Pathogenesis and Clinical Practice in Gastroenterology

June 15–16, 2007
Grand Hotel Bernardin, Portorož

Abstracts
Poster Abstracts
Abstracts of Invited Lectures
Poster Abstracts

Falk Symposium 160

PATHOGENESIS AND CLINICAL PRACTICE IN GASTROENTEROLOGY

Portorož (Slovenia)
June 15–16, 2007

Scientific Organization:
I. Ferkolj, Ljubljana (Slovenia)
P.R. Galle, Mainz (Germany)
A. Gangl, Vienna (Austria)
B. Vucelic, Zagreb (Croatia)
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Session I

Dysphagia and reflux
Physiology of swallowing and antireflux mechanisms: Anything new from a radiologist’s view?

C. Kulinna-Cosentini
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In the evaluation of esophageal function, the barium swallow/video-fluoroscopy competes favorably with other modalities, such as manometry, endoscopy or 24-h pH-metry. Furthermore, videofluoroscopy is easier to interpret and does not require additional expensive equipment or specialized training. Videofluoroscopy has become a widely accepted method, which allows precise assessment and documentation of oral, pharyngeal, and esophageal phases of swallowing.

This talk will primarily cover normal physiology of swallowing demonstrated by videofluoroscopy for easy understanding. Swallowing consists of three phases: oral, pharyngeal and esophageal phase. The voluntary stage of the oral phase includes components as oral filling, chewing, mixing with saliva, loading food on the tongue and voluntary shift of food toward the posterior part of the tongue. The involuntary stage of the oral phase involves glossopalatal expulsion and clearing of the food bolus into the pharynx. Pharyngeal emptying starts as soon as food enters the pharynx, indicating that the pharyngeal phase is involuntary. It includes nasopharyngeal closure, hyoid bone movement, laryngeal elevation, closure of the airways including the vocal cords and pharyngeal peristalsis including pharyngeal constrictor activity. The involuntary esophageal phase lasts about 10 times longer than the oro-pharyngeal phase, includes transportation through the esophagus, opening and closure of the lower esophageal sphincter (LES).

The second purpose of this talk is to give a short review of physiologic antireflux mechanisms and frequent esophageal diseases, which can be visualized by videocinematography. The lower esophageal sphincter and crural diaphragm are the main components of the physiologic antireflux barrier. When these barriers fail, a second line of defense known as esophageal clearance, consisting of esophageal peristalsis and gravity comes into play.

The use of a new imaging technique, fast-dynamic MRI, in evaluation of gastroesophageal diseases with its indications and limitations will be discussed at the end.
Oropharyngeal dysphagia, achalasia, and other esophageal motility problems: Clinical relevance and management

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Dysphagia is amongst the most common gastrointestinal symptoms in the elderly, with a population prevalence in the elderly in excess of 10%. While mechanical obstruction accounts for some portion of this burden, the majority of these subjects do not have strictures or cancer. Motility disorders account for a large portion of the remainder of these patients. Oropharyngeal dysphagia, also called transfer dysphagia, may result from diseases of the mouth, pharynx, and upper esophagus (including the upper esophageal sphincter, or UES). A variety of neurological, myopathic and structural disorders may cause oropharyngeal dysphagia, including stroke, multiple sclerosis, Parkinson’s disease, cancer and Zenker’s diverticulum. The work-up for oropharyngeal dysphagia differs from that of classic esophageal dysphagia, and fiberoptic endoscopic evaluation of swallowing (FEES study), as well as modified barium swallow, are common diagnostic modalities. Management concentrates on the underlying disease state, with preservation and augmentation of remaining function often the primary goal.

The work-up of motility-related esophageal dysphagia often includes upper endoscopy, barium swallow, and esophageal manometry. Motility-related causes of esophageal dysphagia include achalasia, diffuse esophageal spasm (DES), and ineffective esophageal motility (IEM). The worldwide incidence of achalasia appears to be about 1 x 10^5, although there is substantial variation between populations. The appropriate initial management of achalasia remains unclear – both pneumatic dilatation and laparoscopic Heller myotomy are often-used approaches. The rate of recurrent dysphagia and the need for subsequent recurrent intervention is high regardless of the initial management strategy. Diffuse esophageal spasm may present with chest pain and accompanying dysphagia. Pharmacologic intervention in the form of smooth muscle relaxants such as calcium channel blockers and nitrates may provide effective palliation of these symptoms, however myotomy may be necessary to give adequate relief of symptoms. The natural history of this disease state argues for initial conservative management, as a substantial proportion of these patients will have spontaneous improvement of their symptoms. Therapy of IEM centers around promotility agents, as well as amelioration of any ongoing insult to the esophagus from acid, infiltrative disease, other disease state. Given the common nature of esophageal motility problems, the generalist clinician, as well as surgeons and gastroenterologists, should be well-versed in their diagnosis and management.
NERD, ERD and GERD: Which diagnostic tools are available and when are they needed?

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Gastroesophageal reflux disease (GERD) affects 20–30% of individuals in Europe and the USA. In keeping with present accepted guidelines and recommendations, GERD is defined by the presence of typical (heartburn, regurgitation, dysphagia) and/or atypical symptoms (wheezing, hoarseness, coughing, globus sensation) and the presence of endoscopic esophagitis (ERD = erosive reflux disease). In the absence of endoscopic esophagitis the condition is termed non-erosive reflux disease (NERD). In contrast to present guidelines, we recommend omission of the terms “ERD” and “NERD”, they are inaccurate and miss the real focus of the problem. The most sensitive proof for GERD is the presence of columnar lined esophagus (CLE) within biopsies obtained from the squamocolumnar junction. CLE adequately meets the focus of the problem: risk stratification for esophageal adenocarcinoma, a morphologic consequence of GERD and CLE. No one will die because of erosive esophagitis, but 135 individuals get esophageal adenocarcinoma per year in Austria, compared to 30 individuals 15 years ago! This trend is comparable to what has been reported for other European countries and the USA. It seems that our efforts failed to adequately address the issue. May it be that we misunderstood the pathophysiology of the disease? May it be that we used the wrong definitions and criteria? Did we look at the wrong place? We will see that endoscopy, biopsy sampling and histopathology have the largest impact for management of GERD patients. Function tests aim to exclude other esophageal motility disorders and proof esophageal acid exposure. Finally, novel technologies such as esophageal impedance and high resolution manometry are presented.

The pathophysiology of GERD includes loss of function of the lower esophageal sphincter, impaired esophageal body motility and delayed gastric emptying. GERD may, but must not be associated with disturbances of the geometry of the esophagogastric junction (hiatal hernia, attenuated angle of His). Management of individuals with GERD symptoms aims to proof the presence of GERD symptoms (patient history!!!!), exclude morphologic complications of the disease by endoscopy and biopsy sampling (columnar lined esophagus, Barrett esophagus, esophagitis), the presence of gastroesophageal reflux and the underlying disturbances of lower esophageal sphincter function and esophageal body motility (esophageal manometry and ambulatory pH monitoring). Esophageal impedance technology is a novel tool for assessment of bolus transport and reflux along the esophagus. Combined esophageal impedance-pH monitoring enables assessment of acidic and non-acidic reflux. Very recently high resolution manometry has been introduced for assessment of esophageal motility disorders.

Following careful taking of patient history, we have to exclude morphologic consequences of GERD. If patients report dysphagia, videocinematographic barium or gastrografin swallow study is recommended for exclusion of obstruction or stenosis within the esophagus. Endoscopy aims to assess presence or absence of morphologic manifestations of GERD: esophagitis (= endoscopic visible inflammation
within squamous epithelium lined esophagus, graded according to Los Angeles or Savary Miller classification) and endoscopic visible columnar lined esophagus (CLE; = endoscopic visible tongues or segments of gastric type mucosa within tubular esophagus). CLE is of major importance, since it is a premalignant condition. In contrast to esophagitis, CLE may progress towards adenocarcinoma of the esophagus (annual incidence 0.2%–2.0%). Current valid recommendations for GERD patient management harbor three major problems: First, columnar lined esophagus only has impact on patient management if it contains goblet cells (= intestinal metaplasia, Barrett esophagus; precursor lesion of intestinal metaplasia is NOT considered). Second, biopsy sampling of a normal appearing squamocolumnar junction is NOT recommended. This is based on the false assumption, that macroscopy may be more sensitive than histopathology. However, everybody will agree that development of endoscopic visible lesions are preceded by microscopic changes! Third, endoscopy mainly focusses on assessment of inflammation of squamous epithelium lined esophagus (ERD, NERD). Elucidation of this misunderstanding and Babylonian linguistic confusion can only be achieved by understanding esophageal anatomy and histopathology associated with GERD.

After birth, the esophagus is lined by squamous epithelium, whereas the stomach is lined by oxyntic mucosa (acid producing parietal cells, pepsinogen producing main cells within the subfoveolar region of the glands). The lower esophageal sphincter (LES) separates the esophageal from the gastric lumen. It only opens during swallowing to allow passage of food and during venting to allow passage of air. Otherwise the LES is closed, no reflux occurs. Gastric distension-induced relaxations of the distal part of the LES cause transient exposure of the distal esophagus to gastric content (acid, nutrients, bile). This in turn causes damage of the squamous epithelium, sensation of heartburn and replacement of damaged squamous epithelium by COLUMNAR epithelium (= columnar lined esophagus; CLE). At this stage manometry will show normal LES function and a pH probe placed 5 cm above the LES will fail to assess acid exposure (which in fact occurs in the most distal part of the LES, while the proximal part of the LES is still competent). Endoscopy will show absence of inflammation and a normal appearing esophagus lined by squamous mucosa. However, biopsies taken from the squamo-columnar junction will show presence of CLE interposed between squamous and gastric oxyntic mucosa. This condition correlates to NERD (macroscopy normal, biopsy not recommended)! Since biopsy sampling of endoscopic normal appearing junction is not recommended, the earliest morphologic GERD change, MICROSCOPIC columnar lined esophagus (CLE!), is missed in these patients. Over time damage of squamous epithelium lined esophagus continues, length of CLE increases and becomes visible by endoscopy (endoscopic visible CLE tongues and segments). This is endoscopic visible proximal dislocation of the squamocolumnar junction. However, if proximal dislocation of the squamocolumnar junction occurs in symmetrical manner it may be misinterpreted as "normal" appearing junction. Here again, only histopathology of biopsies obtained from the squamocolumnar junction enable assessment of presence or absence of CLE! Visible CLE is associated with abnormal findings during esophageal manometry and presence of abnormal acid exposure, as assessed by pH monitoring. Based on our data, the minority of GERD patients have endoscopic esophagitis, while all GERD patients have histopathologic CLE (see below). In contrast to esophagitis (may be due to nutrients, bacteria, candida, allergy, autoimmune disease etc.), presence of CLE is specific for reflux, since reflux is the
ONLY cause for CLE formation. NO CLE WITHOUT REFLUX, irrespective of presence or absence of symptoms!

The Paull Chandrasoma classification lists the following mucosal types of nondysplastic CLE: cardiac mucosa (mucus cells only), oxyntocardiac mucosa (mixture of mucus and parietal cells within the subfoveolar region of the glands); intestinal metaplasia (= Barrett esophagus) defined by the presence of goblet cells within cardiac mucosa! Intestinal metaplasia may progress towards low and high grade dysplasia and adenocarcinoma of the esophagus. Goblet cells only colocalize within cardiac, but not within oxyntocardiac mucosa. Therefore, individuals with cardiac, but not oxyntocardiac mucosa, are at risk for development of esophageal adenocarcinoma. According to current guidelines, there is no recommendation how to manage individuals with cardiac or oxyntocardiac mucosa. These histologic types simply do not exist, cardiac mucosa is frequently misinterpreted as part of the proximal stomach or only considered as "pathologic", if it contains goblet cells (= Barrett esophagus). Anatomy teaches that the esophagus has submucosal glands. In contrast to that, submucosal glands do not exist in the stomach. Histopathology of esophagogastrectomy specimens revealed colocalization of cardiac and oxyntocardiac mucosa and submucosal glands. In contrast to that, submucosal glands were absent below gastric oxyntic mucosa. This proofs that cardiac mucosa and oxyntocardiac mucosa are of esophageal origin (columnar lined ESOPHAGUS).

Using the Paull Chandrasoma classification and biopsy sampling of the squamocolumnar junction, we recently found that all of 114 GERD patients had biopsy proven CLE, irrespective of endoscopic appearance (normal vs. abnormal squamocolumnar junction. In another study we investigated 102 GERD patients using the Paull Chandrasoma classification and a multi level biopsy protocol around the endoscopic esophagogastric junction. Our data showed that the esophagogastric junction can not be assessed by endoscopy. In one third and two thirds of the patients CLE was detected 1.0 cm and 0.5 cm, respectively, distal to the level of the rise of the gastric folds. Facit: presence of CLE can not excluded by endoscopy. Biopsy sampling of squamocolumnar junction is recommended! The true esophagogastric junction and the true length of CLE can only be assessed by histopathology of multi level biopsies from the esophagogastric junction. The rise of gastric folds is a great reference for biopsy level location. In keeping with Chandrasoma et al., we also found that mucosal types within CLE follow a distinct proximal to distal distribution, cardiac mucosa most proximal and oxyntocardiac mucosa distally. Appearance of intestinal metaplasia commences proximal and progresses distal within CLE over time, irrespective of CLE length (CAVE: endoscopic invisible CLE does not exclude presence of intestinal metaplasia). We found that intestinal metaplasia was present in 17% and 22% of GERD patients with endoscopic normal and abnormal squamocolumnar junction, respectively. A normal appearing endoscopic squamocolumnar junction does not exclude presence of intestinal metaplasia! Highest probability to detect intestinal metaplasia is at the most proximal part of CLE segment(s). Recent work from the Siewert group showed, highest frequency of low, high grade dysplasia and adenocarcinoma within the distal third of a CLE segment. Reason for proximal-distal distribution of mucosal types within CLE is not clear, but is suggested to be pH dependent and may therefore represent the morphologic correlate of a pH gradient over the length of CLE.

Based on the above considerations and the recently published Prague criteria for endoscopy the endoscopic report should include the following information: level of
diaphragm, level of gastric rugae, level of most proximal gastric type mucosal tongue (CLE), level of circular CLE segment, presented as cm from incisors. If gastric folds commence > 2 cm proximal to diaphragmatic impressions the condition is considered as hiatal hernia. Four-quadrant biopsies should be obtained from level of rise of gastric rugae and 0.5 cm distal to that level. Endoscopic visible CLE tongues and segments should be biopsy sampled at 0.5 cm steps. Paul Chandrasoma classification is recommended for histopathology. Dysplasia should be graded according to the Ridell criteria. Surveillance and clinical consequences (PPI treatment, surgery, endoscopic treatment) are described elsewhere in this meeting and in the literature.

Esophageal manometry should be conducted in GERD patients, who are candidates for anti reflux surgery; individuals with GERD symptoms without symptom relieve under PPI treatment (exclude achalasia etc.)

The lower esophageal sphincter functions as a barrier against reflux if it exerts adequate pressure over respective length. Normal pressure and length is considered > 10 mm Hg and 1–2 cm, respectively. If reflux occurs physiologically, it is adequately cleared by effective esophageal body motility. Impairment LES function results in failure of barrier function and gastroesophageal reflux, ineffective body motility results in impaired clearance of refluxed material. Both mechanisms contribute to the pathophysiology leading to GERD. Esophageal manometry aims to assess 1). GERD-associated LES dysfunction and impaired esophageal body motility, 2). to exclude other causes for the symptoms (achalasia, distal esophageal spasm, hypertensive lower esophageal sphincter, esophageal manifestation of mixed connective tissue disease) and 3). to assess the level for pH probe placement for ambulatory pH monitoring. Data obtained during esophageal manometry include length of LES (total, abdominal), length of LES with low resting pressure (< 10 mm Hg; = impaired LES function) and length of LES with normal resting pressure (> 10 mm Hg). Swallow induced relaxation of the LES distal to the respiratory inversion point (RIP) and esophageal body motility is assessed during 10 wet 5 ml swallows of water. Motility is considered normal if 8–10 out of 10 wet swallows are showing amplitude > 25 mm Hg and peristaltic sequence. Swallow induced LES relaxation is considered normal if decreasing towards < 5 mm Hg upon swallowing. Data obtained during esophageal manometry are important for treatment design and management (type of surgery, medical treatment). High resolution manometry represents a very novel technology including numerous pressure sensing probes along the entire length of the LES and the body of the esophagus thus providing detailed information on pressure profile over the whole length of the esophagus (body and LES). It is suggested that the technology will have major impact to improve our understanding of esophageal motility disorders and the management of GERD patients.

Ambulatory pH monitoring aims to assess the presence or absence of pathologic acid exposure within the distal esophagus 5 cm above the manometric LES during 23–24 hours. Placement of the probe without manometric information is not recommended, since pH switch method is inaccurate. Acid exposure within the proximal esophagus is assessed with a system including 2 pH probes 5 and 20 cm above the LES. The Bravo capsule represents a catheter free system for pH monitoring, where a pH probe is attached to the mucosa endoscopically or guided
radiologically. Whenever GERD is to be excluded, patients are recommended to undergo ambulatory pH monitoring.

Combined esophageal impedance-pH monitoring is a fascinating novel technology for assessment of both acidic and non-acidic reflux into the esophagus. Candidates for impedance pH monitoring are those with histopathologic CLE, GERD symptoms (typical and atypical), but normal pH monitoring.

