol 2004;113:115-119

vitkovická NEMOCNICE

Dietery Management

1.Elemental Diet *(Kelly ,Sampson,1995)*

2.Directed elimination diet *(Spergel, 2005)*

3.SFED: 6w food elimination diet *(Kagalwalla, Li,2006)*
Milk, soy, nuts, eggs, wheat, seafood

Improve symptoms, esophageal eosinofilia and endoscopic features
Histological improvement: Children 74%, Adults 52%

Esophageal Dilation in EoE

Review of 84 adult patients
Perforation in 4 (5%)
Chest pain 6 (7%)
Symptomatic improvement 85%
Recurrent symptoms in majority after 3-8 months

Straumann A., et al. Gastroenterology 2003

vitkovická NEMOCNICE

EE - Treatment

Table 2. Current Therapeutic Options for Patients with Eosinophilic Esophagitis

Study	N	Treatment	% Response	Mean time to recurrence after therapy
Adult				
Arora, 2003	21	Fluticasone propionate, twice daily × 6 weeks	100	12–18 months
Remedios, 2006	18	Fluticasone propionate, twice daily × 4 weeks	100	3 months
Attwood, 2003	8	Montelukast	38	3 weeks
Attwood, 1995	12	Esophageal dilation	100	3–6 months
Straumann, 2003	11	Esophageal dilation	90	8 months
Potter, 2003	13	Esophageal dilation	54	3 months

Gonsalves N, et al. Gastroenterol Hepatol 2006

vitkovická NEMOCNICE

EoE: Conclusions I

1. EoE is an important cause of esophageal symptoms

2. Typical patient is young male with a history of atopy and food impaciton

3. Most of the patients have typical endoscopic features

vitkovická NEMOCNICE

EoE: Conclusions II

4. > 15 Eos / hpf is a histological hallmark

5. Topical steroids (Budesonid,Fluticason) first line treatment

6. High-dose PPI worth to try

vitkovická NEMOCNICE

EOSINOPHILIC GASTROENTERITIS

Branislav KUNČÁK

FNsP Nové Zámky, Slovakia

ENTERIC ANTIBODIES AND GUT MOTILITY DISORDERS

A. S. TRUKHMANOV, O. A. STORONOVA

First Moscow State Medical University named after I. M. Sechenov, Russian Federation

There is increasing evidence that a great number of gastrointestinal motility disorders are associated with the presence of circulating antibodies. These antibodies are produced against various molecular targets. This antibodies are known as anti-neuronal nuclear antibody (ANNA-1, anti-Hu) and associated with paraneoplastic motility disorders. Also in literature there is evidence that the presence of distinct auto-antibody profiles is associated with non-paraneoplastic motility disorders.

The diagnosis of a paraneoplastic dysmotility requires the onset of gastrointestinal dysmotility associated with the presence of a tumor and specific serum antibodies. This specific serum antibodies include ANNA-1 (anti-Hu), calcium channel antibodies, antibodies against neuronal nicotinic acetylcholine receptors, antistriational autoantibody, potassium channel autoantibodies Purkinje Cell Cytoplasmic Autoantibody, type 1 (PCA1) etc.

Antibodies associated with paraneoplastic dysmotility (type 1 antineuronal nuclear antibody ANNA-1) recognize the nuclear protein Hu which belongs to a family of conserved RNA binding proteins that includes HuC, HuD, HuR and Hel-N1. Those proteins are expressed in the neurons of the central, peripheral and enteric nervous system. The tumors that may express ANNA-1 include breast, prostate, ovarian carcinomas, lymphomas and small cell lung cancer with associated paraneoplastic gastrointestinal dysmotility.

Type 2 of antineuronal nuclear antibodies (ANNA-2 or anti-Ri) is expressed in neurons of the central nervous system, small cell lung cancer and some breast cancer cells. Usually they are associated with neurological symptoms from midbrain, brain stem, cerebellar or spinal cord dysfunction. But ANNA-2 has not been associated with gastrointestinal dysmotility.

There are distinguished various possible pathogenic mechanisms of paraneoplastic dysmotility. Among them are an impair of the ascending excitatory reflex by anti-Hu antibodies, an enteric neuronal degeneration, anti HuD induced apoptosis and mitochondrial dysfunction leading to subsequent neuronal injury.

Paraneoplastic dysmotility can be shown as pseudoachalasia, paraneoplastic gastroparesis, paraneoplastic chronic intestinal pseudoobstruction and chronic constipation.

Treatment of paraneoplastic dysmotility includes a treatment of the underlying primary malignancy. Also nutritional support either enteral or parenteral, adequate hydration, use of prokinetics, treatment of complications such as bacterial overgrowth should be performed. High dose of IV steroids for 3 days and if there is a clinical response switch to 6-mercatopurine or azathioprine should be prescribed. But, there are no effective treatments available for paraneoplastic dysmotility.

Clinical presentation of a non-paraneoplastic dysmotility syndrome associated with circulating antibodies consists of achalasia, GERD, IBS and chronic intestinal pseudoobstruction. In-

fection, genetic predisposition, spontaneous neurodegeneration and autoimmune mediated ganglion destruction are defined as etiological factors of achalasia.

According to our data, among patients with chest pain pathology of upper GI as its reason, was revealed in 90,6 % of patients. GERD, achalasia, esophageal spasm were observed as main reasons of the chest pain.

All cases of extension of serum level of NO metabolites were observed in patients with a GERD, meanwhile extension of level of NO metabolites wasn't observed in patients with an achalasia and primary esophageal spasm ($p < 0,01$).

Reduction of serum level of NO metabolites was registered in patients with an achalasia. Also, reduction of NO metabolites was observed in patients with GERD combined with secondary esophageal spasm ($p < 0,05$). Reduction of serum level of nitrites/nitrates in comparison with group of healthy subjects was noted in patients with esophageal spasm.

Serum level of NO metabolites was revealed close to normal values in patients with the first type of achalasia ($p < 0,05$).

CELIAC DISEASE – A DIFFERENT VIEW AT THE EFFECTS OF GLUTEN-FREE DIET

Boris PEKÁREK[1], Božena PEKÁRKOVÁ[2], Ľubomír JURGOŠ[3], Peter MLKVÝ[4]

[1] Department of Endoscopy, National Cancer Institute, Bratislava, Slovakia
[2] Private Outpatients' Department GEA s. r. o., Trnava, Slovakia
[3] Private Outpatients' Department, Bratislava, Slovakia
[4] St. Elisabeth Oncology Institute, Bratislava, Slovakia

Introduction: The celiac disease (CD) was also called primary malabsorption syndrome in the past. It can rebound at any age and despite its original title, it does not have to be manifested with malabsorption. The only known effective treatment of celiac disease is gluten free diet, therefore since 2005 certain gluten-free products in Slovakia are available in pharmacies with a prescription.

Aims and methods: The main focus was on what proportion of diagnosed patients with CD are overweight or obese, and how gluten free diet affected BMI, because the gain of weight could negatively affect future morbidity of overweight or obese patients. We also considered the implementation of the legislative act that enabled doctors to prescribe certain gluten free foods that could be partially covered by health insurance, and further focused at the benefit of this new law. The survey was made as a retrospective evaluation of 153 patients with histologically proven celiac disease and a simple questionnaire evaluating how the availability of certain gluten-free foods through doctor's prescription influenced their diet adherence.

Results: We confirmed the assumption that only a relatively small portion of the patients (21.8 %) had their BMI at the level of malnutrition and a good portion (14.5 %) suffered from being overweight or obese. A statistically significant increase of BMI was only confirmed in the case of patients with initially low or normal BMI, not in the case of patients with excess weight or obesity. We compared the adherence to gluten free diet in the group of patients that were diagnosed before the implication of the health insurance coverage of gluten free foods, to the group of patients diagnosed while this option was available. However, there was no statistically significant difference between these two groups (80.1 % vs. 88.1 %) of patients within our statistical sample.

GASTROENTEROLOGY UZBEKISTAN TASHKENT 2012

IgG4-RELATED SCLEROSING CHOLANGITIS

Petr DÍTĚ

Academic Center for Gastrooncology, Medical Faculty Ostrava, Czech Republic

IgG4 is a new clinical pathological entity which is characterised by high plasmatic level of IgG4 and massive infiltration of the tissue by globulin G4. Besides this a typical finding is the tissue infiltration of T-lymphocytes by obliterative phlebitides.

The salivary and lacrimal glands, lungs, kidneys, prostate, retroperitoneal connective tissue and biliary system can be affected. The most frequent is autoimmune pancreatitis. Diagnostics, besides above mentioned markers, is in particular histopathological. In the case of the autoimmune form of pancreatitis and IgG4 sclerosing cholangitis the use of imaging methods is indicated, including ERCP! IgG4 – related inflammation of extrapancreatic organs without pancreatic involvement have been also reported.

IgG4 SCLEROSING DISEASES – CLINICOPATHOLOGICAL FINDINGS

PANCREAS	**AUTOIMMUNE PANCREATITIS**
BILE DUCT	**IgG4 RELATED SCLEROSING CHOLANGITIS**
GALLBLADDER	**IgG4 RELATED SCLEROSING CHOLANGITIS**
SALIVARY GLAND	**IgG4 RELATED SIALADENITIS**
RETROPERITONEUM	**IgG4 RELATED RETROPERITONEAL FIBROSIS**
KIDNEY	**IgG4 RELATED TUBULOINTERSTIAL NEPHRITIS**
LUNG	**IgG4 RELATED INTERSTITIAL PNEUMONIA**
PROSTATE	**IgG4 RELATED PROSTATITIS**

Inflammatory pseudotumors (liver, lung, hypophysis) may be part of this disease.

Corticoids are on the first place in the treatment of this group of diseases; their effect can be expected in approximately 90 % of treated patients. The diagnostics of these diseases as well as differential diagnostics of malignity are completely fundamental and in their consequences they prevent e.g. non-indicated and dispensable surgical treatment.