**Conclusion:** The terms NERD and ERD should be omitted from our vocabulary and replaced by information on presence or absence of CLE within biopsies obtained from the squamocolumnar junction. Presence of CLE is proof of gastroesophageal reflux, irrespective of endoscopic appearance. Workup of GERD patients is recommended to include endoscopy, multi-level biopsy sampling for assessment of presence or absence of CLE and premalignant metaplasia and cancer risk stratification. Function tests include esophageal manometry, pH monitoring and/or combined impedance pH monitoring. Radiologic examinations prior to endoscopy are indicated in those with dysphagia.

**Literature:**


Outcomes of different approaches to GERD

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Gastroesophageal reflux disease (GERD) can be divided into esophageal and extraesophageal syndromes according to the recently published MONTREAL definition and classification, which may manifest singly or in combination. The form of its manifestation largely determines the therapeutic objectives and thus the therapeutic options. In principle these latter include general measures, drugs, endoscopic procedures and antireflux surgery.

General measures, for example, having the patient sleep with the trunk elevated, and lose weight may ameliorate or even eliminate symptoms in the individual case. Their impact on the lesions in the esophagus has not been documented. As the sole means of treatment, such measures should be considered only for patients whose symptoms are infrequent.

Drugs are the therapeutic option of choice. Antacids or low-dose H₂ blockers may be administered to ameliorate occasional reflux symptoms. Otherwise, proton pump inhibitors (PPI) are currently considered the first-line drugs – whether as acute or long-term treatment – for GERD, irrespective of its severity. Some one-third of patients with non-erosive reflux disease (NERD) prove to be therapy-resistant and in these patients, there is often no relevant reflux to account for the symptoms. Here, tricyclic antidepressants or serotonin-reuptake inhibitors impacting on the visceral perception threshold may be helpful. In patients with reflux esophagitis, healing of the lesions and, usually, also satisfactory symptom control can almost always be achieved. Rigorously applied long-term application of PPI treatment very probably also reduces the risk for such complications as stricture and Barrett’s carcinoma.

Endoscopic antireflux procedures must still be considered experimental, since their effectiveness and safety have not yet been confirmed in appropriate studies. The sole procedure with a confirmed effect not only on symptoms but also on reflux is the Plicator. However, long-term outcomes are not yet available, nor can the safety profile be definitively assessed.

Antireflux surgery (usually laparoscopic fundoplication) has an established role to play and is effective. With regard to its effectiveness, it is roughly equal to that of appropriate PPI treatment. However, failed treatment is not a rare occurrence, and the rate of such surgery-specific consequences as dysphagia, gas bloat syndrome and diarrhea is not insignificant. For this reason, this procedure should be done only in carefully selected patients. It should also be noted that the surgical outcome is largely dependent on the individual skill of the surgeon.
Barrett’s esophagus: Screening, surveillance, treatment. Are all questions answered?

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Introduction:
Barrett’s esophagus today is understood to be a complication of gastroesophageal reflux disease (GERD), but unlike GERD, it is seldom seen in daily clinical practice. In 1957, the surgeon N.R. Barrett described an esophagus lined with a too short inner mucosal layer. Over the course of many years, specialists collected a vast amount of information on the etiopathology, endoscopic and histopathologic diagnosis, surveillance and treatment of this condition. So it seems clear that the definition of Barrett’s esophagus has evolved over the last two decades from the columnar-lined lower esophagus to intestinal metaplasia in the esophagus without specification of length and circumferential extent.

Diagnosis, screening, surveillance:
Patients with chronic GERD are those most likely to have Barrett’s esophagus. It is well accepted that the duration of GERD correlates directly with the prevalence of Barrett’s esophagus. Though the epidemiology of Barrett’s esophagus is described incompletely, it is a fact that the highest yield of intestinal metaplasia is found in white males with symptoms of chronic GERD. The most effective tool for detecting Barrett’s esophagus is upper GI endoscopy, which therefore is absolutely indicated for GERD patients. The recognition of Barrett’s esophagus in asymptomatic individuals still remains a problem and underscores the need to assess the distal esophagus carefully in all patients undergoing upper GI endoscopy regardless of indication. The identification of the squamocolumnar junction during every endoscopy is essential for recognition of Barrett’s mucosa. Esophagitis or erythema alone may be confused with Barrett’s mucosa macroscopically, so systematic and multiple biopsy is essential to establish the diagnosis. To select biopsy sites more accurately, chromoscopy with various stains has been introduced into routine clinical endoscopy for patients with suspected Barrett’s. Methylene blue staining seems to be the most useful and promising technique as evidenced by the fact that stain-targeted biopsies produce a higher yield of detected metaplastic – and above all – dysplastic areas. For individuals with established Barrett’s esophagus the rationale for surveillance is based on the increased risk of developing adenocarcinoma. Therefore, the grade of dysplasia determines the endoscopy interval as dysplasia is the best current indicator of the risk of developing cancer. It is important to realize that dysplasia is the first step in the neoplastic process and that any grade of dysplasia may be accompanied by coexisting carcinoma. It must be emphasized that every diagnosis of dysplasia, regardless of histologic grading, warrants a repeat endoscopy with extensive biopsies under chromoscopy.

Therapeutic management:
As the treatment goals for Barrett’s and GERD are the same, the diagnosis of Barrett’s does not lead to a specific therapeutic regime. The control of GERD’s
symptoms is the best and most effective treatment of Barrett’s esophagus without any dysplastic lesions. Therapy with proton-pump inhibitors is accepted as the standard therapy in this group of patients. Individuals for whom surgery is indicated may elect antireflux surgery since fundoplication effectively controls specific symptoms. If dysplastic or premalignant epithelium exists, neither conservative nor surgical treatment is able to eliminate the risk of an adenocarcinoma. This group requires special attention with regard to any resective procedure, either endoscopic or surgical. Because dysplasia tends to be multifocal, endoscopic mucosal resection should preferably be performed as a one-piece resection (ESD) rather than piecemeal (EMR), though strictures occur more commonly after complete circumferential resection than after partial resection. Other or recently developed endoscopic therapeutic modalities such as photodynamic therapy or the HALO® system seem to be promising, as they are effective and rarely involve complications. Esophagectomy performed at a high-volume institution remains a reasonable strategy in the surgically fit patient; the given morbidity and mortality, especially in low-volume institutions, suggest reserve and caution under those circumstances.

**Conclusion:**
As Barrett’s esophagus is a well known and now well defined pathologic entity, its diagnosis and management, as far as specific surveillance and therapeutic procedures are concerned, should be carried out in highly specialized institutions. A close interdisciplinary approach among gastroenterologists, pathologists and gastrointestinal surgeons is the only guarantee for the maximum range of diagnostic and therapeutic management.
Session II

Helicobacter pylori, NSAID, gastric cancer
**Helicobacter pylori** infection: Diagnosis, treatment and risks of untreated infection

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*H. pylori* infection is associated with various gastroduodenal pathologies ranging from gastritis, peptic ulcer disease to gastric cancer. The most current guidelines for the diagnosis and management of *H. pylori* are outlined in the third Maastricht Consensus conference. The diagnosis of *H. pylori* infection is best established using invasive or non-invasive methods. Non-invasive tests are the urea breath test, stool antigen tests and serological kits with a high accuracy. Eradication of *H. pylori* infection is recommended in patients with gastroduodenal pathologies such as peptic ulcer disease and low-grade gastric mucosa-associated lymphoid tissue lymphoma, atrophic gastritis, first-degree relatives of gastric cancer patients, unexplained iron deficiency anaemia and chronic idiopathic thrombocytopenic purpura. Triple therapy using a PPI with amoxicillin and clarithromycin or metronidazole given twice daily remains the recommended first choice therapy. Bismuth containing quadruple therapy is also a first choice treatment option. Rescue therapy should be based on antimicrobial susceptibility. The risk of untreated *H. pylori* infection appears to be highest in patients who require long-term treatment with non-steroidal anti-inflammatory agents. Untreated *H. pylori* infection also leads to pre-cancerous and cancerous stomach lesions. Therefore, eradication of *H. pylori* has the potential to reduce the risk of gastric cancer development.
Gastrointestinal endoscopy and anticoagulation

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Approximately 1% of the general population receives oral anticoagulant treatment for prevention of thromboembolic events. The management of these patients in case of acute or elective endoscopic procedures remains a clinical challenge. Discontinuation of anticoagulation is associated with a significant thromboembolic risk, maintenance of anticoagulation during endoscopy with an increased risk of bleeding. Based on clinical experience rather than randomized controlled clinical studies, guidelines of the American Society of Gastrointestinal Endoscopy have been published providing practical guidance. These recommendations are mainly based on estimations (1) of the risk and harm of a potential bleeding due to the intervention and (2) the risk and harm of thrombosis due to the underlying prothrombotic disorder. Although patients’ management should be individualized, patients with a low risk thrombosis undergoing endoscopic procedures with a high risk of bleeding should discontinue anticoagulation, while no interruption of anticoagulation is preferred in patients with a high thromboembolic risk undergoing low risk endoscopic procedures such as diagnostic esophagogastrroduodenoscopy with or without biopsy. The thromboembolic risk of patients interrupting oral anticoagulation might be reduced via pre- and postprocedure administration of low molecular heparin, although clinical studies are lacking. The lecture will focus on the clinical applicability of these guidelines using different clinical scenarios.
Prevention and treatment of NSAIDs-induced lesions of the gastrointestinal tract

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Non-steroidal anti-inflammatory drugs (NSAIDs) are mainly taken for musculoskeletal pain. Long-term treatment with low dose acetylsalicylic acid is mainly taken for cardiovascular prophylaxis. As life expectancy increases, the number of patients on these drugs increases continuously. They take their medications at a higher age as well as for longer time periods compared to former generations. NSAIDs may cause side effects either in the gastro-duodenum, or in the lower gastrointestinal tract. The range goes from epigastric discomfort to mucosal lesions like erosions, deeper ulcers, perforations or bleeding. In how far early mucosal lesions during NSAID therapy progress to deeper lesions, is unclear, but the number of serious events is time dependent and the risk of significant side effects increases with the length of therapy.

The incidence of clinically significant upper gastrointestinal events from NSAID therapy is 1–2 per 100 person-years of therapy. Among the elderly over 65 years of age NSAID therapy contributes significantly to hospitalisation rates with a 4-fold increased risk of death due to ulcer-related complications. Concomitant use of antiplatelet agents may even increase the risk of serious bleeding of the upper gastrointestinal tract (UGIB). Definite risk factors for UGIB are patients on NSAIDs who are over 65 years of age, patients who take additional anticoagulation therapy or on high dose corticosteroids, as well as patients with a previous bleeding event in their past medical history. In preventive guidelines in these patient groups proton pump inhibitors (PPI) should be given as additional therapy. PPIs are superior in their effect to prevent gastroduodenal ulcerations as compared to H₂ blockers, misoprostol or surface protecting agents like sucralfate. They also have less side effects and can be taken for long time periods without substantial risk. However, the long-term costs of these combined therapies are substantial although there has been a sharp prize drop due to generic drugs coming on the market. NSAIDs may also cause significant ulceration and bleeding in the lower GI tract. Since PPIs do not have any protective effect in the small and large bowel a different treatment strategy has been investigated. Cyclooxygenase-2-selective NSAIDs (Coxibs) clearly reduce, but do not abolish the risk of bleeding and ulceration in the lower GI tract as well as in the gastro-duodenum. The selectivity for the enzyme COX-2 comes at a prize. Due to a higher rate of cardiovascular events in several studies Coxibs cannot be recommended as an alternative to unselective NSAIDs especially in patients at risk for cardiovascular disease.

In summary therapy with NSAIDs should be as short as possible. As a primary prevention alternative treatment regimens for musculoskeletal pain should be used. As a secondary preventive strategy concomitant treatment with PPIs should be given in patients at high risk.
Session III

IBD section
The pathogenesis of inflammatory bowel disease (IBD) is only partially understood; various environmental and host (e.g., genetic, epithelial, immune, and non-immune) factors are involved. It is a multifactorial polygenic disease with probable genetic heterogeneity. Much of the recent emphasis in IBD genetics research has focused on the evaluation of candidate disease susceptibility genes within inflammatory bowel disease linkage intervals. Such studies have elucidated associations of numerous gene variants (e.g., NOD2/CARD15, SLC22A4/A5, ATG16L1, IL23R, and DLG5) with inflammatory bowel disease, but most of these require further replication and functional validation. Some genes are associated with IBD itself, while others increase the risk of ulcerative colitis or Crohn’s disease or are associated with disease location and/or behaviour. Recently, some new data have emerged indicating a possible role for genetics in predicting therapeutic success (e.g., intolerance for AZA, response to infliximab or steroids).

Furthermore, there is currently no simple diagnostic laboratory tool available for diagnosing IBD. Biological markers that are potentially useful in inflammatory bowel disease include proteins of inflammation such as C-reactive protein (CRP), fecal calprotectin, and several antibodies. Nonetheless, these biomarkers have many limitations. Acute inflammatory markers, such as CRP or fecal calprotectin cannot be used to differentiate between infectious colitis and a flare-up of inflammatory bowel disease. The detection of further potentially interesting markers (e.g., PF4, MRP8, FIBA or Hpa2 detected by proteomic serum profiling) is focus of current research by different groups. Anti-Saccharomyces cerevisiae antibodies (ASCA) and atypical perinuclear anti-neutrophil cytoplasmic antibody (pANCA) are the only commercially available tests that can be useful in discriminating CD from UC. The association of serological markers with disease behavior and phenotype is becoming increasingly well-established. A growing number of observations confirms that patients with Crohn’s disease who express multiple serological markers at high titers are more likely to have complicated small bowel disease (e.g., stricture and/or perforation) and higher risk for surgery than those without, or with low antibody titers. Creating homogenous disease sub-groups based on serological response may assist in developing more standardized therapeutic approaches and in better understanding the pathomechanism of inflammatory bowel diseases. In addition, an increasing amount of experimental data is available on newly discovered antibodies directed against various microbial antigens. Such antibodies include anti-OmpC (outer membrane porin C), anti-Pseudomonas fluorescens (anti-i2), antiglycan antibodies (anti-laminaribioside carbohydrate antibody [ALCA], anti-chitobioside carbohydrate antibody [ACCA], anti-mannobioside carbohydrate antibody [AMCA]), and the anti-flagellin antibody, CBir1. However, the role of incorporating the above mentioned antibodies into the current IBD diagnostic algorithm is often questionable due to their limited sensitivity. Furthermore, there is also significant variability in detection rates depending on the test used; therefore, their application is currently not recommended for broad clinical practice.
The sequence of events underlying the inflammatory reaction in IBD is extremely complex and involves both, the innate and antigen-driven adaptive immune system. Evidence indicates that dysregulation of mucosal immunity in the gut of IBD patients leads to altered production of inflammatory cytokines (e. g., TNF-α, IL-1, -2, -4, -5, -10, -12, and more recently IL-17 and IL-23) and trafficking of effector leukocytes into the bowel. The latter mechanism leads to uncontrolled intestinal inflammation. Novel biological therapies are directed against several key players in this cascade. Major targets for such treatment are inflammatory cytokines and their receptors, as well as adhesion molecules. Blockade of T-cell proliferation and activation, and inhibition of T-cell cytokines has been most extensively targeted by clinical trials in humans in both, CD and UC. Inhibition of adhesion molecules and the use of selected growth factors seem also to have therapeutic potential. In addition, restoration of regulatory T-cell and dendritic-cell function is still pending further investigation in clinical trials.

In conclusion, the answer to the question, whether genetic, immunology or biomarkers are useful in the current everyday clinical practice, is: maybe. Some of the markers (e. g., CRP, ESR, pANCA or ASCA) are already widely or increasingly used, while accepting their limitation. Further prospective clinical studies are needed to establish the clinical role for other (e. g., genetic or additional serological) tests in IBD. In the future, a diagnostic and prognostic panel that includes various genetic, serological and other biomarkers, as well as clinical and environmental factors (e. g., smoking) could be the most likely approach to diagnosis, prediction of disease course, and response to therapy in inflammatory bowel diseases. In contrast, recent advances in understanding the immunological events of IBD have led to the discovery of novel biological therapies directed against several key players involved in the inflammatory cascade.
European guidelines on the management of IBD
Standard therapy: Evidence-based, not eminence-based

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Margaret Thatcher is credited with the statement “we disagree, therefore we need consensus”. This particularly applies to reaching agreement on management guidelines among experts from different health care systems, scientific background and willingness to compromise. The product of European Crohn’s and Colitis Organisation (ECCO) Consensus on Crohn’s disease (CD) was published in 2006 [1], to transatlantic acclaim [2]. The Consensus on Ulcerative Colitis (UC) convened at UEGW in Berlin 2006; key statements are agreed and supporting text is in press. Evidence was graded [3] after a systematic review of the literature and opinion quantified to give a recommendation grade. The aim is to promote a European perspective on the management of inflammatory bowel disease and its dilemmas.

Each Consensus is grouped into three parts: definitions and diagnosis; current management; and management of special situations. The first section concerns aims and methods of the Consensus, as well as diagnosis, pathology, and classification of UC or CD. The second section on Current Management includes treatment of active disease, maintenance of medically-induced remission and surgery. The third section on Special Situations includes cancer surveillance, paediatrics, pregnancy, psychosomatics, extraintestinal manifestations, and alternative therapy. It also includes post-operative prophylaxis in the CD consensus and pouch disorders in the UC Consensus, as well as a section on the patient perspective.

It is hoped that the Consensus will help guide practice in those countries that do not have their own practice guidelines, and act as a reference to current practice during the design of clinical trials. The talk will highlight evidence on the standard management of IBD and address ways that guidelines move from the bookcase to the bedside to improve practice.