GASTROENTEROLOGY
UZBEKISTAN TASHKENT 2012

IgG4-ASSOCIATED SCLEROSING CHOLANGITIS

Petr Dite, Ivo Novotný

UNIVERSITY HOSPITAL OSTRAVA
UNIVERSITY HOSPITAL BRNO
CZECH REPUBLIC

IgG4 – RELATED SCLEROSING DISEASES - DEFINITION

- Systemic disease characterized histopatologically by extensive IgG4-positive plasma cell infiltration of various organs together with T lymphocytes.
- Major clinical manifestation are apparent in the organ in which tissues with obstructive phlebitis is pathologically induced
- Some inflammatory pseudotumors /liver,lung and hypophysis/may be involved in the diseases
- Occasional association with lymphadenopathy

SOME OTHER CLINICOPATHOLOGICAL FINDING OF IgG4 DISEASES

- Elderly male preponderance
- Frequent elevation of serum IgG4 levels
- Favorite response to steroid therapy
- Differentation from malignancy is h i g h l y important
- Precise pathogenesis and pathophysiology is still u n c l e a r

IgG4 SCLEROSING DISEASES- CLINICOPATHOLOGICAL FINDINGS

PANCREAS	AUTOIMMUNE PANCREATITIS
BILE DUCT	IgG4 RELATED SCLEROSING CHOLANGITIS
GALLBLADDER	IgG4 RELATED SCLEROSING CHOLANGITIS
SALIVARY GLAND	IgG4 RELATED SIALADENITIS
RETROPERITONEUM	IgG4 RELATED RETROPERITONEAL FIBROSIS
KIDNEY	IgG4 RELATED TUBULOINTERSTIAL NEPHRITIS
LUNG	IgG4 RELATED INTERSTITIAL PNEUMONIA
PROSTATE	IgG4 RELATED PROSTATITIS

IgG4 RELATED PSEUDOTUMOURS

LIVER LUNG HYPOPHYSIS

CHARACTERISTICS SINGS

IRREGULAR PROLIFERATION OF MYOFIBROBLASTS INTERMIXED WITH INFILTRATE OF LYMPHOCYTES AND PLASMA CELLS.
PATHOGENESIS – U N K N O W N , CLOSE RELATIONSHIP BETWEEN PLASMA CELL GRANULOMA AND IgG4 – POS.PLASMA CELLS
ASSOCIATION BETWEEN HYPOPHYSITIS AND AIP
CLINICAL MANIFESTATION – HYPOPITUITARISM THERAPY – STEROID THERAPY IS HIGHLY EFFECTIVE

Wong et al 2007
Van den Vliet 2006
Tanabe et al. 2006

MOST OF IgG4 RELATED SCLEROSING DIASEASES ARE ASSOCIATED WITH AUTOIMMUNE PANCREATITIS — BUT IgG4 SCLEROSING DISEASE W I T H O U T AIP HAVE BEEEN REPORTED

Kamisawa et al.World J.,Gastoent.2008

AUTOIMMUNE PANCREATITIS - SUBTYPES

TYP 1 – LYMPHOPLASMATIC SCLEROSING PANCREATITIS – LPSP
- PERIDUCTAL LYMPHOPLASMATIC INFILTRATE
- HIGH AMMOUNT IgG4
- POSITIVE PLASMA CELLS
- SWIRLING FIBROSIS
- OBLITERATIVE VENULITIS

TYP 2 – IDIOPATHIC DUCT-CENTRIC PANCREATITIS – IDCP („non-alcoholic duct destructive pancreatitis“)
- DUCTAL EPITHELIAL CGRANULOCYTIC INFILTRATION

↓

DUCTAL DAMAGE

↓

OBLITERATION

COMPARISON OF TYPE 1 AND TYPE 2 AIP

	Type 1 AIP	Type 2 AIP
Mean age	Sixth decade	Fourth decade
Gender distribution	Predominantly male	Equal
Histological pattern	Lymphoplasmacytic sclerosing pancreatitis	Duct-destructive pancreatitis
Histological hallmarks	Periductal lymphoplasmacytic infiltrate Swirling fibrosis Obliterative venulitis	Lymphoplasmacyic infiltrate Granulocyte epithelial lesion with partial/complete duct obstruction
IgG4 cells on immunostaining	Moderate-severe (98%)	Moderate (40%) in one study
Serum IgG4 levels	Elevated	Normal
Other organ involvement	Chronic sclerosing sialadenitis, IgG4-associated cholangitis, retroperitoneal fibrosis, IgG4-associated tubulointerstitial nephritis	Inflammatory bowel disease Prim. Biliary cirrhosis

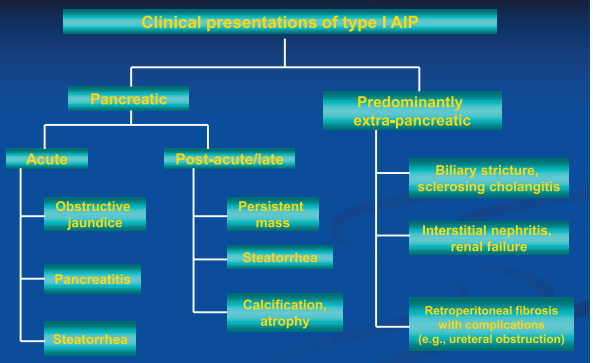
AIP,autoimmune pancreatitis, IgG4, immunoglobulin G4

SERUM AUTOANTIBODY AND IMMUNOGLOBULIN IN PATIENTS WITH AIP

AUTOANTIBODY/IMMUNOGLOBULIN	POSITIVE PREVALENCE %
ANTI-NUCLEAR ANTIBODY (ANA)	65%
RHEUMATOID FACTOR	28%
GAMA GLOBULIN (2,0 g/dL)	46%
IgG (1800 mg/dL)	74%
IgA (500mg/dL)	3%
IgM (300mg/dL)	6%
IgG4 (135mg/dL)	85%

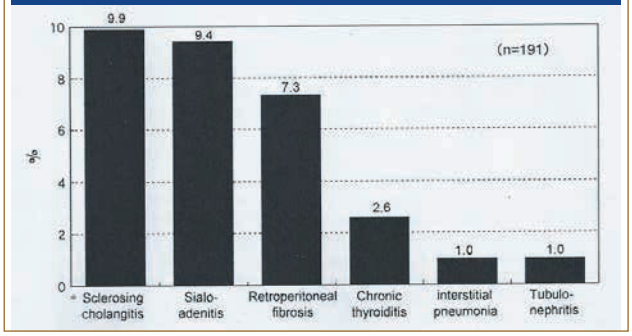
Choi, EK et al, Pancreas 2007

CLINICAL PRESENTATIONS OF TYPE 1 AUTOIMMUNE PACREATITIS



Park, D.H. 2009

EXTRAPANCREATIC LESIONS IN PATIENTS WITH AIP



HOW FREQUENT ARE BILIARY LESIONS IN A I P

43 PATIENTS WITH A I P

34 pts (79%) BILE DUCT STENOSIS
21 pts ONLY LOWER PART STENOSIS
13 pts MIDDLE AND UPPER PART STENOSIS
4 pts HAD ALSO STENOSIS INTRAHEPATICLY
13 pts WITH GALLBLADDER WALL THICKENING

Kamisawa T. et al.Hepato-Gastroenerol. 2009

IgG4 – RELATED SCLEROSING CHOLANGITIS

SCLEROSING CHOLANGITIS IS A HETEREOGENOUS DISEASE AND MAY BE ASSOCIATED WITH

- CHOLEDOCHOLITHIASIS
- INFECTION
- BILIARY TUMOR
- SCLEROSING CHOLANGITIS OF UNKNOWN OROGIN IS CALLED

P R I M A R Y S C L E R O S I N G
CH O L AN G I T I S/PSC/

SOME CHARACTERISTIC OF PRIMARY SCLEROSING CHOLANGITIS

PSC - OCCURS FROM 30 TO 40 YEARS
PSC - PROGRESSIVE DISEASE INVOLVES INTRA / EXTRA HEPATIC BILE DUCTS
PSC - THE DISEASE OF UNKNOWN ORIGIN
PSC - THE EFFECT OF STEROID THERAPY IS QUESTIONABLE
PSC - FREQUENTLY ASSOCIATED WITH IBD
PSC - THE DEVELOPMENT IN LIVER CIRRHOSIS
PSC - THE PANCREATOGRAM FREQUENTLY ABNORMAL

Wiesner et al, Hepatology ,1989
Kamisawa et al.J.Gastroent. 2006

EPIDEMIOLOGY OF IgG4 CHOLANGITIS

PREVALENCE PSC r. 2003 7,0% CANADA
r. 2004 7,0% JAPAN

IgG4 CHOLANGITIS - 128 pts with PSC
r. 2006 1,0% (Mendes,r.2006)

Bjornsson et al 2007

IgG4 SCLEROSING CHOLANGITIS- THE AGE AND GENDER DISTRIBUTION

	Erkelens 1999	Zen 2004	Nakazawa 2005	Van Buuren 2006
Cases	4	17	20	10
Age (range)	48 (19-62)	71 (55-79)	65 (-)	55 (19-80)
Male/ females	4/0	12/5	14/6	10/0

IgG4 RELATED SCLEROSING CHOLANGITIS – CLINICAL PRESENTATION

- OBSTRUCTIVE JAUNDICE IS COMMON CLINICAL PRESENTATION (60-75%)
- PRURITUS
- SERUM BILIRUBIN LEVELS AND ALKALINE PHOSPHATASE SIGNIFICANTLY HIGHER IN COMPARISON WITH CLASSIC PSC

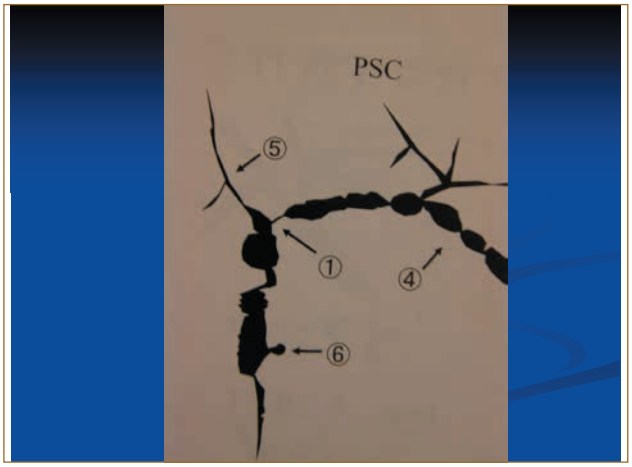
Nakazawa et al. Pancreas 2005

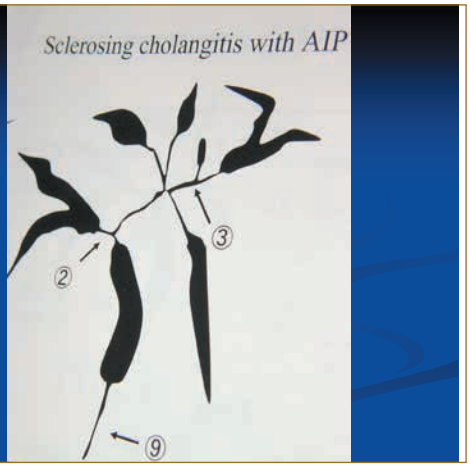
IgG4 RELATED SCLEROSING CHOLANGITIS – HISTOLOGY

- DENSE LYMPHOPLASMATIC INFILTRATION AND FIBROSIS OF THE BILE DUCT WALL
- LYMPHOPLASMATIC INFILTRATION AND FIBROSIS IN THE PERIPORTAL AREA OF THE LIVER
- TRANSMURAL FIBROSIS
- OBLITERATIVE PHLEBITIS
- INFILTRATION OF ABUNDANT IgG4 – POSITIVE PLASMA CELLS IN THE BILE DUCT WALL
- BILIARY EPITHELIUM IS USUALLY ⟶ I N T A C T

DIFFERENCES IN IMMUNOSEROLOGY BETWEEN PSC AND IgG4 SCLEROSIG CHOLANGITIS

- IgG4 LEVEL⟶SIGNIFICANTLY HIGHER IN IAC . IN PSC IN 9O% THE LEVEL IS NORMAL
- IN SOME PATIENTS WITH IAC THE IgG4 INITIALLY COULD BE NORMAL AND DEVELOPED HIGH LEVEL DURING FOLLOW- UP