References:


Levels of Evidence and Grades of Recommendation [3]

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<th>Level</th>
<th>Individual study</th>
<th>Technique</th>
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<tr>
<td>1a</td>
<td>Systematic review (SR) with homogeneity of level 1 diagnostic studies</td>
<td>Systematic review (SR) with homogeneity of randomized controlled trials (RCTs)</td>
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<tr>
<td>1b</td>
<td>Validating cohort study with good reference standards</td>
<td>Individual RCT (with narrow confidence interval)</td>
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<tr>
<td>1c</td>
<td>Specificity is so high that a positive result rules in the diagnosis (“SpPin”) or sensitivity is so high that a negative result rules out the diagnosis (“SnNout”)</td>
<td>All or none</td>
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<td>SR with homogeneity of level &gt; 2 diagnostic studies</td>
<td>SR (with homogeneity ) of cohort studies</td>
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<td>Individual cohort study (including low quality RCT; e. g., &lt; 80% follow-up)</td>
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<td>&quot;Outcomes&quot; research; ecological studies</td>
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<td>Non-consecutive study; or without consistently applied reference standards</td>
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<td>Case-control study, poor or non-independent reference standard</td>
<td>Case-series (and poor quality cohort and case-control studies)</td>
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<td>5</td>
<td>Expert opinion without explicit critical appraisal, or based on physiology, bench research or &quot;first principles&quot;</td>
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Grades of Recommendation

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<tr>
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<td>B</td>
<td>consistent level 2 or 3 studies or extrapolations from level 1 studies</td>
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<td>C</td>
<td>level 4 studies or extrapolations from level 2 or 3 studies</td>
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<td>D</td>
<td>level 5 evidence or troublingly inconsistent or inconclusive studies of any level</td>
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The traditional medical therapies for inflammatory bowel disease (IBD) have been challenged by the recent advent of biologics. The avoidance of steroid dependency and the delay of disease progression over time to surgical resection have been introduced to clinical studies on IBD as stringent secondary outcomes. Whereas traditional therapies either failed to achieve high bar endpoints or solid data are missing, monoclonal antibodies to anti-TNF-alpha are meanwhile established as mainstay in the treatment of moderate to severely active IBD and clearly succeeded in the aim to influence the natural course of disease. New generations of humanized and human monoclonal antibodies directed to TNF-alpha are entering the field nowadays and the current treatment guidelines for IBD advocating a stepwise escalation approach to therapy are coming under scrutiny and soon are likely to be replaced by early positioning of biologics. IBD as a lifelong disease affecting patients from young adulthood or even childhood poses an attractive investment for the biotech industry. The flourishing interest of industry may rather reflect economics than a romantic reality, but for the sake of the patients has elicited an overflowing pipeline of new compounds waiting to be studied in IBD. Even despite some major failure of promising candidates, the quest for the magic bullet has survived and entailed another major achievement, which is a tremendous knowledge base about drug safety on the new therapeutic species exceeding by large what is available from our traditional treatments. But finally, cure of IBD is the goal on that long and winding road our patients are moving, but despite all the industrious efforts still out of sight.
Session IV

Lower GIT
(celiac disease, infection and malignancy)
Celiac disease: Recent developments

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Celiac disease (CD), also known as a gluten-sensitive enteropathy, is a genetically determined, immune mediated, chronic non-infectious enteropathy caused by gluten – a protein found in wheat, rye and barley. There are, therefore, three key components in the development of the disease: gluten, genetic predisposition and an aberrant immune response. Concerning genetic susceptibility, development of the disease is associated with the certain type II HLA i.e. a 95% of the patients carry HLA-DQ2 genes and 3% HLA-DQ8 genes, with a clear gene dose effect as there is a 5-fold increased risk for the development of the disease in homozygote compared to heterozygote patients. However, the fact that only a few genetically susceptible individuals develop CD, although virtually all individuals are exposed to gluten, suggests that the etiology of celiac disease is multifactorial, and that other genetic and environmental factors play a role, being also responsible for its clinical heterogeneity.

Although once thought to occur mainly in childhood, and mostly with the clinical picture of malabsorption and chronic diarrhea, CD is now recognized as a common problem that could be diagnosed at any age. It may present with a wide spectrum of different clinical manifestations affecting various organ systems. Many patients have minimal symptoms and present atypically, and in most adult patients the disease is diagnosed on average 10 years after the first symptoms appeared. Therefore, patients could be first seen by a different specialist such as gastroenterologists, pediatricians, neurologists, psychiatrists, dermatologists, etc. Until recently, it has been considered as a rare condition, but studies have proven that the estimated prevalence is as high as 0.5% to 1%, affecting in Europe approximately 2.5 million of people. However, for each properly diagnosed patient, 5 to 10 remain undiagnosed.

Symptomatic CD associated with a high morbidity and with an increased mortality rate, exceeding that in general population by a factor of 1.9–3.8. As a full histological and clinical remission occurs after gluten is withdrawn from a diet, it is very important to diagnose and start the treatment of the disease on time. For a diagnosis of CD to be made in an adult patient, a typical small intestinal biopsy finding and a clear improvement on a gluten-free diet is required. However, in children below two years of age the procedure is more complicated as there are other conditions which may cause the same clinical picture and have the similar biopsy finding. Therefore, three biopsies of the small intestine are required: i. positive biopsy at disease presentation; ii. normal intestinal finding after a minimum of 2 years of a gluten-free diet; iii. a repeated positive biopsy after a gluten challenge (3–6 months of a normal gluten-containing diet). There are also serologic methods such as measuring IgA antihuman tissue transglutaminase (tTG) and IgA endomysium antibody (EMA) immunofluorescence, both with a high sensitivity and specificity. The roles of the serologic methods are in: a) confirmation of a diagnosis; b) identifying patients in whom biopsy is warranted; c) screening individuals who are at risk; d) following adherence to the gluten-free diet.
The treatment of CD is a strict lifelong gluten-free diet, i.e. not containing wheat, rye or barley. Oat products also need to be avoided due to high risk of contamination with the toxic grains. After 3 to 5 years of the gluten-free diet, excess mortality rate for active CD returns to normal, stressing a special importance of the diet adhearance.

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Gastrointestinal manifestations of AIDS

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Many HIV infected patients have gastrointestinal complications. Major causes of anorexia, nausea and vomiting are medications (especially antiretrovirals, antibiotics, opiates and non-steroid anti-inflammatory drugs), depression, intracranial pathology, gastrointestinal diseases, hypogonadism, pregnancy, lactic acidosis, etc. Treatment of underlying condition is important.

Thrush is presented by white painless plaques on oral mucosa that can easily be scraped off. Because oral candidiasis itself is an opportunistic infection, it is predictive of the disease progression and development of other AIDS-related infections. The cause of aphthous ulcers is unknown. In differential diagnosis herpes simplex virus (HSV), cytomegalovirus (CMV) and drug-induced ulcers should be considered. Anaerobic bacteria cause gingivitis (from linear gingival erythema, necrotizing gingivitis, necrotizing peridontitis to necrotizing stomatitis).

Oral hairy leukoplakia (caused by Epstein-Barr virus) is a raised, white lesion of the oral mucosa, usually seen on the lateral margin of the tongue that can not be scraped off and that not respond to antifungal therapy.

Other oral lesions: the purple-red lesions of Kaposi sarcoma, non-Hodgkin lymphoma (either swelling or ulcers), oral warts, salivary glands may be enlarged by infiltration with CD8+ cells.

The diagnosis of Candida esophagitis is based on presence of thrush, odynophagia, less than 100 CD4 cells/mm³ and good response to treatment. Endoscopy is recommended with atypical presentation or failure to respond to empiric treatment. Beside Candida infection, esophageal diseases in patients with HIV infection could be caused by CMV, HSV or aphthous ulcers.

Diarrhea is defined as at least three loose or watery stools a day. It is helpful to divide diarrheal illnesses into acute, where most patients present almost immediately with symptoms, and chronic, where the symptoms have been present for at least one month and often continue in variable form for many months. It is also helpful to divide the patients with diarrhea into those with a relatively preserved immune system (> 200 CD4 cells/mm³) and those without; in those with > 200 CD4 cells/mm³, most of the causes of virulent infection are easy to diagnose on stool analysis and are treatable or may improve spontaneously. Diarrhea in those with very reduced CD4 counts (< 200 CD4 cells/mm³) and severe immunosuppression is much more likely to be caused by organisms of very limited virulence, is often associated with profound symptoms and weight loss, may not be diagnosed by simple stool analysis and responds poorly to treatment. Diarrhea is medication related (especially protease inhibitors) or pathogen related (bacterial: Salmonella, Shigella, Campylobacter jejuni, Vibrio, Yersinia, Echerichia coli 0157, Clostridium difficile, non-tuberculcus mycobacteriosis; viral: CMV, adenovirus, astrovirus, picornavirus, calicivirus; protozoal: cryptosporidiosis, microsporidiosis, isosporiasis, cyclosporiasis).

The most common identified microbial cause of cholangiopathy (relatively rare diseases, seen primarily in late stage AIDS) is Cryptosporidium, followed by Microsporidia, CMV and Cyclospora.
Major causes of **pancreatitis** are drugs (especially didanosine or didanosine plus zalcitabine; NRTI-associated mitochondrial toxicity; PI-associated hypertriglyceridemia), opportunistic infections (CMV, less common non-tuberculous and tuberculous mycobacteriosis, cryptosporidiosis) and conditions that cause pancreatitis in general population (especially alcoholism; less common gallstones and hypertriglyceridemia). **Hepatic abnormalities** are quite common in HIV-infected population and may be due to viral hepatitis, HIV-related opportunistic infections, medication toxicity (all antiretroviral drugs), alcohol, nonalcoholic fatty liver disease or malignancy (Kaposi sarcoma, non-Hodgkin lymphoma, hepatocellular carcinoma). Communities and populations at high risk for HIV infection are also likely to be at risk for co-infection with **hepatitis B virus (HBV)** or **hepatitis C virus (HCV)**. HIV, HBV and HCV are blood borne pathogens transmitted through similar routes (via injection drug use, sexual contact, from mother to child during pregnancy or birth). Patients infected with HIV are less likely to clear hepatitis C viremia, have high HCV RNA loads and experience more rapid progression of HCV-related liver disease than those without HIV infection. In the era of highly active antiretroviral therapy (HAART), HCV-related liver disease is currently and will continue to be a major cause of hospital admissions and deaths among HIV-infected persons. As such, effective HCV treatment strategies are needed. Treatment with peginterferon plus ribavirin may be effective, particularly for patients with HCV genotype 2 and 3 or those with HCV genotype 1 and a low levels of hepatitis C viral load. Early monitoring of HCV RNA response at treatment weeks 4 and 12 can effectively identify persons with virologic non response to therapy preventing unnecessary exposure to toxicity. HIV infection can accelerate progression of HBV-related liver disease; therefore, treatment of chronic HBV infection is generally recommended for all HBV/HIV-coinfected patients. The best strategy for the management of HBV infection has not been defined, particularly for individuals with chronic HBV infection who do not yet require anti-HIV therapy. For HBV/HIV-coinfected individuals for whom HIV treatment is indicated, most experts recommend the use of an antiretroviral regimen that includes the use of two agents active against HBV (e.g., tenofovir plus emtricitabine or lamivudine). HBV vaccination is indicated for all children and adults who are at increased risk of HBV infection, including HIV-infected patients, patients with multiple sexual partners, men who have sex with men, and patients who engage in IDU.

Various patterns of **abdominal pain** are particularly common in HIV-infected patients. A syndrome of **right upper quadrant** pain is often associated with thickening or dilatation of the bile duct seen on computed tomography or ultrasonography and a raised alkaline phosphatase level. The most common cause of this syndrome is an AIDS related sclerosing cholangitis, the pathology of which is very similar to that of idiopathic sclerosing cholangitis. It is not clear that any treatment helps, although sphincterotomy has been performed sometimes. The pain tends to improve over months or years. **Epigastric pain** may be due to a non-HIV-related condition such as peptic ulcer, but a number of patients with this syndrome have Kaposi’s sarcoma or CMV infection of the distal oesophagus or stomach lining. Lymphoma of the stomach will also produce this pain. **Lower abdominal pain** is often associated with severe constipation and is most frequently caused by opiate use. **Diffuse abdominal pain** often associated with rebound abdominal tenderness may be found in bacterial or CMV causes of diarrhea. **Loin pain** has become a common problem in the era of indinavir use. In up to 4% of patients taking this drug, renal stones occur, composed most commonly of indinavir crystals. Sometimes no stone is found but the patient usually has haematuria or indinavir crystals in the urine.
Wasting syndrome is defined as involuntary loss of at least 10% of original body weight accompanied by persistent diarrhea (at least to bowel movements daily for more than 30 days) or extreme fatigue and/or fever without apparent infectious etiology. Wasting syndrome is an exclusion diagnosis. Weight loss remains an independent risk factor for mortality, even in the era of HAART and every patient should be weighed regularly! The risk for apparent infections is significantly elevated and there is also cognitive impairment in these patients.
Prevention and screening for colorectal cancer

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Colorectal cancer is one of the most commonly diagnosed cancers and a leading cause of cancer deaths in the developed regions of the world. According to the International Agency for Research on Cancer (IARC) estimates, 1,023,000 new cases of colorectal cancer were diagnosed, and 529,000 colorectal deaths were registered worldwide in 2002. Colorectal cancer was the fourth most common cancer diagnose and the fourth most common cause of cancer mortality in men worldwide, whereas in women, it was the third most common cancer diagnose and the fourth most common cause of cancer mortality. In some developed countries, both the incidence and mortality rates for colorectal cancer have been stable and even declining, probably due to primary prevention as well as earlier detection and treatment of adenomatous polyps and non-invasive cancer. However, in other countries that have an improving socioeconomic status, the incidence of colorectal cancer has been rising.

The most important risk factors for colorectal cancer are older age, male gender, diet and poor physical exercise habits, a personal history of inflammatory bowel disease, certain genetic syndromes, and a family history of colorectal cancer or adenomatous polyps. At present, we can deduce that etiology of more than 30% of colorectal cancer is related directly to the environment, namely diet and lifestyle, 15% to the inherited risk factors, namely family history of colorectal cancer and the remainder are the result of interaction between these etiologies. Because the etiology is multifactorial, there is no single major preventable risk factor, neither individual food item nor micronutrient that causes or prevents colorectal cancer, but it seems that lifestyle and diet throughout the entire life are of vital importance. The maintenance of an ideal body weight, promotion of physical activity, reduced consumption of animal fats, and increased consumption of fruits and vegetables have salutary effects beyond the primary prevention of colorectal cancer.

A prolonged use of non-steroidal anti-inflammatory drugs, COX-2 inhibitors and aspirin is associated with reduced risk of colorectal cancer, but there are no recommendations for their use, and chemopreventive drugs are currently no substitute for screening the general population or surveillance of risk groups. Colorectal cancer screening and case-finding can prevent the development of colorectal cancer and reduce the risk for deaths. Four randomized trials have shown that fecal occult blood testing (FOBT) is effective in lowering colorectal cancer mortality rate (15–33%) and its incidence in individuals who undergo screening. FOBTs available for screening are based on two principal technologies: chemical tests and immunochemical tests. The chemical tests use guaiac to detect the peroxidase activity of heme; so, they react to any peroxidase in feces (e. g. plant foods and heme in red meat) and are affected by certain chemicals (e. g. vitamin C). These tests may detect bleeding from any site of gastrointestinal tract. The fecal immunochemical tests use antibodies specific for human globin; so they are not affected by diet and are highly selective for occult bleeding of colorectal origin. Although the sensitivity of a single FOBT is low, in the range of 30–50%, a program of repeated annual testing can detect as many as 92% of cancers. After 18 years of follow-up in the Minnesota trial, FOBT screening performed every year was found to reduce colorectal cancer mortality by 33% and every other year by 21%, a rate...
consistent with the results of the biennial screening in the European trials. Furthermore, in a recent FOBT screening in 478,250 residents of the pilot areas in England and Scotland, the overall positive tests was 1.9% and the rate of detecting cancer was 1.62 per 1000 screened people. The positive predictive value was 10.9% for cancer and 35% for adenoma. Of 552 colorectal cancers detected by screening, 48% of all screen-detected cancers were stage I, and only 1% metastasized at the time of diagnosis. Despite the cost of FOBT screening, it has been accepted as feasible for national health care. The main disadvantages of FOBT screening being its low compliance rate for the first and repeated screening (20–70%) as well as its moderate sensitivity for detecting colorectal cancer and low sensitivity for polyps. The FOBT screening performed every year and combined with flexible sigmoidoscopy every 5 years is more effective than either of the methods alone. However, despite FOBT may be less sensitive for distal colon lesions, both methods together do not greatly improve the detection rates for proximal lesions. The disadvantage of this type of screening are inconvenience, high cost and complications with an uncertain gain in effectiveness. Although there are no randomized studies evaluating whether screening colonoscopy alone reduced the incidence and mortality from colorectal cancer, several guidelines have included colonoscopy as a screening option. Colonoscopy has a proven high sensitivity for detecting polyps and carcinomas of the whole colon. One meta-analysis found perforation rates between 0.06% and 0.2% and mortality between 0% and 0.06% for diagnostic colonoscopy. The choice of a 10-year interval between screening colonoscopies for people at average risk is based on the estimates of the sensitivity of colonoscopy and the rate at which advanced adenomas develop. Double contrast barium enema is less sensitive for the detection of polyps and cancer than colonoscopy. The procedure does not permit removal of polyps or biopsy of cancer and, if polyps and cancer are suspected, an additional colonoscopy has to be performed. Computed tomography colonography and magnetic resonance imaging colonography or virtual colonoscopy have also been evaluated as possible colorectal cancer screening methods. However, due to many disadvantages and higher cost at that time, the use of virtual colonoscopy outside of clinical trials cannot be recommended. Genetic stool testing (e. g. fecal DNA testing) every 5 years was considered to be effective compared to no screening, but inferior to other screening strategies. In 2003, the European Commission issued the recommendations for screening for breast, cervical and colorectal cancer valid in all member countries. The Republic of Slovenia adopted this program and national guidelines for colorectal cancer screening were published. Following the experiences of the 13 EU countries that have a well organized screening program for colorectal cancer, e. g. Finland, France, Great Britain and Spain, we will very soon start with organized screening for colorectal cancer by using immunochemical fecal occult blood test. Organized colorectal cancer screening has greater potential to reduce cancer incidence and mortality due to higher achievable levels of population coverage, follow-up and quality compared with opportunistic screening. However, due to low compliance for colorectal screening in many EU countries, only improved awareness and knowledge of general population about the colorectal cancer risk factors and the benefits of screening can improve compliance.
The integration of new agents in the management of patients with metastatic colorectal cancer

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The management of patients with metastatic colorectal cancer (CRC) has changed dramatically over the last five years, with increasing chances of prolonged survival. Many factors have certainly contributed to this progress. Until the mid-1990’s the only available drug, with limited activity in metastatic CRC, was 5-fluorouracil (5-FU). The development of the cytotoxic agents irinotecan, oxaliplatin and capecitabine and of the biological agents cetuximab, panitumumab and bevacizumab has clearly increased the therapeutic options for patients with metastatic colorectal cancer. It has been shown in randomized phase III trials that bevacizumab, when combined with irinotecan plus bolus 5-FU/LV (IFL) in the first-line treatment of metastatic CRC and with FOLFOX in second-line treatment leads to an increased median survival, progression-free survival (PFS) and response rate compared to the cytotoxic chemotherapy alone. Moreover, it has been demonstrated in a few randomized phase II studies and in a combined analysis of these phase II studies that bevacizumab increases the activity of 5-FU/LV in the first-line setting. It has been shown also in phase II studies that the combination of 5FU/LV/oxaliplatin and bevacizumab leads to a high activity. The recent randomized phase III study of FOLFOX compared to capecitabine plus oxaliplatin ± bevacizumab in the first-line treatment shows that capecitabine is as effective as IV 5-FU/LV when combined with oxaliplatin and that bevacizumab increases the progression free survival of the fluoropyrimidine/oxaliplatin combination. The data from phase 2 studies with irinotecan and capecitabine (without bevacizumab) show also a high activity, although more uncertainty remains on the optimal dose of this combination in view of some reports of higher toxicity of the combination capecitabine plus irinotecan.

Cetuximab is active in epidermal growth factor receptor (EGFR)-expressing irinotecan refractory metastatic CRC. The combination of cetuximab with irinotecan is more active in this setting than cetuximab alone. The combination of cetuximab plus irinotecan leads to an increased RR (23 vs. 11%) and TTP (4.1 vs. 1.5%) compared to cetuximab alone in irinotecan-refractory CRC. It has been shown also that panitumumab, a human monoclonal antibody against the EGFR is active in irinotecan- and oxaliplatin-refractory metastatic CRC. The response rate of the anti-EGFR antibodies cetuximab and panitumumab as single agent in EGFR expressing chemorefractory CRC is consistently around 10%. In a large phase III trial it was shown that panitumumab increased significantly the progression free survival compared to best supportive care in EGFR expressing metastatic colorectal cancer refractory to oxaliplatin and irinotecan. In another large randomized trial of cetuximab versus best supportive care, cetuximab prolonged the progression free survival as well as the survival. Phase II trials with monoclonal antibodies against the EGFR in combination with cytotoxic combinations in the first line treatment of metastatic colorectal cancer have indicated that these combinations are active in patients with EGFR expression.
colorectal cancer show promising efficacy data. Phase III trials are ongoing. The Crystal study randomizing patients between FOLFIRI ± cetuximab will be reported in 2007.

With this information in mind, bevacizumab is often used in clinical practice in combination with an active cytotoxic regimen in the first-line treatment of metastatic CRC (FOLFIRI or FOLFOX) and cetuximab plus irinotecan in chemorefractory CRC, at least if patients are fit and if there are no contraindications for these therapeutic options.

Many open questions and challenges remain in relation to the use of the anti-VEGF and anti-EGFR antibodies in metastatic CRC. Answers are needed to optimize the outcome for patients and the more optimal use of the resources. A crucial challenge is to demonstrate which patients are more likely to respond to bevacizumab-containing regimens and to the anti-EGFR antibodies cetuximab and panitumumab. Until now, large studies validating molecular markers that are useful in the prediction of response to anti-EGFR antibodies are not yet available in metastatic CRC. The clinical studies evaluating the activity of cetuximab and panitumumab have been carried out in EGFR-expressing tumors, as determined by immunohistochemistry (IHC). The intensity of EGFR immunostaining is not related to antitumor activity, and a clinical benefit has also be noted in patients whose tumors had no EGFR immunostaining. EGFR gene mutations have not been demonstrated to play a role in the response prediction in CRC. Although it has been reported in a small study that EGFR gene copy number, as assessed by fluorescence in-situ hybridization (FISH), correlates with the propensity of CRC to respond to EGFR-directed antibodies, this finding is at the moment very controversial. In a few other small studies K-ras mutations were associated with low activity to cetuximab.

A second important challenge is the strategic questions on the best combination, on the best sequence and on the most optimal use of the different cytotoxic agents in combination with the biologicals in CRC. Data from several small phase II trials have shown a high RR, a long TTP and a long median survival in the first-line treatment of metastatic CRC when cetuximab is combined with 5-FU/LV plus irinotecan or 5-FU/LV plus oxaliplatin. These clinical data, as well the preclinical data suggesting an at least additive effect of anti-VEGF and anti-EGFR antibodies, have led to the design of trials looking at the activity of bevacizumab plus cetuximab or panitumumab in combination with cytotoxic regimens, with the hope of further increasing the survival of patients of patients with metastatic CRC.. It will, therefore, certainly be more important to look for the population or group of patients who benefit most from the combination of a doublet of biologicals, so that health resources can be used as rationally as possible. An important challenge is the understanding of the mechanism why tumors that initially respond to a combination of cytotoxics and biologicals may become resistant to this combination.

In conclusion: the biologicals have clearly increased the therapeutic armamentarium of patients with metastatic colorectal cancer and offer also prospects for an increased chance of a longer survival. The major challenge is now to implement strategies in which patients can be selected, based on molecular characteristics and/or pharmacogenomic profiles so that the new drugs and the resources can be used optimally for our patients with metastatic colorectal cancer.
Key references:


Lymphomas of the gastrointestinal tract

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The gastrointestinal tract (GIT) is the most frequently involved extranodal localisation, representing 30–40% of extra-nodal lymphomas and from 4–20% of all NHL cases. In western countries, the most common location is the stomach (approximately 50–60%), followed by the small intestines (30%) and the large intestine (around 10%). Involvement of the esophagus is very rare. These proportions can differ geographically, with small intestinal lymphomas being more common in the Middle East. The most common histological subtype in localized GIT presentations is diffuse large B-cell lymphoma which is present in approximately 60% of the gastric and 70% of the intestinal cases. MALT lymphoma represents about 35% of primary gastric lymphoma but less than 10% of the intestinal ones. Follicular lymphomas are very rare in the stomach but have been reported in up to 17% of intestinal cases. The other histological subtypes include T-cell lymphomas, Burkitt’s lymphoma and mantle cell lymphomas (which in the GIT often present as a multiple lymphomatous polyposis) and are much less common and taken together comprise approximately 5% of the cases. The incidence of gastrointestinal lymphoma may have increased over the past decades. This is likely due to an actual increase but more efficient case registration and improved diagnostic tools have also played a role. There are important geographical variations in the incidence rates of GIT lymphomas, perhaps correlated to the rate of *Helicobacter pylori* (HP) gastric infection in the examined regions. Less consistent epidemiological information is available on intestinal lymphoma. Patients with celiac disease have an increased risk of developing ETCL, although the risk in the most recent studies seems lower than previously thought.

In the past, surgery was considered an essential component of the diagnostic work-up in view of the fact that it provided adequate tumor specimens for diagnosis. However, sufficient material for diagnosis is nowadays obtained in more than 90% of cases by endoscopic biopsy and diagnostic surgery, at least in gastric lymphomas, is not anymore needed. Imaging techniques have also significantly improved and, in the past decade, the introduction of endoscopic ultrasonography has been proven to be useful in assessing the depth of the stomach wall infiltration and the presence of perigastric lymph nodes and in identifying patients at high risk of bleeding and/or perforation. In MALT lymphomas, deep infiltration of the gastric wall is associated with a greater risk of lymph-nodal positivity and a smaller chance of response to antibiotics only.

Until the late 1980s surgical resection with postoperative radiotherapy and/or chemotherapy was standard. However, it has been later clearly shown by several studies that chemotherapy alone or chemotherapy followed by radiotherapy may produce similar results and that gastrectomy is thus redundant. In a recent large German study, 393 with localized primary gastric lymphoma were treated with radiotherapy and/or chemotherapy only or additional surgery. The survival rate at 42 months for patients treated with surgery was 86% compared with 91% for patients without surgery. Hence, the need for surgery for diagnostic purposes has disappeared, at least for the gastric tumors, and the assumption of an increased risk of perforation and bleeding associated with front-line chemotherapy, for which
‘debulking surgery’ was carried out preventatively has not been confirmed in any modern series. On the contrary, several studies have reported a high degree of post-surgical complications that resulted in a delay in the start of chemotherapy and surgical resection has been replaced by conservative therapeutic approaches for gastric lymphomas. For primary intestinal lymphoma, however, there are no studies clearly demonstrating that surgery is unnecessary. Optimal treatment of gastrointestinal lymphomas depends mainly on the histological type, but also on the site and the stage of the disease.

**Diffuse large B-cell lymphoma of the stomach**

Diffuse Large B-Cell Lymphoma (DLCL) represents the most common histological type among GI lymphomas. Patients with locally advanced or disseminated aggressive GI lymphomas appear to behave in the same manner as other advanced lymphomas, with comparable histology and prognostic factors. Therefore, treatment of disseminated DLCL is today based on chemotherapy combined with rituximab. In general, the same guidelines followed for nodal DLCL can also be applied to GI lymphomas with aggressive histologies.

**Marginal zone B-cell lymphomas of the GIT**

Gastric MALT lymphoma is often multimodal within the stomach but is characterised by an indolent natural history and prolonged confinement to the site of origin in most cases. Epidemiological evidence of a plausible etiologic correlation between gastric MALT lymphomas and chronic *Helicobacter pylori* infection has been found; clinical studies demonstrated histological regressions of gastric MALT lymphoma after eradication of *H. pylori* in the majority of the patients who received antibiotic therapy. Nowadays, it is generally accepted that eradication of *H. pylori* with antibiotics should be the sole initial treatment of MALT lymphomas confined to the gastric wall. A strict follow-up after antibiotics is highly advisable, also because it is not possible to completely exclude the presence of a concomitant aggressive diffuse large B-cell lymphoma not demonstrated in the diagnostic gastric biopsies. Post-antibiotic molecular follow-up studies showed in about half of the cases a long-term persistence of monoclonal B-cell after histological regression of the lymphoma but this event is not necessarily heralding a relapse, and its clinical significance remains unclear. For the management of the subset of *H. pylori*-negative cases and for the patients who fail antibiotic therapy a choice can be made between conventional oncological modalities. Very good disease control using radiation therapy has been reported by several institutions. Surgery has been widely and successfully used in the past, but the precise role for surgical resection should be redefined in view of the excellent results achieved with conservative approaches. Patients with systemic disease should be considered for systemic treatment but only few anti-cancer compounds and chemotherapy regimens have been tested specifically in MALT lymphomas. The anti-CD20 monoclonal antibody rituximab also very active and may represent an additional option for the treatment of systemic disease.

IPSID, alpha heavy chain disease, and Mediterranean lymphoma all refer to the same condition, which is presently considered a variant of low-grade MALT lymphoma, characterized by a diffuse lymphoplasmacytic/plasmacytic infiltrate in the small intestine. Most of the cases have been described in the Middle East, especially in the Mediterranean area where the disease is endemic, affecting young adults. Patients usually present with poor performance status and severe malabsorption.
Several authors have reported that treatment with antibiotics can produce clinical, histological and immunologic remissions in early stages.

**Multiple lymphomatous polyposis**
This is a peculiar type of lymphoma presenting with multiple lymphomatous polyps of the GIT. In most cases it represents the intestinal form of mantle-cell lymphoma. The prognosis is quite poor in spite of aggressive chemotherapy, similar to its nodal counterpart. In rare instances multiple polyposis appears as a clinical syndrome produced by different histological subtypes other than mantle cell, thus, the term multiple lymphomatous polyposis should not be used to define a histopathological entity.

**Primary intestinal lymphomas**
The majority of primary intestinal lymphomas are large cell tumors of B-cell lineage, but distinct histological presentations can include intestinal MALT lymphoma or IPSID, enteropathy associated T-cell lymphoma, mantle cell lymphoma, or follicular lymphoma underscoring the importance of skilled histological diagnosis. The management of large B-cell lymphoma is usually with surgery followed by chemotherapy (which is today usually combined with rituximab). In patients where complete tumor resection is not feasible, treatment is the same above described for the gastric localizations. The outcome reported in the literature varies depending on the extent of disease and histology. In a large series of intestinal lymphomas, a 60-75% 5-year survival for patients with B-cell lymphomas is reported but only a 25% 5-year survival for those with T-cell tumors

**Enteropathy-type T-cell lymphoma (ETCL)**
According to the WHO classification, ETCL is a tumor of intraepithelial T-lymphocytes; it usually occurs in the sixth or seventh decades but there have been sporadic reports of cases in young adults. Abdominal pain and/or exacerbation of enteropathy-associated symptoms (malabsorption, loss of responsiveness to a gluten-restricted diet) are the most common presentation features. Approximately 25% of cases present with an intestinal perforation. The clinical course is often very unfavourable.

**Gastrointestinal Burkitt’s lymphoma**
A common childhood lymphoma but very rare in adults, sporadic Burkitt’s lymphoma, often presents with abdominal pain and intussusception. The ileocecal region is the most common site of involvement and most cases are primarily intestinal. The histological and cytogenetic features are similar to those of the classical endemic African form, as is its association with the Epstein-Barr virus. The primary treatment modality is intensive combination chemotherapy. Local and locoregional therapy alone (i.e., surgery and radiotherapy) does not provide adequate treatment, even for patients with localized disease. Surgery remains important for establishing the diagnosis and should also be considered in the presence of a completely resectable mass.
Session V

Clinical challenges in liver diseases
Do we still need liver biopsies?

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Liver biopsies are obtained as a diagnostic measure either to evaluate diffuse liver diseases or focal liver processes. The indication for a diagnostic biopsy is set up by the clinician and a biopsy will only be performed, when the expected gain of information is of significant impact for therapy (planning) and/or prognosis evaluation and cannot be achieved by an easier, cheaper, non-invasive procedure.

In the evaluation of focal liver processes biopsy is not required for some lesions such as Hemangioma and Focal Nodular Hyperplasia, in which the radiological picture is generally diagnostic. It is indispensable for evaluating malignant disease and unsurpassed by any method, since it is the only diagnostic technique to definitely reach the diagnosis. Under these circumstances the biopsy does not only type the disease (benign vs. malignant; primary vs. metastasis, definitive entity) but increasingly provides molecular therapeutic information in metastatic disease, such as breast cancer, GIST, and neuroendocrine carcinoma. A crucial point is whether the biopsy comprises the lesion to a sufficient extent. Only when a definite diagnosis does not imply therapeutic consequences, biopsy may not be necessary; whether planned tumor resection is a valid reason to omit biopsy evaluation is a current matter of debate; biopsy channel metastasis is not a valid argument, since it is rare and has not been shown to influence patient survival.

In diffuse liver diseases liver biopsy is mandatory in any kind of chronic liver disease that remains unclarified in regard to etiology and/or disease progression. In chronic viral hepatitis and steatohepatitis (ASH and NASH) biopsy is superior to any other technique for evaluating disease activity and fibrosis and is thus regarded the gold standard by all consensus conferences. Whether new methods of fibrosis evaluation will change this point of view, will have to be evaluated by controlled trials using biopic evaluation as the reference point. In chronic biliary diseases the role of biopsy is of less impact, since disease activity is more focal, especially in PSC. Biopsy has its role in establishing the type of disease in cases of unclear clinical context, monitoring disease progression, and evaluating conflicting morbidity and autoimmune overlap syndromes. Underestimated is the potential of liver biopsy in the diagnosis of late onset hereditary diseases (α₁-AT-deficiency, genetic iron storage diseases, congenital hepatic fibrosis etc.) and hepatic drug toxicity; in these conditions, etiology frequently remains unclear and only biopsy will help to clarify etiology and extent of the disease.