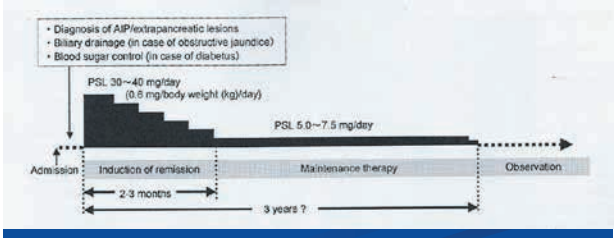


ENDOSCOPIC TRANSPAPILLARY IDUS AND BIOPSY IN THE DIAGNOSIS OF IgG4-RELATED SCLEROSING CHOLANGITIS

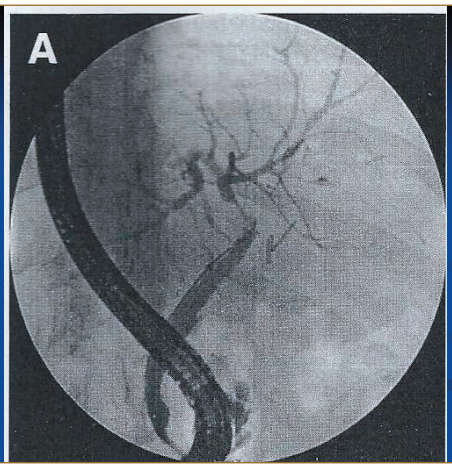
- IDUS SIGNS ⟶ CIRCULAR - SYMMETRIC WALL THICKENESS
  - SMOOTH OUTER MARGIN
  - SMOOTH INNER MARGIN
  - HOMOGENEOUS INTERNAL ECHO IN THE STRICTURE

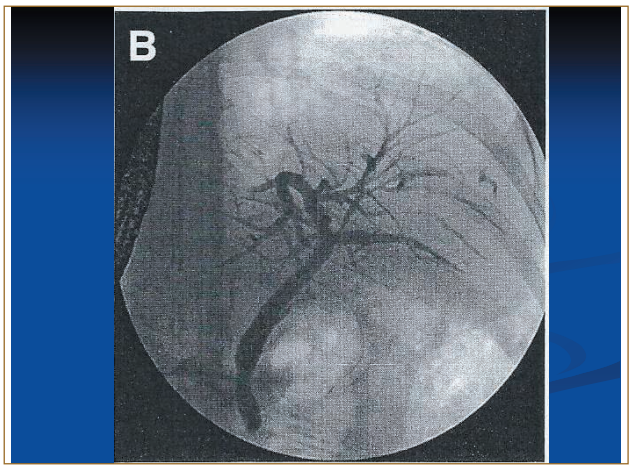
Naitoh,I.et al.J.Gastroent.2009

STANDARD REGIMEN OF STEROID THERAPY FOR AIP WITH OR WITHOUT EXTRAPANCREATIC LESIONS



Ito et al.J.Gastroent.2007





… TAKE A HOME MESSAGE

- IgG4 RELATED SCLEROSING DISEASES – EXTENSIVE IgG4 PLASMA CELL INFILTRATION OF VARIOUS ORGANS + T LYMPGOCYTES
- MOST OF IgG4 RELATED SCLEROSING DISEASES ARE ASSOCIATED WITH AUTOIMMUNE PANCREATITIS
- IgG4 RELATED CHOLANGITIS
  - OBSTRUCTIVE JAUNDICE
  - PRURITUS
  - LONG STENOSES IN BILE PERIPHERIAL BRANCHES
  - HISTOLOGICAL DIAGNOSIS CRUTIAL
  - IgG4 VERY HIGH
  - STEROIDS EFFECT (AS DIAGNOSTIC CRITERION)
  - RELATION BETWEEN IgG4 CHOLANGITIS AND CHOLANGIOCARCINOMA WAS NOT FOUND

AUTOIMMUNE HEPATITIS

Vladimir T. IVASHKIN

I. M. Sechenov First Moscow State Medical University, Russian Federation

Autoimmune hepatitis (AIH) is a generally unresolving inflammation of the liver of unknown cause. A working model for its pathogenesis postulates that environmental triggers, a failure of immune tolerance mechanisms, and a genetic predisposition collaborate to induce a T cell-mediated immune attack upon liver antigens, leading to a progressive necroinflammatory and fibrotic process in the liver. Onset is frequently insidious with nonspecific symptoms such as fatigue, jaundice, nausea, abdominal pain, and arthralgias at presentation, but the clinical spectrum is wide, ranging from an asymptomatic presentation to an acute severe disease. The diagnosis is based on histologic abnormalities, characteristic clinical and laboratory findings, abnormal levels of serum globulins, and the presence of one or more characteristic autoantibodies.

The diagnostic criteria for AIH and a diagnostic scoring system were codified by an international panel in 1993 and revised in 1999. The clinical criteria for the diagnosis are sufficient to make or exclude definite or probable AIH in the majority of patients. The revised original scoring system was developed as a research tool by which to ensure the comparability of study populations in clinical trials and can also be applied in diagnostically challenging cases not readily captured by the descriptive criteria. The treatment response is graded in the revised original scoring system, and a score can be rendered both before and after treatment. Differences between a definite and probable diagnosis of AIH by the diagnostic scoring system relate mainly to the magnitude of serum IgG elevation, titers of autoantibodies, and extent of exposures to alcohol, medications, or infections that could cause liver injury.

Two types of AIH have been recognized based on serological markers, but have not been established as valid clinical or pathological entities. A proposed third type (type 3) has been abandoned, as its serologic marker (anti-SLA) is also found in type 1 AIH and in type 2 AIH. Type 1 AIH is characterized by the presence of ANA, SMA or both, and constitutes 80 % of AIH cases.

Two treatment regimens are equally effective in severe AIH. Prednisone alone (60 mg daily) or a lower dose of prednisone (30 mg daily) in conjunction with azathioprine (50 mg is usually used in the United States or 1–2 mg/kg body weight, which is widely used daily in Europe). Prednisone may be tapered down to an individual level sufficient to maintain a remission from 20 mg daily onward, reduction should be done by 5 mg every week until 10 mg/day are achieved and even further reduction by 2.5 mg/week have been considered up to 5 mg daily. The maintenance regimen is then continued until resolution of the disease, treatment failure, or drug-intolerance.

GASTROENTEROLOGY
UZBEKISTAN TASHKENT 2012

9th International Symposium of Gastroenterology

AUTOIMMUNE HEPATITIS

Prof. IVASHKIN V.T.

31.5 – 2.6.2012 Tashkent, Uzbekistan

20-year old woman

- Single
- Non-smoker
- Alcohol consumption 20g/w
- Studying psychology
- No heredity

- Referred to Sechenov First Moscow State Medical University for follow up in 2010

20-year old woman – medical history

- AIH diagnosed in 2001
- Jaundice, hepatomegaly, splenomegaly, ↑AST and ↑ALT in 2006
- Prednisone 20mg/day and azathioprine 50mg/day since 2006
- Serious worsening of AIH in 2010

20-year old woman – current situation in 2010 – complaints

- Weakness
- Dizziness
- Reduced exercise tolerance
- Severe jaundice

20-year old woman – current situation in 2010

- Jaundice
- Respiratory and cardiovascular systems normal
- BP 110/70 mm Hg, HR 85 min.
- The abdomen is soft to palpation and painless
- Hepatomegaly
- No peripheral edema

Cellular evaluation

- RBC – **2,756*10^{12}/L** (N: 3,7-4,7*10^{12}/L)
- HGB – **98,1 g/L** (N: 115-145 g/L)
- WBC – **15,04*10^{9}/L** (N: 4-9*10^{9}/L)
- ESR – **23 mm/H** (N: 2-15 mm/H)

Biochemical analysis

- ALT – **313 u/L** (N: 10-40 u/L) – *8-fold increased*
- AST – **573 u/L** (N: 10-40 u/L) – *14-fold increased*
- ChE – **2738 u/L** (N: 4200-11200 u/L) – *1,5-fold reduced*
- ALP – **186 IU/L** (N: 20-140 IU/L) – *1,3-fold increased*
- ALB – **2,5 g/dL** (N: 3,5-5,0 g/dL) – *1,4-fold reduced*
- TB – **5,9 mg/dL** (N: 0,2-1,0 mg/dL) – *5-fold increased*
- Conjugated bilirubin – **3,5 mg/dL** (N: 0,0-0,3 mg/dL) – *11-fold increased*

20-year old woman

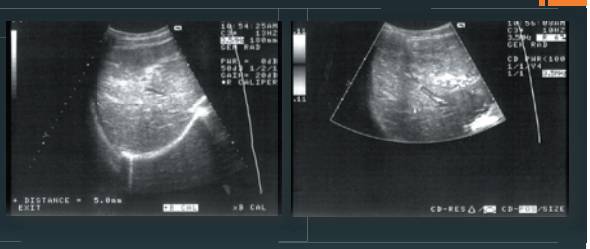
Ig A	**320**	**50 – 300 mg/dL**
Ig M	640	40 – 200 mg/dL
Ig G	3980	600 – 2000 mg/dL

HBsAg	**-**
HBsAb	+
HBeAg	-
HBcor Ab(total)	+
HBcor Ab (Ig M)	-
HBeAb	-
HCVAb	-

AFP, ng/ml	**18,13**	**0-14,4**
CA 15-3, U/ml	16,86	0-30

Hepatitis B vaccinated

Ultrasonography

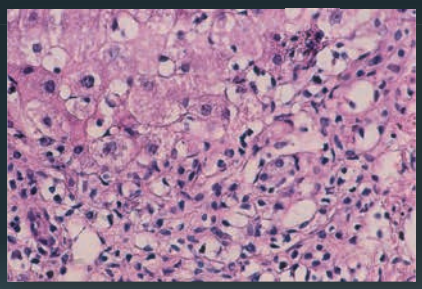


Diffuse changes in the liver and pancreas.
Biliary sludge.

CT scan:

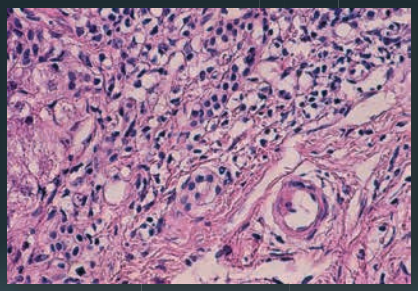
- Diffuse changes of the liver with signs of cirrhotic transformation.
- Minimal ascites.
- Portal vein – 14 mm.
- Biliary sludge.

Liver biopsy



Mononuclear inflammatory infiltrate, liver cell degenerative changes (bridging necrosis). H&E X 400

Liver biopsy



Mononuclear inflammatory infiltrate within the portal tract (H&E X 200)

20-year old woman – autoantibodies

ANA, IU/ml	0,00	0,00 – 1,00
LKM-1	0,00	Negative
AMA, IU/ml	0,0	0,0 – 10,0
ASMA	1:325	Negative
Antibodies to the nuclei of cells in Hep-2	1:1280	1:320 – positive
LC-1	Negative	Negative
SLA/LP	Negative	Negative

Autoantibodies in the Diagnosis of AIH (1)

Antibody	Target Antigen(s)	Type of AIH
Conventional serological repentoire		
ANA	Multiple targets: • Chromatin • Ribonucleoproteins • Ribonucleoprotein complex	Type 1 AIH
SMA	Microfilaments (filamentons actin) and intermediate filaments (Vimentin, Desmin)	Type 1 AIH
LKM – 1	Cytochrome P450 2D6 (CYP2D6)	Type 2 AIH
LC – 1	Formiminotransferase cyclo-deaminase (FTCD)	Type 2 AIH

AASLD Practice Guidelines: Diagnosis and management of autoimmune hepatitis, Hepatology,2010

Autoantibodies in the Diagnosis of AIH (2)

Antibody	Target Antigen(s)	Type of AIH
Useful in Patients who lack conventional autoantibodies		
pANCA (atypical)	Nuclear lamina proteins	Type 1 AIH
SLA	tRNP$^{(SER)}$Sec	AIH
LKM – 3	Family 1 UDP-glucuronosyl-transferases (UGT1A)	Type 2 AIH

AASLD Practice Guidelines: Diagnosis and management of autoimmune hepatitis, Hepatology,2010

Revised Original Scoring System of the International Autoimmune Hepatitis Group

Sex	Female	+2	HLA	DR3 or DR4	+1
AP:AST (or ALT) ratio	>3 <1,5	-2 +2	Immune Disease	Thyroiditis, colitis, others	+2
γ-globulin or IgG level above normal	>2,0 1,5-2,0 1,0-1,5 <1,0	+3 +2 +1 0	Other markers	Anti-SLA, anti-actin, anti LC1, pANCA	+2
ANS, SMA, or anti-LKM1 titers	>1:80 1:80 1:40 <1:40	+3 +2 +1 0	Histological features	Interface hepatitis Plasmacytic Rosettes None of above Biliary changes Other features	+3 +1 +1 -5 -3 -3
AMA	Positive	-4	Treatment response	Complete Relapse	+2 +3
Viral markers	Positive Negative	-3 +3			
Drugs	Yes No	-4 +1	Pretreatment aggregate score: Definite diagnosis >15 Probable diagnosis 10-15		
Alcohol	<20 g/day >60 g/day	+2 -2	Posttreatment aggregate score: Definite diagnosis >17 Probable diagnosis 12-17		

Revised Original Scoring System of the International Autoimmune Hepatitis Group

Sex	Female	+2	HLA	DR3 or DR4	+1
AP:AST (or ALT) ratio	>3 <1,5	-2 +2	Immune Disease	Thyroiditis, colitis, others	+2
γ-globulin or IgG level above normal	>2,0 1,5-2,0 1,0-1,5 <1,0	+3 +2 +1 0	Other markers	Anti-SLA, anti-actin, anti LC1, pANCA	+2
ANS, SMA, or anti-LKM1 titers	>1:80 1:80 1:40 <1:40	+3 +2 +1 0	Histological features	Interface hepatitis Plasmacytic Rosettes None of above Biliary changes Other features	+3 +1 +1 -5 -3 -3
AMA	Positive	-4	Treatment response	Complete Relapse	+2 +3
Viral markers	Positive Negative	-3 +3			
Drugs	Yes No	-4 +1	Pretreatment aggregate score: Definite diagnosis >15 Probable diagnosis 10-15		
Alcohol	<20 g/day >60 g/day	+2 -2	Posttreatment aggregate score: Definite diagnosis >17 Probable diagnosis 12-17		

20-year old woman

- Total points = *24 (Definite diagnosis)*

Pretreatment aggregate score:	Posttreatment aggregate score:
Definite diagnosis >15	Definite diagnosis >17
Probable diagnosis 10-15	Probable diagnosis 12-17

Simplified diagnostic criteria (2008) of the international autoimmune hepatitis group

		Points
Autoantibodies	ANA or SMA or LKM > 1:40	1
	ANA or SMA or LKM > 1:80 SLA/LP Positive (>20 units)	2
IgG (or gamma-globulius)	Upper normal limit	1
	>1,10 times normal limit	2
Liver histology	Compatible with AIH	1
	Typical for AIH	2
Absence of viral hepatitis	Yes	2
	No	0

Simplified diagnostic criteria (2008) of the international autoimmune hepatitis group

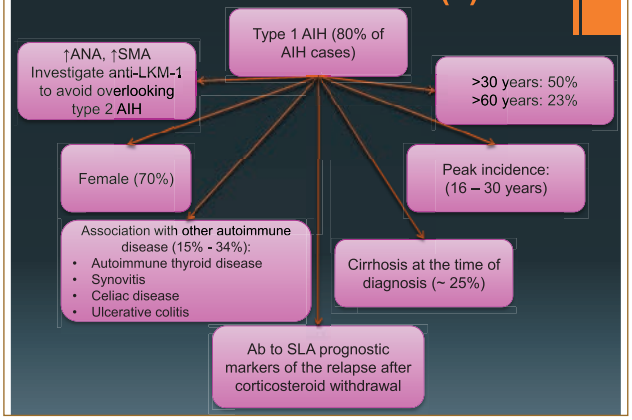
		Points
Autoantibodies	ANA or SMA or LKM > 1:40	1
	ANA or SMA or LKM > 1:80 SLA/LP Positive (>20 units)	2
IgG (or gamma-globulius)	Upper normal limit	1
	>1,10 times normal limit	2
Liver histology	Compatible with AIH	1
	Typical for AIH	2
Absence of viral hepatitis	Yes	2
	No	0

20-year old woman

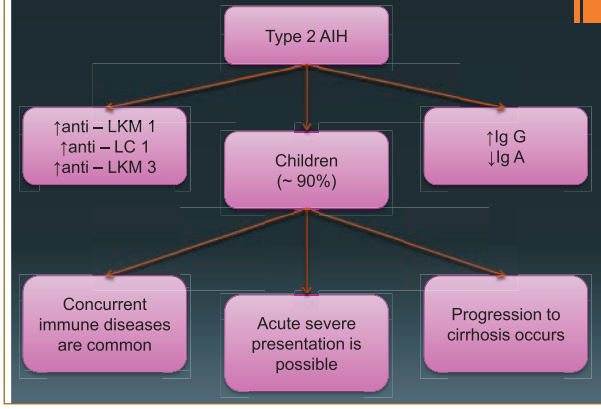
- Total points = *8 (Definite diagnosis)*

Definite autoimmune hepatitis (AIH): ≥7 points
Probable AIH: ≥6 points

AIH classification (1)



AIH classification (2)



Diagnosis:

- AIH Type 1. Cirrhosis. Portal hypertension: ascites, portal vein 14 mm
- Biliary sludge

Indications for Immunosupressive Treatment of AIH

Absolute	Relative
Serum AST≥10-fold ULN	Symptoms (fatigue, arthralgia, jaundice)
Serum AST≥5-fold ULN and γ-globulin level ≥ 2-fold ULN	Serum AST and/or γ-globulin less than absolute criteria
Bridging necrosis or multiacinar necrosis on histological examination	Interface hepatitis
Incapacitating symptoms	Osteopenia, emotional instability, hypertension, diabetes, or cytopenia (white blond cell counts ≤ 2500/ml or platelet counts ≤ 50 000/ml)

AASLD Practice Guidelines: Diagnosis and management of autoimmune hepatitis, Hepatology,2010

Immunosupressive Treatment for Adults in AIH

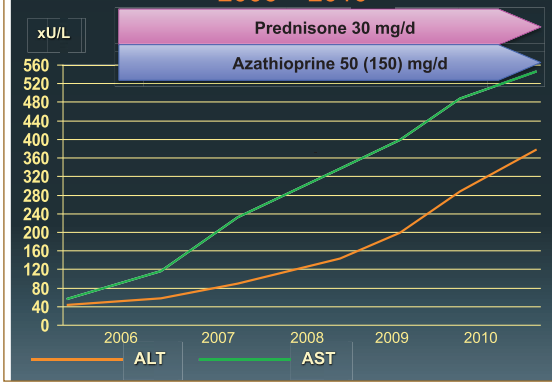
	Combination Therapy		
	Monotherapy	Azathioprine	
	Prednisone only (mg/day)	Prednisone (mg/day)	(mg/kg/day)
Week 1	60	30	1 – 2
Week 2	40	20	1 – 2
Week 3	30	15	1 – 2
Week 4	30	15	1 – 2
Maintenance therapy	20 and less	10	1 – 2
Reason for preference	Cytopenia TPMT deficiency		Postmenopausal state Osteoporosis Brittle diabetes Obesity Acne Emotional lability Hypertention
	Pregnancy Malignancy Short course (≤6 months)		

Endpoints and Courses of Action in AIH

Treatment endpoints	Criteria	Courses of action
Remission	Symptoms (-); N: aminotransferases, bilirubin and γ-globulin; N: morphology or inactive cirrhosis	Withdrawal of prednisone over 6-week period
Treatment failure	↑Symptoms (+), ↑laboratory, ↑histological features Jaundice(+), ascites(+) or hepatic encephalopathy(+)	Prednisone 60 mg daily; prednisone 30 mg daily and azathioprine 150 mg daily for at least 1 month
Incomplete response	Some or no improvement despite compliance with therapy after 2-3 years	Reduction in doses of prednisone until lowest level possible (≤10 mg daily)
	No worsening of condition	Indefinite azathioprine therapy (2mg/kg daily) if corticosteroid intolerance
Drug toxicity	Cosmetic changes, osteopenia, hypertention, brittle diabetes, progressive cytopenia	Reduction in dose or discontinuation of offending drug. Maintanance on tolerated drug

Dynamics of serum ALT, AST

2006 – 2010



Treatment failure

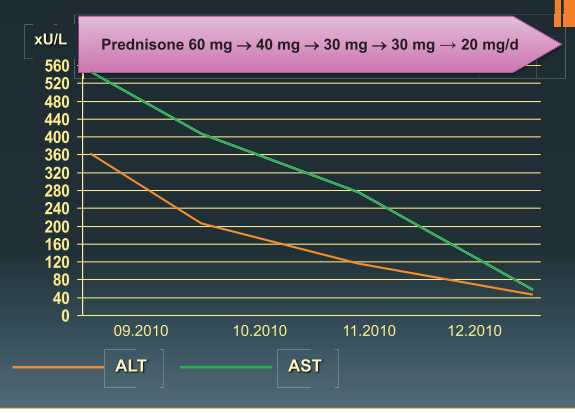
Criteria	Actions
Deterioration of clinical, laboratory, and histologic features, despite treatment	Prednisone 60 mg/d or prednisone 30 mg/d + azathioprine 150 mg/d

AASLD Practice Guidelines: Diagnosis and management of autoimmune hepatitis, Hepatology,2010

Therapy:

- Prednisone 60 mg/d
- Gradual dose reduction to maintenance levels

Dynamics of serum ALT, AST



Liver transplantation

- Transplantation is effective in decompensated patients in whom corticosteroid therapy has failed
- 5-year survival 83 - 92%
- Disease recurs in 12 – 46%, 1-8 years after transplantation, mainly in recipients who are inadequately immunosupressed

PERCUTANEOUS TRANSHEPATIC CHOLANGIOGRAPHY AND DRAINAGE OF BILIARY DUCTS IN PATIENTS WITH JAUNDICE AND ACUTE CHOLANGITIS

Anton VAVREČKA, Marián BÁTOVSKÝ, Rudolf HRČKA, Ľudovít JANČULA

Clinic of Gastroenterology of LF SZU and UN Bratislava, Hospital of St. Cyril and Metod, Slovakia

Abstract

Background: Percutaneous transhepatic cholangiography (PTC) is a diagnostic method which consists in applying a thin needle (called Chiba) through the skin and liver parenchyma to the intrahepatic bile ducts and subsequent application of contrast agent that displays biliary system and enable the identification of pathological changes. PTC followed by therapeutic intervention, most external or combined biliary drainage ducts (PTD). It is indicated in patients with obstructive jaundice in inoperable biliary tract tumors, in cases where it is unsuccessful or impossible endoscopic retrograde cholangiography (ERC). Less common indications are benign bile duct strictures (especially hepaticojejunoastomosis) and planned cholangioscopy. The success of the exercise is given between 80 to 100 %, partly depending on the presence of dilatation of the intrahepatic bile ducts. Complications in PTC occur in 5 % in the PTD 10 to 20 %, mortality is 1–3 %.