Questions regarding the value of liver biopsy in the diagnostic process have referred mainly to three points: lack of representativity for the process, intra- and interindividual variability in the evaluation, and lack of significant and standardized information. Large studies have proven that intra- and interobserver variability does exist but is relatively low for experienced liver pathologists and does not afflict the diagnostic superiority of the biopsy. Representativity is certainly an issue e.g. in biliary diseases and crucially depends on the quality and amount of biopsy tissue obtained. Furthermore overall diagnostic power of the biopsy crucially depends on the clinical and serological informations provided together with the biopsy, a meticulous work-up of the biopsy by an experienced pathologist, and the possibility of clinicopathological interaction making the quality of liver biopsy evaluation a true interdisciplinary task.
Microenvironment and cancer: Inflammation, cytokines, microRNA and p53

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Free radicals are ubiquitous in our body and are generated by normal physiological processes, including aerobic metabolism and inflammatory responses, to eliminate invading pathogenic microorganisms (1). Because free radicals can also inflict cellular damage, several defenses have evolved both to protect our cells from radicals – such as the p53 pathway and antioxidant scavengers and enzymes – and to repair DNA damage (2). Free radicals can cause an adaptive increase in certain of the protective base excision repair enzymes. Paradoxically, if the increase in enzymes is imbalanced, e.g., the DNA glycosylase is increased more than the apurinic endonuclease, frameshift mutations occur as a novel etiology of microsatellite instability (3). Understanding the relationship between chronic inflammation and cancer provides insights into the molecular mechanisms involved. In particular, we highlight the interaction between nitric oxide and p53 as a crucial pathway in inflammatory-mediated carcinogenesis.

MicroRNA (miRNA) expression profiles for lung cancers were examined to investigate the miRNA involvement in lung carcinogenesis (4). miRNA microarray analysis identified statistical unique profiles, which could discriminate lung cancers from noncancerous lung tissues as well as molecular signature that differ in tumor histology. miRNA expression profiles correlated with survival of lung adenocarcinomas including those classified as disease stage I. High hsa-mir-155 and low hsa-let-7a-2 expression correlated with poor survival by univariate analysis as well as multivariate analysis for hsa-mir-155. The miRNA expression signature on outcome was confirmed by real-time RT-PCR analysis of precursor miRNAs and cross-validated with an independent set of adenocarcinomas. Similar studies are ongoing using human liver, colon and esophageal cancer. These results indicate that miRNA expression profiles are new class of diagnostic and prognostic markers of human cancer.

The balance of pro- and anti-inflammatory cytokines within cancers and in the tissue macroenvironment also predicts lung and liver cancer diagnosis and prognosis (5, 6). Current studies are investigating the mechanistic interactions between these cytokines and microRNAs.
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Session VI

Viral hepatitis
New insights in the immunology of viral hepatitis B and C

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Protection from viral infections requires the co-ordinate activation of the different elements of innate and adaptive immunity. The innate immune system (Type I IFNs, NK cells, dendritic cells) has a role in protecting the host during the initial period of virus infection by directly reducing replication and virus spread. Its activation is also essential for the proper functional activation and expansions of the different elements (helper and cytotoxic T-cells, B-cells) of the adaptive immune response, which are required to achieve successful virus control and long-term protection of the host.

I will follow the kinetics of the virological and immunological events occurring during HBV and HCV infection in humans to illustrate the interplay between innate and adaptive immunity and how the early events after infection might influence the development of the adaptive immune response necessary to protect the host from viral infections. I will then review the quantitative and qualitative defects that affect HBV and HCV-specific T cells in patients with chronic infections. Persistent exposure to viral antigens, often lead to deletion or to functional impairment of virus-specific T-cells which have been show to express high levels of programmed death 1 molecule (PD-1). Since blocking of PD-1 engagement with his ligand (PD-L1) leads, in animal model of chronic viral infection, to an enhancement of virus-specific T-cell function and to a recovery of infection, the expression patterns of PD-1 molecules and the functional consequences of its blockage on HBV and HCV-specific CD8+ T-cells present in hepatitis B and C chronic patients will be discussed.
HBV-associated liver cirrhosis and cancer are among the most common diagnoses leading to liver transplantation in the western world. While viral elimination (i.e. HBs seroconversion) is rarely accomplished by current treatments, progression of liver disease can be halted by timely diagnosis and start of treatment. Pegylated interferons are the only drugs so far offering HBe-positive or -negative patients a chance of long-term virological and histological response after a timely limited treatment course. However, 60–70% of patients will not respond or relapse and therefore need alternative therapies. Nucleos(t)ide analogues are thus increasingly becoming the mainstay of HBV treatment owing to their excellent antiviral potency and tolerability. Main limitations are the lack of viral elimination and the development of resistance mutations on long-term treatment. As these counteract the therapeutic effect and mediate resistance against different substances of the same class, development of resistance should be avoided as possible. As lamivudine resistance is developing extraordinarily fast and common, adefovir and entecavir became the choice for first line treatment. However, further new drugs are under clinical development. Entecavir offers the highest barrier in nucleoside-naive patients and therefore represents the drug of choice in patients with high viremia or progressive liver disease (i.e. liver cirrhosis). The emergence of viral resistance is suggested by a reincrease of viral load by more than 1 log from the nadir under current treatment. Substance specific mutations can be detected by PCR and are helpful to direct further treatments. In case of lamivudine resistance, the combination of lamivudine with adefovir is more active than a switch to adefovir monotherapy. In case of adefovir resistance, lamivudine or entecavir should be added. The role of upcoming new nucleos(t)ide analogues within the already existing therapeutic repertoire will have to be established.
New aspects of treatment of HCV

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Pegylated interferon alfa in combination with ribavirin administered for 48 and 24 weeks has been approved as standard antiviral treatment in patients with HCV genotype 1 (4–6) and 2/3 infection, respectively, in many countries. Different virus- and host-related baseline parameters are known to predict the probability of sustained virologic response including HCV genotype, HCV viral load, gamma-glutamyltranspeptidase (GGT) levels, age and liver fibrosis. While HCV genotype 2, 3-infected patients are generally treated for 24 weeks, management of therapy is based on early discontinuation rules in HCV genotype 1 infected patients with a low or no chance of further sustained virologic response. Thereby, a decline of less than 2 log_{10} steps at week 12 in comparison with baseline (early virologic response, EVR) and detectable HCV RNA at week 24 by a sensitive assay (detection limit ≤ 50 IU/ml) can be safely used as stopping rules with predictive values of 98–100% for virologic non-response. Future developments are aiming for individualization of treatment duration based on HCV RNA concentrations before initiation of therapy and decline early during therapy. Rapid virologic response (RVR) defined as undetectable HCV RNA at week 4 of therapy (≤ 50 IU/ml) together with low baseline viral load (≤ 600,000 IU/ml) were introduced as parameters for shortening of treatment duration in HCV genotype-1 infected patients without a loss of the probability of sustained virologic response. Vice versa in patients with a slow virologic response which become HCV RNA-negative at the first time at week 24 of therapy prolongation of treatment duration to 72 weeks seems to be associated with increased sustained virologic response rates. Similar in HCV genotype 2/3 infected patients reduction of treatment duration from 24 to 12–16 weeks was investigated in different clinical trials. However, in several studies shortening therapy to 12–16 weeks higher relapse rates were reported and future trials are needed to define subgroups of patients with specific baseline parameters (e.g. genotype, viral load, degree of fibrosis) and RVR at week 4 for a safe reduction of treatment duration.
Chronic inflammation, apoptosis and hepatocarcinogenesis

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Chronic inflammation and cell death by apoptosis are cardinal features of chronic liver and biliary tract diseases. Chronic inflammation constitutes a mutagenic environment and apoptosis enhances cell turnover. The combination of cell turnover in a mutagenic environment predisposes to the development of hepatocellular and biliary tract cancers. Elegant studies have now demonstrated that inhibition of cell survival pathways, such as those initiated by NF-κB, promote liver cell carcinogenesis. It is presumed that the inhibition of cell survival pathways promotes cell deletion by apoptosis thereby enhancing cellular replication. Perhaps the recruitment and/or propagation of stem cells in this replicative environment enhances the carcinogenicity of chronic inflammation coupled with increased apoptosis. In the biliary tract, the mutagenic environment can be traced to nitrosative and oxidative stress. The accumulation of 8-oxodeoxyquarine, a marker of oxidative damage to DNA, is clearly enhanced in chronic inflammatory diseases of the liver and biliary tract. The activation of developmental signaling pathways such as NOTCH and perhaps WNT, contributed to the increased cell proliferation. Within the early carcinogenesis compartment itself, apoptosis must ultimately be blocked for the cells to undergo malignant transformation. In the biliary tract, an expression of the anti-apoptotic protein Mcl-1 is strongly enhanced by a multitude of mechanisms. These data have implications for chemopreventive therapy of hepatocellular and biliary cancers. Inhibition of liver injury such as with caspase inhibitors may actually be anticarcinogenic as has been shown in the transgenic hepatitis B surface antigen expressing mouse. Ways to circumvent Mcl-1 cytoprotection may prove to be therapeutically useful in the treatment of hepatobiliary tract and hepatocellular carcinomas such as the use of GX-15-070.
Session VII

Metabolic and autoimmune liver injury
NASH: Metabolic syndrome of the liver

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Non-alcoholic steatohepatitis (NASH) is part of the spectrum of Non-Alcoholic Fatty Liver Disease (NAFLD) that ranges from simple steatosis through to NASH and ultimately cirrhosis. NAFLD is strongly associated with obesity, insulin resistance and dyslipidaemia and accordingly is considered to be the liver manifestation of the metabolic syndrome. It is extremely common, occurring in up to 30% of the normal population and in more than 70% of patients, with obesity and type 2 diabetes. The most common presentation of patients with NAFLD is incidental abnormal liver blood tests although fatigue and right upper quadrant are often present on direct questioning. The vast majority of patients with NAFLD have normal liver function tests. The diagnosis is usually one of exclusion, along with a compatible ultrasound. Older patients (> 45 yrs) with type 2 diabetes and with an AST/ALT ratio > 1 are more likely to have advanced disease and may require liver biopsy to provide prognostic information. NAFLD almost certainly accounts for the majority of cases of cryptogenic cirrhosis. Importantly, once patients with NAFLD develop cirrhosis they have a 50% chance of requiring a liver transplant or dying a liver related death within five years and a one in ten chance of developing hepatocellular carcinoma. NAFLD may be a contributory cause of insulin resistance, metabolic syndrome, type 2 diabetes and even associated cardiovascular disease. The management of NAFLD consists of treating the individual components of the metabolic syndrome which has a significant impact on mortality and will almost certainly improve the liver disease, although data from large randomised controlled trials are currently lacking. At present the best evidence exists for weight loss by diet and exercise, obesity surgery for morbidly obese patients, metformin and glitazones. Patients with advanced disease should be screened for the development of liver cell cancer and offered liver transplantation when indicated. It is important that the components of the metabolic syndrome are actively treated before and following liver transplantation since there is a high risk of disease recurrence.
Mechanisms of liver injury and fibrosis due to iron and copper

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Iron and copper are essential micronutrients for humans. The capacity of readily exchanging electrons in aerobic conditions makes them ideal bio-catalysts of oxidation-reduction reactions that are fundamental for life. Iron is involved in DNA synthesis and transport of oxygen; copper in antioxidant defenses, catecholamine formation and pituitary peptide hormone maturation. Both are essential for terminal enzymes of electron transport and oxidative phosphorylation in mitochondria as well as collagen metabolism. Paradoxically, their own chemistry sets the basis for their toxicity: the versatility for catalysing chemical reactions may lead to uncontrolled production of toxic free radicals responsible for oxidative stress, cell damage and fibrogenesis. The liver, a central organ in the metabolism of both iron and copper, is also a main target of their toxicity. In recent years, the number of proteins implicated in iron and copper homeostasis has increased dramatically; and genetic causes have apparently been identified for the major disorders associated with tissue iron and copper overload. Hemochromatosis (HC) and Wilson disease (WD) represent the prototypic hereditary disorder of iron and copper metabolism, respectively.

HC was originally considered an unusual autopsy finding that was probably alcohol-related. Over a century later, it was finally recognized as a hereditary disorder caused by mutation of an HLA-linked protein thought to be involved in intestinal iron transport. Soon after the identification of HFE as “the cause” of the disease, other apparently unrelated hemochromatosis proteins emerged. In addition, it gradually became clear that HFE played no direct role in intestinal iron transport. The definition of hemochromatosis and its pathogenesis has become increasingly confusing, particularly for clinicians. As we recognize it today, HC results from the non-linear interaction of pathogenic mutations in a variety of genes involved in hepcidin synthesis/activity, the iron hormone, and environmental factors, such as alcohol (1). The most common form of HC (prevalence of genetic predisposition to the disease is 5/1000) is characterized by gradual iron accumulation potentially leading to organ disease, particularly liver cirrhosis, during the 4th–5th decades of life. This adult-onset form is usually caused by pathogenic mutations in the HFE gene (2), or, in rarer cases, in the gene encoding the serum transferrin receptor 2, TfR2 (3) or, even more rarely, ferroportin (FPN). In the phenotypic form known as juvenile hemochromatosis iron loading occurs at a greatly accelerated rate: individuals are more likely to present with cardiomyopathy and/or endocrine disease. This form is usually due to hemojuvelin, HJV, mutations (4), a bone-morphogenic protein co-receptor required for hepcidin transcription (5). The precise function of HFE and TfR2 is currently unknown, but patients with pathogenic mutations in these genes seem also to produce inappropriately low levels of hepcidin. Finally, rare cases of juvenile hemochromatosis have also been linked to mutation of the hepcidin gene (HAMP) itself (6).
WD is an autosomal recessive disorder of copper metabolism characterized by impaired copper biliary excretion and reduced copper incorporation into ceruloplasmin (7). This leads to copper accumulation into the liver and, consequently, to progressive liver damage. Subsequent overflow of copper determines accumulation in other organs mainly in the brain, kidneys, and cornea. WD is caused by disease-specific mutations of the copper transporting ATPase, ATP7B. In most populations, WD has a prevalence of approximately 1:30,000 with a carrier frequency of 1 in 90 (8). Approximately 300 mutations have been found in WD patients including single base insertions and deletions, frame-shifts and missense, nonsense and splice site mutations (http://uofa-medical-genetics.org/Wilson). The large number of mutations and high prevalence of compound heterozygotes reported to date render genotype-phenotype correlation analysis difficult. The diagnosis is established by clinical and biochemical means, though advances in molecular diagnostics will someday permit de novo diagnosis. The patient may present with hepatic, neurologic, or psychiatric symptoms, or a combination of these. As in the case of HC, both environmental and extragenic effects contribute to the varied of phenotypic presentations of this disease. Patients can be treated effectively with chelating agents or zinc salts, or with liver transplantation (9). Liver cell transplant and gene therapy offer potential cures for this disorder, but at present only data from preclinical studies on animal models are available.

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Autoimmune hepatitis

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Autoimmune hepatitis (AIH) is a necroinflammatory liver disease of unknown etiology that occurs in children and adults of all ages. Although the pathomechanism of the disease is still unknown, an underlying genetic predisposition has been suggested due to the fact that patients are predominantly of female gender (women to men ration equals to approximately 6:1) and the association of the disease with certain human leucocyte antigens (HLAs), particularly B8, DR3; DR4. In addition, further autoimmune disorders such as Hashimoto thyreoditis are frequently found in AIH patients. Consensus about ist definition and diagnostic requirements have been formulated (1). Autoantibodies (ANA, SMA, LKM, SLA/LP), the absence of viral hepatitis and a selective IgG elevation are key laboratory findings. However, there is no single test proving the diagnosis of AIH (an exception could be anti-SLA/LP autoantibodies). Therefore, liver histology remains of central importance. Since percutaneous liver biopsy is afflicted with a high sampling error with respect to the staging of fibrosis and cirrhosis we frequently perform (mini-)laparoscopic guided liver biopsy in AIH patients.

If untreated, severe AIH has a very high mortality rate of up to 50% after 3-5 years of diagnosis (2). Immunosuppressive therapy with corticosteroids, usually in combination with azathioprine is considered the gold standard to induce and maintain remission and at the same time response to immunosuppressive therapy confirms the diagnosis of AIH. The therapeutic goal should be complete normalisation of transaminases since progression to liver cirrhosis may occur in patients with remaining inflammatory activity within the liver. On the other hand side-effects of therapy should be acceptable. Under immunosuppression the vast majority of patients achieve complete remission. In patients that do not respond sufficiently to immunosuppressive therapy the diagnosis of AIH should be reevaluated. In some patients an overlap-syndrome of AIH with primary biliary cirrhosis or primary sclerosing cholangitis can be a reason for insufficient response to immunosuppression.

For some reason the development of hepatocellular carcinoma is a very rare complication in patients with AIH, even though many patients have established liver cirrhosis at the time of diagnosis and although patients are immunosuppressed. This fact might give further insight in the pathogenesis of liver carcinogenesis. Although AIH runs a very chronic course with relapses under therapy (if immunosuppression is rapidly reduced) and particularly after discontinuation of immunosuppressive therapy long-term prognosis of AIH patients is excellent provided close medical surveillance and/or treatment (3).
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Immunological considerations of primary biliary cirrhosis and primary sclerosing cholangitis

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The most difficult issue in autoimmune disease is the problem of cau sation. Although there has been considerable progress made on dissection of the effector mechanisms involved in immunopathology, there is still an enormous intellectual gap with respect to etiology. Clearly there is a genetic predisposition which involves a promiscuous host and often a family history of multiple autoimmune diseases. This is very well exemplified by the paradigm of primary biliary cirrhosis (PBC). PBC is a progressive autoimmune liver disease with female predilection characterized by immune-mediated destruction of intrahepatic small bile ducts, leading to decreased bile secretion, fibrosis, and eventual liver failure. PBC is particularly interesting in this respect because of its high degree of concordance in identical twins, clinical uniformity and the presence of a highly specific serologic marker, AMA, that is directed at the E2 subunits of 2-oxo-acid dehydrogenase complexes. In addition, the MHC class I and class II-restricted T-cell epitopes of liver-infiltrating, autoreactive T-cells appear to localize to the same inner lipoyl domain of PDC-E2 as does the dominant autoreactive B-cell epitope. Recently, we have completed a large epidemiologic study involving more than 1000 patients with PBC as well as an equal number of age-, sex-matched and even zip code-matched controls. Our data reflects the considerable homogeneity of features amongst patients, more so than most autoimmune diseases. Of particular interest is the significant family history of other autoimmune diseases, i.e. systemic lupus. In addition, patients seem to have a higher risk of previous urinary tract infections and chemical exposures. The latter is of note because of a recent study suggesting that patients with severe PBC are more likely to live near toxic waste sites. Our laboratory has been operating on the preposition that there are several steps which lead to PBC. These include 1) a genetic predisposition; 2) an incredibly focused response of autoantibody; 3) higher autoreactive CD4 and CD8 T cell responses in the liver; and 4) the possibility that a chemically modified autoantigen leads to loss of tolerance. We further propose that small bile ducts are not innocent victims; their unique apoptotic immunobiology determines their targeting and fate.