Patients and method: Between 2007–2011 were performed 222 PTC–PTD in 138 patients, 69 men and 69 women. In more than 70 % of patients was indication of inoperable malignant biliary obstruction with or without acute cholangitis, where was unsuccesful ERCP (the most frequent hilar cholangiocarcinoma and carcinoma of the head of pancreas. From benign biliary strictures most frequent was obstruction of hepaticojejunoanastomosis.

Results: The success rate of PTD was 94.15 %. Minor complications were observed in 9.0 %, severe in 2.1 % (including 1 exitus).

Conclusions: Based on clinical success and risk of complications, date from literature and own experience we can conclude, that the PTC and PTD are valuable methods in therapy of obstructive jaundice and acute cholangitis when ERCP is impossible or unsuccessful.

GASTROENTEROLOGY UZBEKISTAN TASHKENT 2012

THE GERONTOLOGICAL ASPECTS OF GASTRODOUDENAL PATHOLOGIES

S. I. SADIKOVA [1], M. T. RUSTAMOVA [2], H. T. SODIKOV [3]

The Tashkent Medical academy, Uzbekistan
[1] Sodikova Saida – associate professor, Doctor of philosophy in medicine
[2] Rustamova Mamlakat – professor, Doctor of philosophy in medicine
[3] Sodikov Khamro – Doctor of philosophy in medicine
e-mail: m_u@bk.ru, tel.: +998977852134

The ageing of the Uzbek population in many respects defines importance and necessity studying the gerontologic problems. Persons of elderly and senile age have enough big and burden list of diseases demanding of daily reception on the average to 6 preparations of a different orientation which as a result of the pharmacokinetics and pharmacodinamycs influence a condition of a gastroenteric path. In this connection the urgency of research of character and frequency of defeat of the top floor of a digestive path at persons of elderly and senile age does not raise the doubts.

Materials and research methods. We had been carried out the analysis clinical-gastroezofageal researches of 85 persons of advanced age (60–75 years). Visual inspection was spent by what showed complaints illnesses of bodies of digestion specifying in presence.

Results of research have shown, that received EFGDS-data testify to considerable morphological changes on all extent gullet-gastroduodenal zones. So GERB 1 items it is diagnosed for 34,5 % and GERB 2 items at 16,4 % which are caused by a hernia of gullet diaphragm apertures – 13,7 %, diverticular desease – 2,7 %, expansion of veins of a gullet 1 items – 5,5 of %. It was specified In a normal condition of a mucous membrane of a stomach only at 4,1 % surveyed whereas changes of mucous 12 rings of a gut it has been revealed at 100 % of cases. Prevailing it has appeared total diffuse gastritis – 74 %, at 26,0 % antral gastritis with erosion mucous of membrane defeat. In 12 rings of a gut erosion (15 %) are found out in 78 % surveyed against duodenal ulcer, fresh ulcers (4,1 %), deformation of duodenal guts (22 %). Hp-obsemenyonnost it is revealed at 76,7 % of the cases mainly moderated and high degree of activity.

Thus, at creation of rehabilitation programs for persons of the senior generation it is necessary to include high functional defeats of top departments GKT at persons of the senior generation, features of clinical displays of a pathology.

PROTECTIVE EFFECT OF SILDENAFIL AGAINST ETHANOL AND ACETALDEHYDE TOXICITY IN LIVER CELLS

Katarzyna KRÓL, Justyna SEMENIUK, Olga SŁABCZYŃSKA, Martyna KANDEFER-SZERSZEŃ, Agnieszka SZUSTER-CIESIELSKA*

Department of Virology and Immunology, Institute of Microbiology and Biotechnology, Maria Curie-Skłodowska University, Lublin, Poland

*Correspondence: szustera@hektor.umcs.lublin.pl, ph: +48 81 537 59 43, fax: +48 81 537 59 40

Introduction

Alcohol consumption is the major cause of variety metabolic and pathological alterations in the liver. Ethanol induces liver cells injury, mainly via oxidative stress, leading to alcoholic liver fibrosis or cirrhosis.

Aim

The aim of this study was to evaluate the hepatoprotective potential of sildenafil, specific inhibitor of phosphodiesterase-5 (PDE-5), in HepG2 human hepatoma cells and CFSC-2G rat liver stellate cells.

Materials and Methods

Influence of sildenafil on hepatocytes or stellate cells (alone, with ethanol or acetaldehyde) viability was determined by MTT assay. Cells of both lines were also preincubated with different concentration of sildenafil and provoked to "oxygen burst" by ethanol or acetaldehyde; O_2^- and H_2O_2 production was measured by cytochrome c reduction or phenol red peroxidation assay respectively. Additionally migration assay with stellate cells was performed.

Results

Sildenafil (1–25 μM) was non toxic alone for hepatocytes and stellate cells regardless of incubation time (24–72 hrs), however, in higher concentration used (50–100 μM) was more toxic for CFSC-2G than HepG2 cells. Sildenafil, depending on its concentration (1 or 25 μM), significantly inhibited O_2^- and H_2O_2 production in hepatocytes as well as in stellate cells after ethanol (50 mM) or acetaldehyde (175 μM) treatment. Moreover, sildenafil inhibited ethanol- and acetaldehyde-induced liver stellate cells migratory activity.

Conclusion

Sildenafil protects liver cells against ethanol- and acetaldehyde-induced oxidative stress and silencing ethanol- or acetaldehyde-activated stellate cells ability to migration.

GASTROENTEROLOGY UZBEKISTAN TASHKENT 2012

ALPHA-KETOGLUTARATE AS A POTENT ANTIFIBROTIC AGENT

Olga SŁABCZYŃSKA, Justyna SEMENIUK, Katarzyna KRÓL, Martyna KANDEFER-SZERSZEŃ, Agnieszka SZUSTER-CIESIELSKA*

Department of Virology and Immunology, Institute of Microbiology and Biotechnology, Maria Curie-Skłodowska University, Lublin, Poland

*Correspondence: szustera@hektor.umcs.lublin.pl, ph: +48 81 537 59 43, fax: +48 81 537 59 40

Introduction

Alcohol abuse leads to major pathological disorders in the liver. Following liver injury (e.g. in the presence of ethanol) hepatic stellate cells (HSC), the major cell type involved in liver fibrosis, undergo activation. Advanced liver fibrosis results in cirrhosis, liver failure, and portal hypertension, and often requires liver transplantation.

Aim

The aim of this study was to determine the antifibrotic potential of alpha-ketoglutarate (AKG), a key intermediate in the Krebs cycle, in CFSC-2G rat liver stellate cells.

Materials and Methods

Toxicity of different AKG (1–100 mM) concentrations was measured using MTT and NR (Neutral Red) assays. Influence of AKG on proliferation of CFSC-2G cells was also evaluated with MTT assay. Stellate cells were also preincubated with different AKG concentrations (10 or 25 mM) and then treated with ethanol (10 or 50 mM) or acetaldehyde (75 or 175 µM); superoxide anion production was measured using cytochrome c reduction assay. Additionally wound assay with stellate cells was performed, as evaluation of CFSC-2G activation.

Results

Alpha-ketoglutarate (1–30 mM) was non toxic for CFSC-2G cells regardless of incubation time (24–72 h), however, higher concentrations (40–100 mM) provoke inhibition of proliferation. AKG in both used concentrations (10 and 25 mM) significantly decreased an oxygen burst (O_2^- production) induced by ethanol or acetaldehyde. Acetaldehyde alone increased stellate cells migration more intensively than ethanol. None of used AKG concentration alone influenced stellate cell migratory activity. However, presence of AKG (10 and 25 mM) inhibited CFSC-2G cells migration after their activation with acetaldehyde.

Conclusions

Alpha-ketoglutarate protects stellate cells against ethanol- and acetaldehyde-induced oxidative stress and inhibits acetaldehyde-activated stellate cells migration.

GASTROENTEROLOGY UZBEKISTAN TASHKENT 2012

LITHOGENICITY OF BILE ANT THE BILIARY TRACT MOTOR ACTIVITY AFTER CHOLECYSTECTOMY

E. U. PLOTNIKOVA, K. A. KRASNOV, O. A. KRASNOV

SBEI HVE KemSMA of the Ministry of Health and Social development, Regional liver centre at Podgorbunskogo MBHI CCH No.3, Kemerovo, Russian Federation

Goal of research: treatment and rehabilitation procedures increase for cholelithiasis patients after cholecystectomy (CE), biliary insufficiency detection and correction, biliary pain syndrome treatment.

Materials and methods: we observed 45 female patients after cholecystectomy (performed 2–17 years before), aged 21–66, who were diagnosed with post cholecystectomy syndrome (PCES). All the patients went through clinical research, fractional minute intubation, biochemical screen of bile with lithogenicity indexes definition, dynamic ultrasound investigation of choledochus and fiberoptic gastroduodenoscopy. Differences between parameters were considered statistically different if $p \leq 0.05$.

Results: Fractional duodenal intubation detected indirect signs of duodenal hypertension in 14 patients (A portion volume and tension increase) ($p \leq 0.05$), Oddi's sphincter insufficiency in 24 patients, Oddi's sphincter hypertension in 1 patient and the others had normal Oddi's sphincter function. Only in 7 patients C portion volume and tension were normal, in the others these parameters were substantially increased ($p \leq 0.05$) over control – 136.5 ± 3.24 ml and 34.5 ± 0.92 ml respectively. All the patients from the RCE group had statistically relevant bile acids decrease ($p \leq 0.05$), lithogenicity indexes were changed ($p \leq 0.05$) to bile lithogenicity increase. During dynamic ultrasound investigation of choledochus the choledochus diameter was no more than 8 mm in all the patients. Against the background of 3-month Ursosan (12 mg/kg of the body mass) and Duspatalin treatment C portion volume and tension statistically relevantly decreased to 57.5 ± 4.78 ($p \leq 0.05$).

Conclusion: Thus the acquired data speak about the necessity of the complex treatment for cholelithiasis patients after cholecystectomy. The pharmaceutical treatment of the Oddi's sphincter disfunction should be aimed at the recovery of smooth muscles normal tonus of the Oddi's sphincter (200 mg of mebeverin hydrochloride 2 times a day after 1–3 month from the cholecystectomy, and then if needed – for biliary pain syndrome treatment). For hepatocellular dyscholia and biliation treatment and liver exocrinous function normalization we recommend taking the ursodeoxycholic acid medication Ursosan (10–15 mg/kg of the body mass) from 6 months to 2 years with bile lithogenicity control.

Desired form of participation: report and theses.

COMMON HEPATITIS FEATURES IN FIRST LIFE YEAR CHILDREN

R. A. USHAKOVA, O. P. KOVTUN

"Ural State Medical Academy"
State Budgetary Educational Institution of Higher Professional Education
Ministry of Health and Social Development Russian Federation; Ekaterinburg, Russian Federation

Relevance. Occurrence of hepatobiliary disorders in infants is an obvious fact in the era of environmental deterioration and is associated with activation of agents that cause opportunistic infections.

Purpose. To evaluate the earliest clinico-laboratorial markers of liver injury in first life-year children born in a risk group of perinatal infection.

Patients and methods. Verification of viral hepatitis B, C and TORCH-infections causative agent was performed through polymerase chain reaction and ELISA. Desmet scale was taken to evaluate the stage of fibrosis. Chi-square calculations were used for comparative analysis of observed characteristics.

Results. Viral hepatitis B and C (group 1) was diagnosed in 47 children. Group 2 consisted of 100 patients with hepatitis and markers of TORCH-infections. Children from group 1 were examined for perinatal introduction of hepatitis B and C: HBV was revealed in 5 %, HCV in 27 %, genotype 3a in 69 % and 1b in 31 % of patients. Viral hepatitis declared itself by the increase of transaminase levels after 6 months ($p = 0,0005$). Children from group 2 showed markers of CMV infection 55,5 %, ureaplasmosis 2 %, Epstein-Barr virus 1,4 %, mixed-infection was verified in 7 % of patients. Prolonged jaundice and hyperbilirubinemia was observed in 85 % of newborns ($p = 0,0005$), cytolysis syndrome in 72 % of children aged to 3 months ($p = 0,0138$); 66 % of children came up with elevation of AST level ($p = 0,0009$), 71 % suffered from splenomegaly ($p = 0,0005$), anemia in 61 % ($p = 0,0005$), enterocolitis in 55 % ($p = 0,0014$), hypotrophy in 42 % ($p = 0,0031$), posseting in 37 % ($p = 0,0006$). Children with TORCH-hepatitis were prematurely born in 19 % of cases ($p = 0,0123$), central nervous system disorders were identified in 65 % ($p = 0,0005$), pyramidal insufficiency in 34 % ($p = 0,0009$), hydrocephalic syndrome in 31 % ($p = 0,0029$) and myatonia in 28 % ($p = 0,0147$). Children with TORCH-hepatitis suffered from acholia (10 %), hemangioma (4 %), convulsive disorder (6 %) and hyperexcitability syndrome (10 %). Liver biopsy revealed 3st stage of fibrosis in 3 infants, liver cirrhosis in 6 cases, lethal outcome in 2 (1,4 %) from group 2.

Conclusion. Prolonged jaundice, hyperbilirubinemia, cytolysis syndrome, the variety of clinical syndromes of developing liver damage, development of cirrhosis in the first year of life were typical clinical and laboratory markers of TORCH-associated hepatitis**.** Congenital hepatitis C has been proved to have mild atypical course and to generate chronic hepatitis with fibrosis of the 1st stage.

STATE OF THE ART: NOTES FROM THE LABORATORY TO CLINICAL PRACTICE

José ARMENGOL MIRÓ

Hospital Valle de Hebron-Universitat, Spain

GASTROENTEROLOGY
UZBEKISTAN TASHKENT 2012

IATROGENIC PERFORATION OF THE OESOPHAGUS

Tomasz MAREK

Silesian Medical University, Katowice, Poland

ENDOSCOPIC TREATMENT OF OBESITY

Evžen MACHYTKA

University Hospital Ostrava, Czech Republic

ENDOSCOPIC TREATMENT OF PANCREATIC FLUID COLLECTIONS

Julius ŠPIČÁK

Institute of Clinical and Experimental Medicine, Prague, Czech Republic

Pancreatic fluid collections comprises a variety of distinct entities. Acute fluid collection lack a well defined wall and occurs within 48 hours in the course of acute pancreatitis. Pseudocyst enclosed by a wall of non-epithelialized fibrotic tissue requiring at least four weeks to be formed contains a pure liquid and arises as a consequence of either acute or chronic pancreatitis. Walled-off pancreatic necrosis reflects a natural development of necrotizing pancreatitis and contains juice and debris. Pancreatic abscess is on the other side relatively homogenous collection of pus. Abscess is always an indication for immediate drainage, which in the other above mentioned conditions results from evaluation of symptoms, clinical course and multidisciplinary teamwork. Pre-drainage consideration has to exclude other collections like true cyst, neoplasma and stomach duplication. The diagnoastic work-up is based on the two of three imaging methods: CT, endoscopic ultrasound and MR. Fluid collection can be approach transpapillary, and either by EUS or non-EUS guided transmural drainage. Transpapillary approach can be used in pure liquid collections. Transmural drainage can be approached from the stomach or duodenum by the incision and dilatation. Besides the drainage the cavity can be explored by the scope and even large pieces of debris and necrotic tissue can be removed. The sterile collection becomes usually secondarily infected after drainage. The other risks of the endoscopic treatment consist in the bleeding caused usually by the aggressive contact with the cavity wall. The endoscopic treatment become a valuable alternative to the surgery.

GASTROENTEROLOGY
UZBEKISTAN TASHKENT 2012

ACUTE PANCREATITIS COMPLICATIONS FROM A SURGICAL POINT OF VIEW

Joaquin BALSELLS

Hospital Vall d'Hebron, Barcelona, Spain

Around 20 % of acute pancreatitis episodes are severe with local and extrapancreatic complications. Pancreatic necrosis is the main local complication that is initially sterile but can become infected in 40 to 70 % of cases and the mortality rate increases, in this situation, from 12 % to 30 %.

The management of pancreatic necrosis continues to present a challenge and to evolve, and there is some uncertainty regarding the optimal management.

Patients with proven infected necrosis and patients with sterile necrosis with persistent pain and/or inability to eat and recover must be operated on.

Late necrosectomy, 3–4 weeks after the onset of acute pancreatitis, is preferred over early necrosectomy, with a lower rate of complications and mortality.

Surgery involves removing the pancreatic necrosis, called necrosectomy. Nowadays we have the classical option, open surgery, or the different options of minimally-invasive necrosectomy: radiological, endoscopic or laparoscopic approaches. The gold standard continues to be open necrosectomy although minimally-invasive treatments are being increasingly used. The benefits of the minimal approach is to maintain compartmentalisation of the infectious focus and reduce the incidence of complications caused by open abdominal surgery.

Open surgical necrosectomy has a high complication rate (34–95 %) and a median mortality rate of 25 % (11–39 %).

With radiological drainage, around 75 % of patients have clinical improvement and about 45 % have a complete cure of collection with catheter drainage alone; the mortality rate is about 15 % (0–27 %).

Endoscopic drainage is performed under endoscopic ultrasound control, a communication is performed between the stomach and the pancreatic collection, and several sessions of necrosectomy are needed. The mortality rate is low, from 0 to 12 %, with a high success rate, more than 80 % and the main complication is bleeding. Surgical treatment is required in approximately 4 % of cases.

In comparison to open necrosectomy, laparoscopic drainage has the advantages of less mortality and morbidity, less tissue aggression and pain, and fewer laparotomy-associated herniae. Disadvantages include instrument rigidity, limitation of the operating field, difficulty with evacuation and aspiration of necrotic materials due to their viscosity, formation of enterocutaneous or pancreatic fistulae and, finally, infection of the abdominal cavity. Studies with a relatively small number of patients showed a low mortality rate (0–10 %) and a high success rate (87–100 %).

Retroperitoneal drainage needs radiological percutaneous access to the necrosis cavity that is dilated until it permits the insertion of an operating laparoscope to remove the necrotic material in multiple procedures. The mortality rate is around 20 % (10–27 %) and the success rate from 60 to 80 %.

Although the International Acute Pancreatitis Guidelines advise that infected necrosis should be removed, recent experiences showed that this may not always be necessary, and a "step-up" approach (first step: percutaneous or endoscopic transgastric drainage; if no clinical improvement occurs after 72 h: a second drainage procedure; second step, after 72 h: a video-assisted retroperitoneal débridement with postoperative lavage) may have advantages in selected patients.

In a randomised study comparing the minimally-invasive step-up approach and open necrosectomy, patients in the step-up approach had significantly fewer complications, less new-onset multiple-organ failure, and a lower rate of incisional herniae and new-onset diabetes than patients in the open necrosectomy group. 35 % of patients of the step-up approach were treated with percutaneous drainage alone. The mortality rate did not differ significantly between both modalities.

We can conclude that the care of these patients must be in the hands of a surgeon, and a multidisciplinary management must be undertaken to take into account the different approaches to minimally-invasive necrosectomy as an option to open surgery.

ENDOSCOPIC THERAPY OF LEAKAGE AFTER LAPAROSCOPIC CHOLECYSTECTOMY

Miquel MASACHS

Hospital Vall d'Hebron, Spain

GASTROENTEROLOGY
UZBEKISTAN TASHKENT 2012

LARGE FLAT LESIONS IN THE RIGHT COLON

Ilja TACHECÍ

2nd Dpt. of Internal Medicine, Hradec Králové, Czech Republic

Early studies confirmed the positive impact of colonoscopy on colorectal cancer incidence without distinguishing between right and left sided lesions (1–3). The same effect was expected for all localizations of cancer, and the studies proving little protection of colonoscopy against proximal colon cancer were a big surprise (4–7). Another recent data specified that proximal colon cancer protection is achievable (8–9), but is less than in distal lesions. There are several explanations for this phenomenon. The first one is the quality of endoscopy. The relation between the adenoma detection rates and colon cancer risk reduction was published (10). Incomplete colonoscopy and insufficient bowel preparation are the main risk factors for missing the right sided lesions. Caecal intubation and higher polypectomy rates predicts proximal colon cancer protection (8). Proximal colon cancer protection was shown to be operator dependent too, with lower risk of developing proximal colon cancer for patients investigated by gastroenterologist (in comparison with endoscopists of other specialties) (7). Another potential factor is different morphology and tumour biology for right sided lesions. The higher prevalence of flat and depressed lesions in right colon is considered. Flat lesions can be identified by slight changes in the surface, color and vascular pattern. High-definition colonoscopes and image enhancement techniques are very useful in identification of those lesions. Different tumour biology is represents by the so called serrated lesions. In the right colon the most common serrated lesion is sessile serrated lesion, typically subtle and difficult to detect because its flatness, paleness, a tendency toward vaguely defined borders and mucin cap covering and masking the surface. Many sessile serrated lesions have a 2a shape (according to the Parris classification). Occasional sessile serrated lesions have cytologic dysplasia and the areas of dysplastic mucosa in these lesions often have microsatellite instability. This type of lesion (called as mixed lesion) represents progression to the cancer sequence. Data confirming that undetected serrated lesions during screening colonoscopy are an important cause of cancers developing between two screening endoscopies (so-called interval cancers). Interval cancers are more likely to be in the proximal colon, are more likely to be microsatellite unstable, and to have the CpG island methylator phenotype (CIMP). Serrated lesions should be identify and fully resected – mostly by endoscopic mucosal resection technique. The borders of the lesion and suspected residual tissue should be treated by means of argon plasma coagulation method. Lesions resected piecemeal may necessitate early endoscopic control in a few months. Another interesting group of right sided lesions lesions are laterally spreading tumours (LSTs) of the colorectum, defined as lesions greater than 10 mm in diameter with a low vertical axis that extend laterally along the luminal wall. The lesions are subdivided into two categories: granular-type (G-LST), which endoscopically consist of numerous nodules having a homogenous colour in comparison with the surrounding colonic mucosa and flat-type (F-LST). The flat-type propensity for the right colon was described and also a higher incidence of submucosal invasion compared with G-type lesions.