PSC has been more difficult and has not provided the same degree of molecular data as found in PBC. Clearly, an understanding of the immunobiology of primary sclerosing cholangitis (PSC) is essential to improving both diagnosis and treatment. There have been significant gains in the discovery of genetic polymorphisms that generate susceptibility to disease, but only limited data on etiologic events that may initiate the inflammatory response. Colonic inflammation produces memory T-cells that have the ability to bind both biliary and colonic endothelial cells. One possible mechanism for the development of PSC is the homing of these memory T-cells to the biliary tree. In addition, TNFα may contribute to the oxidative damage of the biliary system. Finally, although speculative, mononuclear cell responses against biliary epithelial cells may create a persistent inflammatory response, eventually leading to
fibrosis. There are enormous voids in our knowledge. However, what is greatly
needed is a more sophisticated approach to the epidemiology of PSC. In addition,
more studies of isolated mononuclear cells from livers should be studied with respect
to phenotypic and functional characteristics, including their cytokine, chemokine and
cognate receptor features. Finally, the role of inflammation in not only initiation, but
also the progression of disease, including the development of cholangiocarcinoma,
needs vigorous attention.
Alcoholic hepatitis

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Alcoholic liver disease (ALD) with its complications is still one of the most frequent causes of death in the Western world. Treatment modalities for both its major inflammatory complication, namely alcoholic steatohepatitis (AH) as well as liver cirrhosis are insufficient. Severe AH is associated with a high mortality and, although glucocorticoid treatment has been reported to improve survival, meta-analyses of clinical trials to date have failed to show a convincing benefit of such an approach. The treatment of patients with alcohol-related cirrhosis is mainly symptomatic and no therapies are currently available besides orthotopic liver transplantation for end-stage liver disease. Independent of the stage of disease, abstinence from alcohol is the cornerstone of management.

One of the first therapeutic aspects is to treat alcohol withdrawal with benzodiazepines or related drugs. The administration of fluid, calories, vitamins and minerals is usually required. Overhydration should be avoided, as this may increase ascites, lower the plasma sodium concentration, and precipitate gastrointestinal hemorrhage from varices. Vitamin K is usually administered to patients with a prolonged prothrombin time, even though this regimen is typically ineffective because coagulopathy reflects more underlying liver failure. Correction of the coagulopathy with fresh frozen plasma is not recommended in the absence of active hemorrhage, as it might increase the risk of variceal hemorrhage in a patient with portal hypertension. Admission to an intensive care unit should be considered in the unstable patient. Airway protection should be assured in encephalopathic patient.

The main progress in the understanding of these diseases, especially in AH has come from cytokine studies. Various pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNFα) have been proposed to play an important role in its pathophysiology. This knowledge, however, so far has not led to new therapies as only a few innovative studies such as anti-TNF studies have been performed in recent years with mixed results. Treatment of severe AH has been a field with almost no progress in the last years. Current clinical strategy favors a watch-and-wait strategy awaiting disease progression (Discriminant Factor $\geq 32$). Such a strategy might be counterproductive in a severe disease with high mortality and is an uncommon strategy in modern medicine. In addition, patients with a DF $\geq 32$ finally often have contraindications for corticosteroid treatment. Therefore, besides new treatment approaches based on a better understanding of its pathophysiology, less restrictive clinical and better clinical scores might open the field and help to identify best candidates for an anti-inflammatory and more effective therapy.
Session VIII

Complications of cirrhosis
Hepatorenal syndrome in cirrhosis

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- Hepatorenal syndrome (HRS) is a functional renal failure that mainly occurs in patients with cirrhosis, ascites and liver failure. It is characterized by impaired renal function, marked alterations of cardiovascular function and over-activity of the endogenous vasoactive systems. HRS is diagnosed by excluding other types of renal failure.

- Type-2 HRS is the result of spontaneous progression of the circulatory dysfunction in cirrhosis, which is mainly determined by increased splanchnic vasodilation. It is characterized by moderate, slowly evolving renal failure and is frequently associated with refractory ascites.

- Type-1 HRS is caused by acute and severe impairment of circulatory function related to increased peripheral vasodilation. Progression to severe renal failure is rapid. Survival of patients is extremely short, and they often show rapid deterioration of liver function and hepatic encephalopathy. Type-1 HRS may occur after a precipitating event, usually spontaneous bacterial peritonitis (SBP). Type-1 HRS can be prevented in patients with SBP by albumin infusion.

- Patients who develop type-1 HRS can improve by administration of vasoconstrictors (terlipressin, midodrine or norepinephrine) plus albumin, or by transjugular intrahepatic portosystemic shunt (TIPS). However, liver transplantation is the only treatment that provides long-term survival.

- Although vasoconstrictors plus albumin and TIPS can reverse type-2 HRS, randomized controlled trials are required in order to determine whether their use is suitable.

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Variceal bleeding

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Ascites, hepatocellular carcinoma and variceal bleeding are the most common complications of liver cirrhosis. Out of these bleeding is the most acute and dangerous event. The risk of bleeding is dependent on the degree of liver failure, the amount of portal hypertension as well as on the local anatomical situation of the vessels with the potential to bleed.

There are several goals with respect to variceal bleeding:
- prevention of the formation of varices,
- prevention of first bleeding,
- treatment of acute bleeding,
- prevention of rebleeding.

Having in mind that liver cirrhosis is a systemic disease, treatment and prophylaxis of variceal bleeding is accompanied by therapeutic approaches that influence systemic inflammation, portal hypertension and cerebral dysfunction.

Prevention of formation of varices
There are several drugs that might inhibit progression of fibrosis, decrease intrahepatic resistance or reduce portal hypertension and therewith affect the formation of varices, such as AT1-receptor antagonists, statins, non-selective β-blockers, interferons or CB1-receptor antagonists (1–4). Although there might be a real potential in long-term pharmacological modulation of portal hypertension and liver cirrhosis, no trials exist, to date, that prove the validity of this concept. There was only one large trial that could not find any beneficial effect of long-term treatment with a non-selective β-blocker (timolol) in the prevention of variceal formation (5).

Prevention of first bleeding
Prevention of first bleeding has been performed with considerable effort within the past decades. The results of numerous controlled trials allow us to give the patients valid recommendations (6, 7). Large esophageal varices and – according to one trial – also small varices represent an indication for treatment to prevent first bleeding (7, 8, 9). The treatment of choice is still a non-selective β-blocker, although ligation of varices is probably equally effective (7, 13). Both reduce the bleeding risk on average by 50%. Since it harbours more potential acute complications, most physicians advice ligation only in case of contraindications for β-blockers, side-effects or non-compliance. It remains to be shown whether the concept to switch those patients who do not show adequate hemodynamic response to β-blockers to ligation is superior to ligation or β-blockers alone without hemodynamic monitoring.

Treatment of acute bleeding
Patients with acute bleeding should receive medical treatment (terlipressin, octreotide) that reduces portal and variceal pressure as soon as possible, even before endoscopic prove of varices together with antibiotics (7). The latter – for not fully cleared reasons – decrease the early rebleeding risk and increase survival. Endoscopy should be performed as soon as possible and ligation is the procedure of choice to achieve acute hemostasis and initiate rebleeding prophylaxis (7). If ligation
is too difficult in the acute situation injection of glue or sclerosant can be performed to achieve acute hemostasis. Intrahepatic stent shunt (TIPS) is reserved for patients in whom endoscopic hemostasis fails (10).

**Prevention of rebleeding**

Prevention of rebleeding is necessary since the risk of rebleeding is high (around 70%) after successful acute hemostasis (11). Ligation together with propranolol is probably the best initial rebleeding prophylaxis (11). Again it remains to be shown whether medical treatment (β-blockers ± nitrates) is the best primary rebleeding prophylaxis for those patients who show adequate reduction of the portal pressure. Such a trial with hemodynamic monitoring has not been performed to date.

Shunt procedure should be reserved for patients in whom non-shunt approaches fail (7). In patients with well compensated cirrhosis open surgical shunt is equally effective as TIPS or vice versa (12).

**Literature:**


Surveillance and prevention of HCC

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Surveillance for hepatocellular carcinoma (HCC) is considered worth because this tumor is a relevant cause of cancer-related death world-wide, and early detection is the only practical approach to improve treatment outcomes. Surveillance programs for HCC have been facilitated since the target population is readily identifiable, the test adopted (abdominal ultrasound – US) is user friendly and acceptable to the population, while it has high diagnostic accuracy. Chronic carriers of the hepatitis B virus (HBV) and patients with compensated cirrhosis of any etiology are the target population for screening and surveillance. Based upon studies of tumor volume doubling time, 6 month has been selected by most as the ideal interval of screening with US, an abnormal screening test needing to be confirmed by either an US-guided liver biopsy or imaging-studies. The diagnostic algorithm (in patients with cirrhosis) largely depends upon the size of the nodules. Lesions of at least 1 cm identified during surveillance and those of at least 2 cm detected at first imaging examination, need to be investigated with two coincident techniques among contrast-US, spiral CT and MR, whereas a single imaging technique is enough to diagnose a HCC whenever wash-out of contrast medium following arterial hypervascularization can be demonstrated. In a few patients, diagnosis of HCC can be obtained combining an imaging technique with greater than 400 ng AFP. Smaller than 1 cm nodes are difficult to diagnose with imaging (and liver biopsy) since they lack unpaired arteries, which increase in parallel with increasing size of the tumor. Enhanced follow-up at 3 month intervals can however provide a final diagnosis. Though it is reasonable to assume that screening increases survival of patients with a HCC, this is far from being evidence-based. There is, in fact, only one randomized controlled study based on semi-annual investigation with US and AFP that was carried out on 18,816 Shanghai urban residents aged 35–59 years with serum evidence of HBV infection or chronic hepatitis. After a total follow-up of 38,444 person-years for the surveillance individuals and 4,077 for controls, HCC was detected in 86 and 67 patients, respectively and a 37% increase in survival was demonstrated for the former individuals compared to the latter ones. However, in view of the differences in HCC epidemiology and treatment options, the results of this study unlikely are transferable to field practice in the West. In Milan, a reanalysis of 112 patients with a HCC detected during surveillance, showed higher survival rates for patients who were treated for a liver cancer detected during the last 5 years of surveillance than previously (90% vs. 55%, p = 0.0009). Increased survivals could be confidently attributed to a significant reduction in the mortality rates of treated patients (from 34% to 5%, p = 0.003), due to wider application of curative treatments and improved selection of patients undergoing ablative treatments.

Prevention is the only realistic approach for reducing mortality rates associated with HCC. The substantial reduction in hepatitis B and C transmission among the general population achieved through screening of blood donations and anti-hepatitis B vaccination programs could have favourably impacted on HCC incidence. Approaches which alter susceptibility to HCC or slow progression of hepatitis to cirrhosis may also prevent or delay the appearance of HCC. Two randomized
prospective studies in Asia showed interferon (IFN) and lamivudine to prevent or delay the onset of hepatitis B-related HCC, respectively. In Japan, a prospective randomized controlled study showed reduction of HCC in IFN treated patients with chronic hepatitis C, independently from a virological responses though a number of flaws in the study design attenuate the importance of this report. Two meta-analyses of interferon trials revealed slight (10–20%) reduction of HCC risk in patients with chronic hepatitis C who achieved a sustained virological response, and doubtful results in cirrhotic patients. Evidence for secondary prevention of HCC is still inconclusive due to poor methodologies and scientific background of the studies.
In the last two decades hepatocellular carcinoma (HCC) has experienced a progressive increase in its incidence, constituting nowadays the third cause of cancer-related death and the main cause of death among cirrhotic patients (1). Potential curative treatments are only applicable in 30–40% of patients, mostly diagnosed in the setting of surveillance programs. Scientific societies recommend surveillance for HCC in cirrhotic Child-Pugh’s A–B patients with biannual abdominal ultrasound (2). The American Association for the Study of Liver Diseases (AASLD) has recently reported a diagnostic strategy based on non-invasive diagnostic criteria for HCC (Fig 1) (2). Briefly, this diagnosis can be confidently established in cirrhotic patients if liver nodules present a contrast uptake in the arterial phase followed by wash-out in venous/delayed phases in dynamic imaging studies. This pattern needs to be recognized by one imaging technique (CT scan, MRI or contrast-US) in nodules sized > 2 cm, and by two imaging techniques in nodules between 1–2 cm. Lesions showing atypical vascular patterns need histological confirmation. The recent advances in the knowledge of gene expression profiles will allow incorporating genome analysis as a tool to early HCC diagnosis (3).

Once HCC has been confidently diagnosed, prognosis and treatment will depend upon several variables: tumor status, liver function, physical status and treatment received. Among the new staging systems proposed, the Barcelona-Clinic Liver Cancer (BCLC) classification has been consistently validated in European and American cohorts and has been endorsed by the EASL and AASLD (4). This classification links tumor staging with treatment allocation. The BCLC staging system considers five stages (Fig 2). Patients at Stage 0 (very early) or A (early stage) will benefit from potential curative therapies, including resection, liver transplantation, and percutaneous ablation, and the expected 5-years survival exceeds 50–60%. Patients with multinodular asymptomatic tumors without vascular invasion/extrahepatic spread are categorized as Stage B (intermediate stage). Chemoembolization have shown to improve survival in randomized controlled trials (RCT) trials (5) and meta-analysis (6), and thus it is considered the standard of care. Patients presenting either cancer-related symptoms (ECOG 1–2) or invasive tumoral pattern (vascular invasion/extrahepatic spread) are at stage C (advanced stage). Several RCTs assessing primary treatments for these patients have been conducted during the last thirty years with negative results. Recently, a multicenter, double-blinded placebo-controlled RCT assessing Sorafenib, a mutikinase inhibitor against b-raf kinase, VEGFR and PDGFR, in advanced tumors has recently shown a significant survival advantage with marginal toxicity. Therefore, it is expected that Sorafenib will be considered as the standard of care for advanced HCC among scientific societies and regulatory agencies. Further research is required to translate the growing knowledge of the molecular pathogenesis of this complex disease into the clinical setting. In fact, there are already available several drugs able to abrogate the signal transduction pathways involved in the progression and dissemination of this neoplasm.
Figure 1: Diagnostic strategy to apply upon US detection of a hepatic nodule in patients with cirrhosis. Reproduced with permission (2).

Figure 2: Strategy for staging and treatment assignment in patients diagnosed with HCC according to the BCLC proposal. Adapted with permission (2).
References:


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Surgical therapy of liver cancer: Resection and transplantation

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Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and is estimated to cause approximately half a million deaths per year. Most tumors (80%) develop in cirrhotic livers caused by viral hepatitis C or B and alcoholic liver disease. In the Western World only a minority of patients is amenable to surgery.

With regard to the surgical approach to be performed, diagnostic workup is an important problem. Detailed assessment of the tumor is highly unreliable: Number and even size of lesions cannot be predicted due to the underlying cirrhosis. Lesions of less than 1 cm in diameter are usually missed.

Liver surgery is hampered by the functional impairment of the liver. In addition to that, up to 100% of the patients experience recurrent disease within 5 years after hepatic resection. Long-term survival is influenced by cirrhosis: More than 30% of the patients die from cirrhosis and not from recurrence. Five-year survival following liver resection ranges from 10–50% depending on the underlying disease and on the respective tumor features.

Liver transplantation (LT) was assumed to be superior to conventional surgery. Early results including patients with advanced disease did not exceed a five-year survival of 20–25%. Presently Milan criteria defining the indication of LT in HCC (1 nodule ≤ 5 cm or ≤ 3 nodules ≤ 3 cm) are generally accepted. Based on these criteria the 5-year survival is 60–70%. Whereas patients with more than one small nodule are obviously treated best by LT, the indication for resection versus LT in patients with small and singular nodules remains a controversial issue. If the HCC may be cured by hepatic resection, sparse liver grafts will be saved and LT may be an option for those patients who experience tumor recurrence. Unfortunately, LT as a rescue approach proved to be possible only in a few resected patients and the results were inferior to LT as a first treatment option. Nevertheless, liver resection is performed in many centers if feasible. We prefer to perform LT as the first treatment option even in singular tumors.

Due to the lack of donor organs, patients with HCC who are candidates for LT, have to wait until an organ is available. During waiting time the tumor may exceed the listing criteria and the patients have to be delisted. There are several approaches to bridge this period: radiofrequency ablation, ethanol injection, chemoembolization or even liver resection.

The crucial issue remains to select those patients whose tumor is suitable for LT. Even if tumors with vascular invasion and poorly differentiated tumors are usually excluded from LT, reliable biological markers capable of selecting appropriate tumors are urgently needed.
In our experience comprising more than 650 patients, about 30% were suitable for liver surgery. Liver resection was performed in 109 patients. In 61 of 109 patients HCC occurred in a noncirrhotic liver. 5-year survival in noncirrhotic patients was 51% compared to 38% in cirrhotic patients. In 119 patients liver transplantation (LT) was performed. In the majority of these patients (n = 69) the HCC was identified during the preoperative workup. The rate of incidentalomas was 28%. Crude survival following LT was 57%, recurrence rate after 5 years was 22.5%. Waiting time was bridged by TACE. TACE pretreatment was repeatedly performed (in average 5.7 cycles). Patients with stable disease during that pretreatment experienced a very low recurrence rate (6.5%) compared to patients with minimal tumor progress (61.5%; P = 0.0001). Repeatedly performed TACE pretreatment may, therefore, not only bridge the waiting time but select biologically favourable tumors suitable for LT.
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Primary sclerosing cholangitis has a specific hemodynamic behaviour that is not observed in other cholestatic or hepatocellular liver diseases

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Introduction: Microcirculatory disturbances in the peribiliary vascular plexus may contribute to ischemia and ductal injury in PSC and might be associated with hemodynamic changes in liver vascular flow.

Aim: 1) to evaluate hepatic flow in patients with PSC.

Methods: Group 1: Patients with PSC cholangiogram-confirmed (n = 16), Group 2: Patients with PBC (AMA+ and florid bile duct lesions) (n = 20). Group 3: Patients with PCR-HCV+ hepatitis, therapy-naive (n = 20). Hemodynamic parameters were measured by Doppler US by two blind operators in two different occasions. Results were averaged. Hepatic artery resistance index was calculated.

Results: No significant differences were observed in portal diameter, portal or suprahepatic velocity. A larger diameter of the hepatic artery was observed in Group 1 (5.1 ± 0.7 mm, 4.4 ± 0.5 mm, 4.6 ± 0.7 mm, \( p = 0.7 \)). Patients with PSC presented a lower hepatic artery resistance index in comparison with patients in Group 2 (0.5 ± 0.1 vs. 0.9 ± 0.1, \( p = 0.005 \)) and Group 3 (0.5 ± 0.1 vs. 0.8 ± 0.1, \( p = 0.006 \)). Lower intrahepatic resistance in Group 1 was dependent of a higher hepatic artery end of dyastole velocity (23.0 ± 8.2, 18.7 ± 8.3, 19.1 ± 9.1 mm/sec, \( p = NS \)). Within Group 1 all patients with (n = 7) or without cirrhosis (n = 9), presented the same hemodynamic behaviour. In the subgroup with cirrhosis, a lower suprahepatic vein velocity was observed compared to patients with PSC without cirrhosis (34.8 ± 7.3 vs. 46.8 ± 6.7 cm/sec, \( p = 0.006 \)).

Discussion/Conclusion: PSC is associated with a low hepatic artery resistance index that is not observed in PBC or HCV. This finding is not modified by the development of cirrhosis. Physiopathological relevance of this finding should be clarified.
Organic extract of chamomile flowers causes significant improvement in patients with hemorrhoid

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Purpose: We aimed to establish therapeutic effects of the organic fraction of chamomile flower in the patients with symptomatic hemorrhoid.

Patients and methods: Twenty-four patients (16 male with 48 median age and 8 female with 45 median age) with acute hemorrhoid bleeding were enrolled in that study. Patients consumed extract of chamomile flower fraction for 2 months at a daily dose of 0.02 ml/kg body weight. All cases were reanalyzed with routine anal examination and rectoscopy at the end of the study.

Result: The frequency and severity of the hemorrhoid attacks were significantly reduced during the study period and that all of the complaints were almost abolished at the end of treatment. Grade of hemorrhoids were significantly reduced at the end of treatment.

Conclusions: It seems possible that constituents in the extract fraction of chamomile flowers have significant potential to inhibit inflammation and to increase micro circulation in the bowel, thereby ameliorating hemorrhoid and bleeding.
Surgical treatment of colorectal and non colorectal liver metastases

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Introduction: Liver resection is a well accepted procedure in the treatment of colorectal and noncolorectal liver metastases. In a ten years period the authors performed 345 operations for these cases.

Methods: In 57 cases noncolorectal (17 breast cancer, 7 pancreas tumor, 4 genital malignancies, 2-2 kidney and adrenal gland tumor, and 1-1 case carcinoid, retroperitoneal tumor and sarcoma were the primary neoplasms) and in 288 cases colorectal metastases were operated. During operations CUSA-US scalpel was used to perform the liver resection. In 1 + 21 cases mesohepatecomy, in 4 + 41 cases anterior hemihepatectomy, in 43 + 175 cases segmentectomy and in 9 + 51 cases metastasectomy were performed. In 68 of the cases the resection was performed laparoscopically. The average tumour size was 11 cms. In the postoperative period we followed up the laboratory changes (like serum bilirubin and cholestatic enzymes, hemostatus). We calculated the average operating time, blood loss and consumption. Following metastasectomies patients received complex onco-therapy.

Results: In the early postoperative period we found fever, bile leakage and pleuritis in 43 of the cases. The mean blood consumption was 400 ml of RBC concentratum. The average operating time was 128 minutes the mean nursing days were 11 days. 137 patients are still in alive the average follow up period within them is 58.4 months. 130 patients died, the average survival time was 8 months. 48 patients were not followed up because of non-compliance.

Discussion/Conclusion: On the basis of the authors opinion liver resection is an acceptable treatment for secondary malignant liver diseases.
Clinical manifestations and morpho-functional changes of gastroduodenal mucous of children having polyps of upper units of digestive system

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Introduction: Find out peculiarities of clinical manifestations, characteristics of morpho-functional changes of gastroduodenal mucous of children with polyps of upper units of digestive system, and approach of surveillance of given patients.

Methods: Polyps has been discovered among 128 patients (2.5% of cases), aged from 3 to 16 years old (77 boys and 51 girls). Polyps discovered in cardiac and antral parts of stomach (55.4 and 32.0%), in stomach body (7.8%), and descending part of duodenum (0.5%). Protrusions' sizes varied from 0.4 to 2.0 cm. Clinical symptoms were not specific, but reflects course of chronical gastroduodenitis: in 60.1% – abdominal pains after food intake or after physical activity have been observed; sickness and emesis – in 22.4% of cases, heartburn and air eructation – among 49.0% patients. In objective inspection of children in 77.5% of cases painfulness of epigastric abdomen area has been observed. Among 35 children presence of hyperplastic polyps is registered. Adenomatous polyps are registered among 4 patients (7.8%). Juvenile type of polyps is registered among two patients. In 74.5% of cases symptoms of chronical inflammation in polyps' tissues are observed.

Results: Endoscopic polypectomy has been performed for 12 patients suffering with mature polyps. For each child treatment of chronic gastroduodenitis is prescribed. Checking examinations during next 3 years have not revealed recurrences of polypogenesis.

Discussion/Conclusion: Genesis of polyps of upper units of digestive system among children could be connected with protractedly existent chronical pathologic process in gastrointestinal tract. Dynamics of polyps’ state depends on intensity of aggressive factors of gastroduodenal mucous. This should be taken into account in treatment of patients with such pathology.
Acute pancreatitis attributed to the use of peginterferon alpha-2b

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Acute pancreatitis complication of the interferon treatment is very rare. There have been only 10 acute pancreatitis cases that developed during the treatment of chronic hepatitis C (CHC), in the English literature. However, of these 10 patients only one case was occurred with peginterferon therapy.

Case Report: A 45-year-old man was admitted with newly diagnosed asymptomatic CHC with positive HCV-RNA-PCR (10,542,000 copies/ml) and elevated aminotransferases (AST: 92 U/L, ALT: 126 U/L) for the treatment. Physical examination was normal. He had no concomitant medical disorders, drug usage or alcohol abuse. Her complete blood count and ultrasonography was normal. The patient was started peginterferon alpha-2b subcutaneously 120 µg/week and ribavirin 1200 mg peroral daily. At the 5th week of the therapy, he had developed severe epigastric pain, nausea and vomiting. Laboratory testing was notable for high levels of serum amylase: 634 U/L (N: 28–100) and lipase: 856 U/L (N: 7–60). Ultrasonography revealed pancreatic edema, mild heterogenity and hipoechogenity as consistent with pancreatitis. The gallbladder and choledoc appeared normal and no gallstone was noted. A magnetic resonance cholangiopancreatography was normal. The therapy was stopped and the patient was treated with supportive care. Her epigastric pain resolved and the amylase level decreased to normal-limits 10 days after cessation the treatment. The treatment was not started again and he did not develop recurrent pancreatitis during 1 year of follow-up.

Conclusion: The present case has been the second-male acute pancreatitis case in which the causative drug was peginterferon, in the literature. Although, this is a rare side effect observed during this treatment, the physicians should aware of acute pancreatitis, when a CHC patient on the treatment admits with severe epigastric pain.
Effect of anti-TNF mAb on colitis in mice

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Introduction: Piroxicam feeding (days 0–14) induces colitis and cancer in IL-10-deficient mice.

Methods: Using a 14.1 T mouse MRI, the stages of colitis-induced cancer and effects of anti-TNF mAb were assessed to noninvasively detect active versus recovering colitis and identify early dysplasia.

Results: In preliminary studies, right sided colon wall masses were detected by high spatial resolution MRI that histologically correspond to invasive adenocarcinoma (d 74 after piroxicam feeding). These studies are ongoing. During the first 28 d, MRI imaging detected increased wall thickness (0.90 ± 0.15 mm) in areas of severe colitis (3.7 ± 0.2/4.0 histology score) compared to controls (0.20 ± 0.02 mm) whereas mice treated with anti-TNF Ab exhibited significantly reduced colon wall thickness (0.35 ± 0.1 mm). Normal colon and colitis were further characterized by differences in T1 and T2 relaxation times.

Discussion/Conclusion: These studies demonstrate that in vivo MR imaging accurately parallel the progression of colitis and suggest that inspecting fine details of mucosal inflammation, may be useful in monitoring colitis progression and onset of dysplasia. Studies are progressing to determine if anti-TNF mAb prevents dysplasia.

Acknowledgement: Supported by Centocor, PHS, and NIAID/1R01AI061701
Celiac disease associated rare complications – Report of two cases of liver cirrhosis and a case of lichen oris

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Celiac disease is often associated with other autoimmune diseases. In one part of the cases classical symptoms are missing and only recognition of an associated disorder lead to the diagnosis. Hepatological complications are common, elevated transaminase levels can occur in many patients. Liver cirrhosis based on chronic hepatitis is a late, severe complication, which may develop even in young people.

Cases of three young female patients are presented. In two of them examinations were performed due to cryptogenic cirrhosis. One of them suffered from diarrhoea, the other had mild abdominal symptoms. Besides exclusion of other causes of liver cirrhosis we suspect celiac disease, which was later proved by serological and histological tests. Significant improvement was noticed after the introduction of diet. In the third case non-healing mouth ulcers drew the attention to celiac disease. The patient did not suffer from gastrointestinal symptoms. Lichen oris was reported after dermatological examination. Serological and histological tests proved celiac disease. During the gluten-free diet the ulcers healed. Simultaneous occurrence of celiac disease and lichen oris is rare only two cases have been reported in the literature.

Our cases draw the attention to rare disorders associated with celiac disease. Recognition of the association may lead to the diagnosis of celiac disease and a diet introduced in due course may help to prevent late, severe complications.
The difference between postoperative follow-up for patients after restorative proctocolectomy with ileo-anal J-pouch anastomosis due to ulcerative colitis or familial adenomatous polyposis

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Introduction: At the Department of General, Gastroenterological and Endocrinological Surgery at the University of the Medical Sciences in Poznań, Poland, from 1985–2006, restorative proctocolectomy with ileo-anal J-pouch anastomosis was performed on 354 patients: 198 with ulcerative colitis (postoperative histopathology changed the diagnosis from ulcerative colitis to Crohn’s disease in 7 cases), 151 with familial adenomatous polyposis, 3 with multiple colon cancer and 2 with other diseases.

Methods: In our study we compared the long-term results of restorative proctocolectomy in patients operated on due to ulcerative colitis and familial adenomatous polyposis. During postoperative follow-up and control examination of the patients we used routine histological, histochemical, electron microscope and manometric examinations.

Results: In 74% of the patients we observed adaptive changes in specimens of the small bowel mucosa taken from the ileal reservoir, but in 13 cases (6.5%) pouchitis was diagnosed (often in the patients treated due to ulcerative colitis). In our examined groups during control endoscopic examination, we diagnosed polyps (adenomas) in pouches in 15 patients – all with familial adenomatous polyposis. In 2 cases of patients operated due to familial adenomatous polyposis malignancy (adenocarcinoma) were found.

Discussion/Conclusion: In the examined patients, we observed the differences in pouch mucosal morphology between the ulcerative colitis and familial adenomatous polyposis groups which were characteristic for these diseases. Regular control endoscopic examination (with biopsy) of patients after restorative proctocolectomy with ileo-anal J-pouch anastomosis should be a standard procedure of postoperative follow-up.
The level of MAP kinase activity in the stomach stump in rats after subtotal gastrectomy

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Introduction: MAPK (Mitogen-Activated Protein Kinase) is one of the elements of kinase cascades, regulating cellular proliferation and differentiation processes. In some human carcinomas a significant increase of MAPK activity is described.

Methods: The material comprised segments of gastric mucosa of the stomach stump of 15 rats after subtotal gastrectomy. Part of the rats after procedure was administered carcinogen orally (MNGG). The MAPK activity was determined by western blotting method with the use of IgG against MAPK p42

Results: In 8 cases we observed the increase of MAP kinase activity. We established probable correlations between the increase of MAPK activity and histological and ultrastructural changes. Among 5 cases diagnosed as adenoma tubulare in 5 we observed the increase of MAPK activity. A clear increase of MAPK was present in 5 cases diagnosed as adenocarcinoma

Discussion/Conclusion: The increase of the MAPK activity may be one of the causes of the neoplasm development.
Introduction: The aim of our study was to find the correlation between the degree of inflammation, in resected large bowel mucosa in patients with colitis ulcerosa, and morphological changes in the intestinal reservoir (J-pouch) mucosa.

Methods: 34 patients (21 females, 13 males, median age 34.5 years old) after restorative proctocolectomy due to ulcerative colitis were observed. We studied specimens of the large bowel mucosa obtained during the operation, and specimens of the intestinal reservoir (J-pouch) mucosa obtained at the same patients during endoscopic follow-up examination (4 to 5 years after surgery). In all cases the routine histological examination was done. The patients were divided into two groups: Group I (without dysplasia, n = 16 patients) and Group II (with mild and severe dysplasia, n = 18 patients). During the follow-up examination the PDAI score was used to description of pouchitis.

Results: On morphological level in the large bowel mucosa we observed a typical change for colitis ulcerosa. In group II mild dysplasia was detected in 11 cases, severe dysplasia in 7 cases. In patients investigated after proctocolectomy we observed pouchitis (recognized if PDAI ≥ 7 pts) in 12 cases: 4 in group I, 8 in group II. In group II the severity of pouchitis was correlated with severity of dysplasia (mild dysplasia – median PDAI 9.2 pts, severe dysplasia – median PDAI 11.1 pts), but it was no statistical significant.

Conclusion: In our study correlation between dysplasia in large bowel mucosa and severity of pouchitis at the patients after restorative proctocolectomy was found. Occurrence of the large bowel mucosa dysplasia, depend of the severity and advanced of the ulcerative colitis, have a negative effect on adaptation processes of the small intestine mucosa in intestinal J-pouch reservoir.
Endoscopic therapy of early colorectal carcinoma by EMR

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Introduction: The incidence of colorectal carcinoma (CRC) is very high throughout the world, thus early detection and treatment seems to be justified.

Aim of study: to establish prospectively the use and utility of endoscopic mucosal resection (EMR) as curative therapy of early CRC (limited to the colonic mucosa).

Material and methods: 39 pts who were diagnosed with early CRC by colonoscopy underwent EMR. Regarding the aspect of the tumor: flat carcinoma limited to the colonic mucosa (14 pts), adenomatous polyps with severe dysplasia (19 pts), and recurrence after surgery (4 pts). Localization of CRC: rectum and r-s junction (18 pts), sigmoid colon (13 pts), descending colon (8 pts). Technique of EMR: injection of saline and methylene blue for elevation, polypectomy in piece-meal fashion for flat large lesions and big polyps and as a one time procedure for stalked dysplastic polyps. At the end of the procedure India ink was injected at the resection site for follow-up.

Results: EMR was successful in all patients. No severe complications were observed: little-moderate bleeding which stopped spontaneously or after injection of sclerosant agents/clips (6 pts), no perforation. The overall success rate of EMR at 6 months follow-up was over 92%, a recurrence of CRC was observed in 3 pts. One patient was referred to surgery; other 2 pts were retreated by EMR.

Conclusion: EMR should represent the standard procedure for early CRC limited to the mucosa. In experienced hands the risk of complications is low. For future localization of the resection site it is important to spot it with India ink.
Evolution of the gastric cancer, cardia cancer and esophageal cancer

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Introduction: The study is a follow-up of the changes in the prevalence of esophageal and gastric cancer in our region. Romania is a region with high incidence of gastric cancer and also a high incidence of the Helicobacter pylori. The incidence of the cardia gastric cancer is increasing dramatically in the world. This fact led to the new classification of the gastric cancer in non-cardia gastric cancer and cardia cancer.

Methods: We followed-up the evolution of the malignant lesions upon two periods of 5 years: 1990–1994 and 2000–2004. All the patients underwent upper digestive endoscopy and biopsies were taken.