1. Winawer SJ, Zauber AG, Ho MN et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N. Engl. J. Med. 329, 1977–1981 (1993).

2. Citarda F, Tomaselli G, Capocaccia R, Barcherini S, Crespi M. Efficacy in standard clinical practice of colonoscopic polypectomy in reducing colorectal cancer incidence. Gut 48, 812–815 (2001).
3. Thiis-Evensen E, Hoff G, Sauar J, Langmark F, Majak B, Vatn M. Population-based surveillance by colonoscopy: effect on the incidence of colorectal cancer. Telemark Polyp Study I. Scand. J. Gastroenterol. 34, 414–420 (1999).
4. Baxter NN, Goldwasser MA, Paszat LF, Saskin R, Urbach DR, Rabeneck L. Association of colonoscopy and death from colorectal cancer. Ann. Intern. Med. 150, 1–8 (2009).
5. Lakoff J, Paszat LF, Saskin R, Rabeneck L. Risk of developing proximal versus distal colorectal cancer after a negative colonoscopy: a population-based study. Clin. Gastroenterol. Hepatol. 6, 1117–1112 (2008).
6. Singh H, Nugent Z, Mahmud SM, Demers AA, Bernstein CN. Predictors of colorectal cancer after negative colonoscopy: a population-based study. Am. J. Gastroenterol. 105, 663–673 (2010).
7. Singh H, Nugent Z, Demers AA, Kliewer EV, Mahmud SM, Bernstein CN. The reduction in colorectal cancer mortality after colonoscopy varies by site of the cancer.Gastroenterology 139, 1128–1137 (2010).
8. Baxter N, Sutradhar R, Forbes DD, Paszat LF, Saskin R, Rabeneck L. Analysis of administrative data finds endoscopist quality measures asociated with post-colonoscopy colorectal cancer. Gastroenterology 140, 65–72 (2011).
9. Brenner H, Chang-Claude J, Seiler CM, Rickert A, Hoffmeister M. Protection from colorectal cancer after colonoscopy: a population-based, case–control study. Ann. Intern. Med. 154, 22–30 (2011).
10. Kaminski MF, Regula J, Kraszewska E et al. Quality indicators for colonoscopy and the risk of interval cancer. N. Engl. J. Med. 362, 1795–1803 (2010).

PROBLEMS WITH THE DISLOCATION OF STENTS IN THE BILIARY AND PANCREATIC TREE

Joan DOT

Hospital Vall d'Hebron, Spain

CYTOREDUCTIVE SURGERY FOR PROLIFERATING FORMS OF COLORECTAL CANCER

Suleyman B. ABDUJAPPAROV

The Republican Oncology Research Centre of the Ministry of Health of the Republic of Uzbekistan, Uzbekistan

Introduction:
The term "cytoreductive surgery" means surgical interventions aimed at the maximum removal of the mass of tumoural tissue, thus creating a beneficial background for the subsequent antitumour therapy. In the course of time, the concept of cytoreductive surgery has transformed from the deliberately incomplete to the maximum possible removal of a tumour. Cytoreductive surgery has a palliative effect on tumours displaying evident clinical symptoms or urgent complications. The tumour burden reduction decreases its metabolic and immunological activities at the expense of the production of immunosuppressive cytokines and immune complexes. The major effect of cytoreductive surgery consists in the increasing efficacy of conservative therapy.
The international residual tumour classification is used for the assessment of the completeness of cytoreduction within the framework of TNM (UICC, 2002): Rx – presence of residual tumour may not be assessed, Ro – absence of residual tumour, R1 – microscopic residual tumour and R2 – macroscopic residual tumour.

Aim:
To evaluate benefit of cytoreductive surgery in case of colorectal cancer at the III–IV stage in 321 patients.

Methods:
Methodology combining long-term endolymphatic and regional lymphatic polychemotherapy (PCT):
- Long-term endolymphatic PCT
  1) Methotrexate – 50 mg/m^2 per day, 1st day
  2) Fluorouracil – 1,000 mg/m^2 per day, 2nd, 3rd days
- Regional lymphatic PCT
  1) Methotrexate – 50 mg/m^2, 4th day
  2) Fluorouracil – 1,000 mg/m^2, 5th day

Methodology of systemic chemotherapy according to the schedule FOLFOX-4 + Avastin:
- Oxaliplatin (Oxitan) – 180 mg/m^2 by intravenous drip on the 1st day
- Calcium folinate (leucovorin) – 200 mg/m^2 intravenously on the 1st day
- Fluorouracil – 400 mg/m^2 by intravenous jet on the 1st day, then
- Fluorouracil – 2.4–3.0 g/m^2 48-hour intravenous infusion
- Avastin 5 mg/kg by intravenous drip every 14 days

Methodology of systemic chemotherapy according to the schedule FOLFIRI + Avastin:
- Irinotecan (Campto) – 150 mg/m^2 by intravenous drip on the 1st day
- Calcium folinate (leucovorin) – 200 mg/m^2 intravenously on the 1st day
- Fluorouracil – 400 mg/m^2 by intravenous jet on the 1st day, then
- Fluorouracil – 2.4–3.0 g/m^2 48-hour intravenous infusion
- Avastin 5 mg/kg by intravenous drip every 14 days

Conclusion:
As a result of the conducted research, the efficacy of cytoreductive surgery for proliferating colorectal cancer has been proven. It is necessary to more widely use methods of neoadjuvant therapy for proliferating forms of colorectal cancer, because they allow to subsequently perform cytoreductive surgery in the volume R0. The near and more distant therapy results obtained allow to recommend cytoreductive surgery to be performed to a greater extent with regard to patients with proliferating forms of colorectal cancer.

ЦИТОРЕДУКТИВНЫЕ ОПЕРАЦИИ ПРИ РАСПРОСТРАНЕННЫХ ФОРМАХ КОЛОРЕКТАЛЬНОГО РАКА

Сулейман Б. АБДУЖАППАРОВ

Республиканский Онкологический Научный Центр МЗ РУз

Рак толстой кишки в 70–80 % случаев выявляется в III–IV стадиях.

Показатели пятилетней выживаемости колеблются от 45 до 60 % (*Царьков П.В., Одарюк Т.С. 2002г., Кныш В.И. 1997г.*).

Циторедуктивным вмешательством является максимальное удаление опухолевой массы (первичной и метастатической) предпочтительно до остаточной опухоли в виде микрометастазов (Wong, De Cosse – 2007).

Объем циторедукции или классификация циторедуктивных операций по И.А. Савиной и соавт., НИИ Петрова – Ж.Вопросы онкологии, 2003г. – Том 49, №3.С.340–345):

1. Полная циторедукция – удаление первичной опухоли и всех визуальных определямых метастазов (R0);
2. Частичная циторедукция – удаление первичного опухолевого очага и частичное удаление метастазов (в том числе удаление только первичной опухоли без метастазов);
3. Операции, при которых удаление метастазов производиться в различные сроки после радикальной или циторедуктивной операции.

По мнению Г.И. Воробьева и соавт. (Ж.Рос.Онкол.журнал №4 2008.С.17–21) – под термином «циторедуктивные операции» подразумевают хирургические вмешательства, направленные на максимальное удаление массы опухолевой ткани, создающий тем самым наиболее благоприятный фон для последующей противоопухолевой терапии.

Понятие циторедуктивная операция с течением времени трансформировалась от заведомо неполного до максимально возможного удаления опухоли. Теоретические предпосылки для циторедуктивной хирургии при злокачественных опухолях вытекают как из клинического, так и из базовых научных знаний. ЦО оказывают паллиативный эффект при опухолях, сопровождающихся выраженной клинической симптоматикой или ургентными осложнениями. Уменьшение опухолевой массы снижают ее метаболическую и иммунологическую активность за счет уменьшения продукции иммуносупрессивных цитокинов и иммунных комплексов. Важнейший эффект ЦО – повышение эффективности консервативной терапии.

Для оценки полноты циторедукции используют международную классификацию резидуальной опухоли в рамках TNM (UICC, 2002):

- Rx – наличие остаточной опухоли не может быть оценен;
- Ro – отсутствие остаточной опухоли;
- R1 – микроскопически остаточная опухоль;
- R2 – макроскопически остаточная опухоль.

Цель исследования

Изучение результатов циторедуктивных операций у больных с распространенной формой колоректального рака

Объект исследования:

321 больных колоректальбным раком III–IV стадии.

Предмет исследования:

Циторедуктивные операции при колоректальном раке III–IV стадии.

Первичные обязательные исследования:

- ➔ Пальцевое исследование прямой кишки;
- ➔ Ректоскопическое исследование;
- ➔ Фиброколоноскопия;
- ➔ Ирригоскопия;
- ➔ Рентгенологическое исследование грудной клетки;
- ➔ Морфологическое исследование биоптата;
- ➔ УЗИ органов брюшной полости, малого таза и забрюшинного пространства;
- ➔ Компьютерная томография органов брюшной полости и малого таза;
- ➔ Общий анализ крови и мочи, калий, натрий, кальций. Общий белок, билирубин и фракции, общий белок и фракции, АсАТ, АлАТ, ШФ, группа крови, резус фактор, коагулограмма, иммунопробы(до, во время, после лечения).

Возможность удаления раковой опухоли определяется распространением процесса в кишечной стенке, по лимфатическим и венозным путям, переходом на окружающие органы и ткани. Особенно важно правильно определить степень распространения опухоли.

Методика сочетания длительной эндолимфатической и регионарной лимфатической ПХТ авт.свид.№IAP2003288

* **Длительная эндолимфатическая ПХТ**

1) Метотрексат – 50 мг/м² в сутки, 1-день

2) Фторурацил – 1000 мг/м² в сутки, 2,3-дни

* **Регионарная лимфатическая ПХТ**

1) Метотрексат – 50 мг/м², 4-день

2) Фторурацил – 1000 мг/м², 5-день

Методика системной химиотерапии по схеме FOLFOX-4 + Avastin

* Оксалиплатин (Окситан) – 180 мг/м² в/в капельно в 1-й день

* Фолинат Кальция (лейковорин) – 200 мг/м² в/в в 1-й день

* Фторурацил – 400 мг/м² в/в струйно в 1-й день, затем

* Фторурацил – 2,4–3,0 г/м² 48 часовая в/в инфузия

* Авастин 5 мг/кг в/в капельно каждые 14 дней

GASTROENTEROLOGY UZBEKISTAN TASHKENT 2012

Методика системной химиотерапии по схеме FOLFIRI + Avastin

* Иринотекан (Кампто) – 150 мг/м^2 в/в капельно в 1-й день
* Фолинат Кальция (лейковорин) – 200 мг/м^2 в/в в 1-й день
* Фторурацил – 400 мг/м^2 в/в струйно в 1-й день, затем
* Фторурацил – 2,4–3,0 г/м^2 48 часовая в/в инфузия
* Авастин 5 мг/кг в/в капельно каждые 14 дней

Возможность удаления раковой опухоли определяется распространением процесса в кишечной стенке, по лимфатическим и венозным путям, переходом на окружающие органы и ткани. Особенно важно правильно определить степень распространенности опухолевого процесса.

- Выводы
- В результате проведенного исследования доказано эффективность выполнения циторедуктивных операций при распространенном колоректальном раке
- Необходимо более широко использовать неоадьювантные методы лечения при распространенных формах колоректального рака, так как они позволяют в последующем выполнять ЦО в объеме R0
- Полученные ближающие и отдаленные результаты лечения позволяют рекомендовать более широко выполнять циторедуктивные операции у больных с распространенными формами колоректального рака

GALLSTONES IN PATIENTS WITH MORBID OBESITY. RELATIONSHIP TO BODY WEIGH, WEIGHT LOSS AND GALLBLADDER BILE CHOLESTEROL SOLUBILITY

V. P. SHYPULIN, A. IOFFE

National museum of medicine of Ukraine, Kyiv, Ukraine

Obesity is one of the major factors in cholelithiasis occurrence. Risk of the gallstones formation increases upon increasing of the body-mass index (BMI). Women with obesity upon BMI > 30 kg/m^2, have twice higher risk of cholelithiasis occurrence. In case if BMI > 45 kg/m^2 such a risk is higher than seven times comparatively to women with BMI > 24 kg/m^2.

Men with obesity have a lower risk of gallstone disease than women.

The probability of formation of gallstones increases with weight loss. The reasons for this are the increase in the concentration of cholesterol in the bile, cholesterol crystal formation and reduced contractility of the gall bladder.

The formation of "new stones" occurs in approximately 25–35 % of obese people, who quickly lost the weight because of various reasons.

It is known that an increase in fat consumption in the low-calorie diet (< 600 kcal/day) prevents the formation of stones. The risk of stone formation during weight loss diet is much lower (0–17 %) in those patients who keep a low calorie diet (> 800 kcal/day), which contains 15–30 grams of fat per day.

In the postoperative period in patients after laparoscopic gastric banding with a loss of 1.5 kg/wk body weight ursodeoxycholic acid was administered at a dose of 10 mg/day for the prevention of gallstone disease. This is because the intake of 4 grams of fat or less reduces the function of emptying of the gallbladder, which may lead to cholelithiasis. The course of treatment was 6–8 months. Of the 36 patients, who initially did not have cholelithiasis, who took ursodeoxycholic acid in the postoperative period, none have been no formation of gallstones.

Conclusion: Due to the increased risk of stone formation in patients with morbid obesity after bariatric operations we consider it necessary to recommend the prescription of ursodeoxycholic acid for 6–8 months after surgery at a dose of 10 mg/kg/day.

GASTROENTEROLOGY
UZBEKISTAN TASHKENT 2012

TREATMENT OF DYSLIPIDEMIA IN PATIENTS WITH METABOLIC SYNDROME USING SIMVASTATIN AND URSODEOXYCHOLIC ACID

O. M. DRAPKINA, V. T. IVASHKIN

I. M. Sechenov Moscow Medical University, Moscow, Russian Federation

INTRODUCTION: Nonalcoholic fatty liver disease (NAFLD) is a common condition associated with Metabolic Syndrome (MS). Many patients with NAFLD and MS have hyperlipidemia, their elevated serum aminotransferase levels make physicians warry about prescribing statins. However, the benefits NAFLD and MS patients would derive from statin therapy would most likely outweigh any theoretical risk of liver injury.

AIMS & METHODS: Ursodeoxycholic acid (UDCA) has been suggested in recent years to be an effective therapy of NAFLD. Combination of UDCA and simvastatin is perspective for the treatment dyslipidemia and NAFLD. Our aim was to assess the efficacy of UDCA and simvastatin in MS patients with NAFLD and dyslipidemia. We examined 40 MS patients (27 men; average age 48 ± 13 years; BMI = 33.6 ± 5.2 kg/m^2; waist circumference = 113.2 ± 11.1 cm) with clinic, laboratory, ultrasound proven NAFLD and laboratory proven dyslipidemia. Liver biopsy was performed in 18 patients with elevated liver function tests and showed histological findings proven non-alcoholic steatohepatitis (NASH). All patients received UDCA in doses of 15 mg/kg/day and simvastatin 20 mg/day over a period of 6 months.

RESULTS: In the NASH group the mean serum ASAT levels decreased from 87.2 ± 46.5 to 35.1 ± 15.3 IU/L, serum ALAT levels from 77.9 ± 34.4 to 33.9 ± 16.3 IU/L at the end of the treatment period ($p < 0.0003$). After 4 weeks we had no one case of increasing ASAT or ALAT levels on the UDCA and simvastatin therapy. 94.5 % patients (n = 17) with NASH reached normal liver function tests. All 40 patients decreased total cholesterol levels from 232.1 ± 48.7 to 170.2 ± 23.3 mg/dl, triglyceride from 263.7 ± 121.6 to 160.3 ± 49.4 mg/dl, LDL from 130.9 ± 49.7 to 82.8 ± 23.7 mg/dl, increased HDL from 40.9 ± 14.1 to 48.2 ± 11.7 mg/dl at the end of the study ($p < 0.000006$).

CONCLUSION: A significant improvement in the levels of aminotransferases and lipids levels was obtained with combination of UDCA and simvastatin in NAFLD patients. These results reveal that UDCA and simvastatin may be considered an effective treatment in patients with NASH and MS. Thus, lipid-lowering agents and UDCA should be prescribed for patients with NAFLD unless contraindicated, with careful monitoring of transaminase levels during therapy.

GASTROENTEROLOGY UZBEKISTAN TASHKENT 2012

NONALCOHOLIC STEATOHEPATITIS

Alexander NERSESOV

Scientific-Research Institute of Cardiology and Internal Medicine of the Ministry of Health, Almaty, Kazakhstan

UNMASKING AUTOIMMUNE HEPATITIS: CLINICAL CASE

M. MAEVSKAYA, A. DRIGA, V.T. IVASHKIN

1st Moscow Medical State University named after I.M. Sechenov; Hospital of Internal Disease, Gastroenterology, Hepatology; Hepatology Department, Russian Federation

Case history: 40-year-old female pt. complained about fatigue was referred to the Hepatology department of University Hospital. The pt. has long history of obesity (since childhood, BMI ≈ 44 kg/m*2), 5-year history of type 2 diabetes mellitus, increased level of cholesterol and decreased level of HDL since 2010. So she met criteria of metabolic syndrome. Her medications were metformin and sibutramine. Liver functional tests were normal up to March of 2010. On March 2010 due to diabetes mellitus decompensating she was admitted to the Endocrinology department. Metformin dose was increased up to 2000 g a day and glucose level went normal range. At the same time thioctic acid was prescribed at the daily dose of 600 mg IV. In a few days later she developed fatigue and lab tests were checked again. Extremely high level of ALT and AST were found. Her family history is negative for any chronic disease. She doesn't have any bad habits (alcohol consumption or smoking). On exanimation: BMI – 49,8 kg/m*2 (Height – 170 cm. Weight – 144 kg). Skin and sclera were slightly icteric, no extrahepatic sings, mild hepatomegaly and palpable right lobe. Laboratory tests: ALT – 2040 U/L (51× ULN), AST – 1059 U/L (26× ULN), GGTP – 67 U/L (N 11 – 61), AP – 96 U/L (N 32 – 92), Total bilirubin – 3,7 mg/dl (3,7× ULN), Total albumin – 3,1 g/dl (N 3,5 – 5,0), INR – 1,1, Total cholesterol – 198 mg/dl (ULN – 175 mg/dl), Glucose – 83 mg/dl (ULN – 110 mg/dl), Creatinine – 0,8 mg/dl (N). Abdominal sonogram: no liver mass or dilated bile ducts; upper endoscopy: no esophageal varicose veins dilatation. Preliminary diagnosis: Drag-induced liver injury induced (DILI) by combination of metformin and thioctic acid and metabolic syndrome as an associated disease. Differential diagnosis: viral hepatitis – (anti-HCV – neg, HBsAg – neg, anti-HAV IgM – neg, HEV RNA – neg, CMV – neg, EBV – neg), nonalcoholic steatohepatitis, autoimmune hepatitis (AIH) – (gamma-glob – N, SMA – 1 : 40, ANA – neg, anti-LKM – neg), severe alcoholic hepatitis (no history of alcohol abuse), Wilson disease (normal level of serum ceruloplasmin). Probable diagnosis of DILI was assessed by CIOMS/RUCAM scale with Score – 1, which means unlikely adverse drug reaction. Moreover discontinuation of drug treatment led no normalization of lab tests in a month. First liver biopsy was performed on April 2010. Histological examination of the biopsy specimen showed severe fibrosis and inflammatory activity with lymphoid infiltration and piecemeal necrosis; plasmacytosis and eosinophils also were found, no steatosis or bile ducts lesion. Followed the data of pt. evaluation the diagnosis of Drug-induced autoimmune hepatitis (pretreatment score – 15 by criteria of the International Autoimmune Hepatitis Group) was made. Also the pt. had associated disease – metabolic syndrome. The patient was started on budesonide at a dose of 9 mg/day, one month later the aminotransferases and bilirubin level had returned to normal levels and her fatigue had resolved. The budesonide dose was decreased gradually and then stopped. Six months late upon recurrence of aminotransferases elevation she was retested for autoantibodies and high titer of SMA (1 : 1360) was detected, the pt. underwent second liver biopsy and moderate fibrosis, moderate lymphoid infiltration and piecemeal necrosis were found; as well as focal steatosis. Steroids were started again and aminotransferases were going down. After ten months the pt. remained with normal range of lab tests under the maintenance dose of budesonide 3 mg/day. Then she stopped

taking the drug on their own and aminotransferases was going up again; steroids were started third time with good response. SMA titer was remaining very high 1 : 1280. The clinical diagnosis was revised and made as true autoimmune hepatitis type 1 (post treatment score – 18 by criteria of the International Autoimmune Hepatitis Group which means definite diagnosis) with associated disease – metabolic syndrome. We consider that this case represents unmasking of true AIH.

To conclude: In clinical practice the diagnosis of AIH may be challenging as illustrated by the presented clinical case. There are no pathognomonic features of AIH. Moreover histology, serology findings and corticosteroid treatment response are similar between AIH and DILI-AIH. Metabolic syndrome (obesity, diabetes mellitus etc.) might predispose the patient to DILI.