Results: The results showed a statistically significant difference between the incidences of cancers in the 2 periods of time. In the period of 10 years there were diagnosed 779 patients with esophageal and gastric cancer, 414 in the period 1990–1994 and 365 in the period 2000–2004. From these 182 were esophageal cancers and 597 gastric cancers. In the years 2000–2004 the non-cardia gastric cancer is decreasing in incidence with 12.75%. The incidence of the lower esophageal cancer is increasing with 5.44% and also cardia cancer with 12.77% in this period. There were no statistically significant differences between the age and gender of the patients from the 2 periods of time investigated.

Discussion/Conclusion: The incidence of the lower esophageal cancer and cardia cancer are increasing statistically significant in the past 10 years, p < 0.05. This could be the results of the decreasing in incidence of the Helicobacter pylori infection, but further data are needed.
Causes and outcome of nonvariceal upper gastrointestinal bleeding – Evaluation of patients at General Hospital Izola in 2005

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Introduction: Upper gastrointestinal (UGI) bleeding remains a common medical condition, resulting in significant morbidity and mortality. The aim of this study was to evaluate the causes, the precipitating factors and the outcomes of UGI bleeding.

Methods: 87 patients hospitalized in 2005 with nonvariceal UGI bleeding at General Hospital Izola were retrospectively evaluated. A number of clinical variables were reviewed from their records.

Results: 48 of patients were males (55%), 39 females (45%), the mean age was 62.5 ± 15.8 years. Nonsteroidal anti-inflammatory drugs were used in 45 (51.7%) patients, Helicobacter pylori infection was present in 48% of tested. Endoscopy was done within 24 hours in all patients. The most common causes of bleeding were duodenal ulcer, 34 (39.1%); gastric ulcer, 31 (35.6%); Mallory-Weis tear, 8 (9.2%); gastric erosions, 6 (6.9%) and gastric cancer, 3 (3.4%). The cause of bleeding was not identified in 1 patient. Endoscopic therapy (injection sclerotherapy) was used in 43 (49.4%) patients, active bleeding was identified in 30 (34.5%) and stigmata of recent hemorrhage in 13 (14.9%). Rebleeding occurred in 9 (20.9%) of patients that had endoscopic therapy. 4 (4.6%) patients needed surgery. 4 (4.6%) patients died (only one death was directly attributed to bleeding). 53 (60.9%) patients received blood transfusion (2.8 ± 1.5 units), their initial haemoglobin value was 84 ± 24 g/L. The mean length of stay in hospital was 7.4 days.

Discussion/Conclusion: Peptic ulcer disease remains the most common cause of nonvariceal UGI bleeding. Rebleeding and mortality rate in our study are similar to those reported in previous studies.
Impact of hepatitis B core antibody (antiHBc) seropositivity on interferon/ribavirin treatment response in patients with chronic hepatitis C

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Background and aim: Occult hepatitis B virus (HBV) infection is characterized by the presence of HBV DNA in the absence of hepatitis B surface antigen (HBsAg) in the patient serum. Although such infections have been identified in patients with chronic hepatitis C, the clinical significance of those co-infections is still not understood. Our aim was, therefore, to assess the impact of anti HBc antibody (antiHBc ab) on response to interferon and ribavirine combination therapy in naive patients with chronic hepatitis C.

Patients and methods: The study population consisted of 35 patients (20 having occult HBV) with naive chronic hepatitis C treated with IFN/ribavirin. Early responses (6th months), end of treatment responses (12th months) and sustained (18th months) responses of patients with and without occult HBV infection were compared. The liver histopathological findings were also studied.

Findings: The rate of occult HBV infection among patient with chronic HCV infection was 57.1%. Sustained response rates (normal ALT and undetectable serum HCV RNA) of cases with and without occult HBV infection were 36.1% and 42.9%, respectively (p > 0.05). Accordingly, end of treatment and early response rates of cases with and without occult HBV infection did not show any statistically significant difference (p > 0.05). While the average histologic activity index and fibrosis scores were numerically higher in the liver biopsy of cases with occult HBV before the treatment, there was no statistically difference between both groups.

Conclusion: Anti-HBc antibody seropositivity does not have a significant impact on treatment responses to interferon/ribavirin therapy in patients with chronic HCV infection.
Leptin in non-alcoholic fatty liver disease

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Background and aim: Nonalcoholic fatty liver disease (NAFLD) is a prevalent condition associated with obesity and insulin resistance. Leptin is an adipocyte-derived hormone that plays a key role in the control of energy balance, and insulin sensitivity. We examined whether serum leptin level correlates with insulin resistance and the severity of histological changes in NAFLD.

Methods: Fifty-two patients (M/F = 28/24; median age = 30) with no alcohol intake and biopsy-proven diagnosis of NAFLD were studied. We measured serum ALT, AST, alkaline phosphatase (ALP), gamma-glutamyltranspeptidase (GGT), bilirubin, total cholesterol, triglycerides, fasting insulin, glucose and serum leptin. Serum leptin was measured by radioimmunoassay. Insulin resistance (IR) index was calculated by HOMA (homeostasis model assessment). Histological examination was done using the evaluation system described by Brunt.

Results: There was no statistical difference in leptin levels between patients with non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). On the bivariate analysis, serum leptin was significantly associated with female gender (p = 0.0001), and with BMI (p = 0.002). The females had significantly higher BMI than the males (p = 0.04). We found no statistical association between leptin levels and fasting insulin, and HOMA-IR. ROC curve and multiple regression analysis revealed no association between the severity of histological changes and serum leptin levels.

Conclusion: In this study, we did not find any significant association between serum leptin, fasting insulin levels, HOMA-IR and hepatic histology. We speculate that leptin does not play a major role in the pathogenesis of NAFLD.
The incidence of extrahepatic manifestations in infection with hepatitis C virus

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Introduction: The infection with virus C is one of the main causes of chronic hepatic pathology.
In some cases of infection with hepatitis C virus symptoms and signs may be manifested as extrahepatic manifestations: systemic vasculitis, essential mixed cryoglobulinemia, arthralgias, glomerulonephritis, polyarthritis or cutaneous porphyria.

Aim: The aim of this study was to appreciate the incidence of extrahepatic manifestations and their characters in infections with hepatitis C virus.

Material and method: We studied 102 patients with chronic hepatitis C, with anti HCV antibodies, hospitalised in Medical Clinic II of Emergency Hospital of Craiova between 01.01.2005–01.01.2007.

Results: The patients where 72 females (70.5%) and 30 males (29.5%) with average 47.1 years. Extrahepatic manifestations were on 46 cases (45.9%). The repartition of extrahepatic manifestations where: endocrine manifestation on 19 cases (18.6%), hematological manifestations on 14 cases (13.7%), skin manifestations on 11 cases (10.7%), vasculitis on 12 cases (11.7%) and other manifestations on 3 cases (2.9%).

Conclusions: Extrahepatic manifestations in infection with hepatitis C virus are frequent and there are described many other manifestations.
Insulin resistance in chronic viral hepatitis: Is different from non-alcoholic steatohepatitis?

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Introduction: Insulin resistance (IR) is the main factor in non-alcoholic steatohepatitis (NASH) pathogenesis. Whether IR is the cause of hyperglycemia in chronic hepatitis C (CHC) is still under discussion. The aim of this study was to evaluate IR and the relationship between IR and clinical, biological and histological features in patients with CHC and chronic hepatitis B (CHB).

Methods: A total of 42 consecutive naïve patients with CHC and 38 CHB were enrolled to study. Also 80 patients histologically biopsies proven NASH were enrolled to study as a control group. Patients suffering from cirrhosis, diabetes mellitus, morbid obesity, and taken steroid therapy were excluded from the study. Serum insulin, C-peptide, total cholesterol, triglyceride levels were studied. Body mass indexes (BMI) were recorded at baseline. “Homeostasis model assessment“ (HOMA) scoring system was used for IR.

Results: There was no statistically difference between all groups for BMI. Mean HOMA scores for CHC, CHB, and NASH were 3.48, 2.52 and 4.97, respectively. HOMA score was significantly higher in NASH group than other groups (p < 0.01). HOMA score was greater in CHC than CHB but there was no statistically difference (p > 0.05). There was a correlation between HOMA score and BMI in CHC but NASH. There was no correlation between BMI and inflammation and fibrosis in all groups.

Discussion/Conclusion: There is a tendency HOMA score is greater in CHC than CHB. In contrast to NASH, marked relationship between increased BMI and IR in CHC show the mechanism of IR development may be different from NASH.
The significance of serum transforming growth factor-β1 in detecting of gastric and colon cancers

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Introduction: TGF-β1 is a growth factor with wide ranging effects on proliferation, differentiation, immune suppression, apoptosis and matrix remodeling. We aimed to clarify the clinical significance of circulating levels of TGF-β1 as a tumor marker in gastrointestinal tract cancers by comparing it to CEA across a range of parameters such as cancer type and severity.

Methods: Sera collected from patients with gastrointestinal tract cancers (32 gastric, 36 colon) and from 25 healthy volunteers were analyzed for TGF-β1 and CEA. Relations between serum TGF-β1 levels and tumor stage and tumor grade were also evaluated.

Results: Mean serum TGF-β1 levels were higher in patients with gastric or colon cancer compared to the control group (p = 0.001). In both types of cancer there were no differences in TGF-β1 levels associated with serosal involvement, lymph node involvement, vascular invasion, distant metastasis or tumor size. Mean serum TGF-β1 levels were also not statistically different across histopathological tumor grades in either type of cancer. The sensitivity of TGF-β1 was higher in patients with gastric cancer than in patients with colon cancer. TGF-β1 had greater sensitivity than CEA in gastric cancer patients.

Discussion/Conclusion: TGF-β1 has higher sensitivity in gastric and colon cancers. Since it may be increased even in cancer without closed and distant metastasis, TGF-β1 may be used as a tumor marker and combined with CEA particularly in gastric cancers.
The effect of age and *Helicobacter pylori* infection on gastric epithelial cell proliferation

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**Introduction:** *Helicobacter pylori* infection is a known risk factor for gastric cancer and associated with proliferation of epithelial cells. The aim of this study was to determine the effect of *Helicobacter pylori* and age on gastric epithelial cell proliferation.

**Methods:** 157 patients (92 men, median age: 58.5 years, range: 18–85) who had undergone upper gastrointestinal endoscopy due to dyspeptic symptoms were enrolled into the study. Six antral biopsy samples were obtained for flow cytometric DNA analysis (expressed as proliferative index, S+G2/M phase), presence of *Helicobacter pylori* (CLO-test, culture and histology) and histopathological examination.

**Results:** 84 (53.5%) of the patients were *Helicobacter pylori*-positive and 93.3% of patients had diploid pattern and 6.7% expressed aneuploid pattern. The mean proliferative index (PI) was 4.8 ± 0.2 (SEM) for the whole group studied. As for *Helicobacter pylori* (+) patients, PI was 5.14 ± 0.33 and 4.26 ± 0.36 for *Helicobacter pylori* (-) patients (p = 0.017). When age groups were taken into account, PI was found higher in patients over 75 years of age (n = 14, PI 6.66 ± 1.3) compared to patients under 35 years of age (n = 25, PI = 3.83 ± 0.41, p = 0.014). There were no correlation between histological changes and PI. *Helicobacter pylori* (p = 0.045) were independent factor that affect PI.

**Discussion/Conclusion:** Proliferative index of gastric antral mucosa is increased in patients with *Helicobacter pylori* infection. Although PI increases by age, *Helicobacter pylori* is the only factor that significantly and independently influences the rate of epithelial cell proliferation, suggesting this bacteria may be initiative step in gastric carcinogenesis.
Natural history of ascites in cirrhotic patients

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Aim of the study: To assess the natural history of ascites as well as to identify prognostic factors, including the MELD coefficient, for dilutional hyponatremia (DH), refractory ascites (RA), hepatorenal syndrome (HRS) and survival.

Material and methods: 231 cirrhotic patients (mean age 57.8 ± 12.4 years) were followed for 56 ± 8 months after their first episode of ascites. At entry 35 patients were Child-Pugh class A, 142 class B and 54 class C. The mean MELD score was 9.4 ± 6.08 points.

Results: During follow-up 75 patients (31.2%) developed DH, 34 (14.1%) RA, and 23 (9.8%) HRS (type 1: 9; type 2: 14). The 3-year probability of DH, RA and HRS development was 24.4%, 12.1% and 9.1%. 81 patients (33.7%) died. The probability of survival at 3 years was 67.2%. The independent predictors for survival were baseline age (p = 0.02) and serum creatinine (p = 0.001), as well as DH (p = 0.02) and RA (p = 0.002) development. The overall median survival (47 months) decreased to 30, 31 and 1 month when patients developed DH, RA and HRS type 1, respectively (median survival 28 days for type 1 vs. 165 days for type 2, p < 0.001).

Conclusions: 1. Survival of cirrhotic patients with ascites is influenced by age and serum creatinine at the time of ascites decompensation, as well as by DH and RA development. 2. The probability of RA and HRS is relatively low at 3 years. 3. MELD score is not useful for long-term prognosis assessment in cirrhosis with ascites.
Elevated plasma nociceptin (N/OFQ) level and alteration of brain N/OFQ system in experimentally induced cholestasis in bile duct ligated (BDL) rats

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Background: Nociceptin (N/OFQ) is endogenous agonist of opioid-receptor-like receptor. Elevated plasma N/OFQ-level has been described in primary biliary cirrhosis (PBC). Opioid-antagonists alleviate the cholestasis associated itching in PBC indicating the opioids’ role in pruritus. N/OFQ induced itching in mice has been published.

Aim: To investigate N/OFQ-levels in plasma, liver- and brain-tissue in experimentally induced cholestasis.

Methods: Cholestasis was induced by common-bile-duct ligation in 14 F344 rats. Twelve sham-operated animals served as control. Animals were sacrificed on 14th postoperative day by bleeding to death through the canthus. Blood was collected in K-EDTA- and aprotinin-containing vacutainers. N/OFQ was measured by ¹²⁵I-radioimmunoassay kit (Phoenix Pharmaceuticals).

Results: High plasma N/OFQ-level was found in BDL rats compared to the controls (2.43 ± 1.2 pg/ml vs. 1.02 ± 0.5 pg/ml; p = 0.006). There was no difference in liver tissue N/OFQ-levels between the two groups (8.2 ± 2.9 fg/mg vs. 7.6 ± 3.3 fg/mg). Histology and laboratory data confirmed cholestasis without cirrhosis or tumor.
In BDL-rats N/OFQ-level was elevated in hypothalamus, but decreased in hippocampus compared to controls (43.22 ± 31 vs. 15.13 ± 12 pg/100 mg tissue; p = 0.03 and 45.4 ± 24.2 vs. 115.4 ± 38.2 pg/100 mg tissue; p = 0.0009). There weren't differences in N/OFQ-levels either in the liquor or in the striatum.

Conclusions: Bile-duct-ligation induced cholestasis causes alteration of N/OFQ system in rats. The elevated plasma N/OFQ level is in concordance of human data. Not the liver itself, but the brain may be involved in the production of excess N/OFQ as indicated by the hypothalamic elevation of this polypeptide. Further investigations are needed to explain the hippocampus-hypothalamus shift and the significance of alteration of opioid system in cholestasis.
Knowledge of chronic hepatitis C amongst general practitioners and ways of improving poor knowledge

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Introduction: The Department of Health (DH) estimates that in UK between 200,000 to 400,000 patients are infected with chronic hepatitis C. Only 10% of these individuals are aware of their infection. The remainder of patients are asymptomatic and have not been diagnosed. With this in mind the DH launched a second campaign on hepatitis C providing all GPs with educational material about this condition in August 2006. This is the first study to assess the knowledge of General Practitioners following this campaign.

Aims and methods: A 12 point questionnaire was validated for face and content validity and sent out to 550 GPs in North London. This assessed their knowledge on transmission, risk factors, screening, diagnosis, treatment and referral. Then we endeavoured to improve GPs knowledge using a postal service or educational lunch and learn meetings using a pre- and post-test questionnaire.

Results: Significant deficits in knowledge regarding hepatitis C among GPs remain despite a second campaign. Knowledge was particularly poor on maternofetal transmission, screening at risk groups, interpretation of hepatitis C antibody tests and treatment. Educational meetings using lunch and learn sessions improve knowledge but are labour intensive and have poor attendance rates. Postal distance learning is a more convenient and effective way of learning. However, post-test questionnaires do not address knowledge retention.

Conclusion: Knowledge still remains poor regarding hepatitis C among GPs despite a second campaign. Educational initiatives such as distance learning postal services or educational meetings can help improve this knowledge.
Decreased oxidation susceptibility of plasma low density lipoproteins in patients with Gilbert’s syndrome

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Background: The association of hyperbilirubinemia in Gilbert’s syndrome with a decrease in prevalence of coronary artery disease is a well known phenomenon. In this study, the state of LDL oxidation which has been postulated to be a significant determinant at the etiopathogenesis of atherosclerotic disorders was investigated among the individuals with GS.

Methods: For this purpose, serum cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, uric acid, apolipoprotein A and B, bilirubins, thiobarbituric acid-reactive substances and the sensitivity of LDL oxidation levels as well as serum ALT, AST, GGT, ALP activities were determined in 17 patients with Gilbert’s syndrome and 15 healthy adults.

Results: There was no significant difference between the groups except the indirect bilirubin parameter (p < 0.001). In comparison with the healthy individuals, LDL oxidation levels between 75–120 minutes were significantly lower (p < 0.005) along with prolonged lag-phase in GS patients, indicating a delay in oxidation susceptibility.

Conclusion: It is suggested that the chronic hyperbilirubinemia leading to a lag phase prolongation in LDL oxidation and a decrease in LDL oxidation may be reason of the low percentage of coronary artery disease.
The risk factors in chronic hepatitis C infection

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Introduction: The hepatitis C virus (HCV) infection represents an important public health issue on world and national level. The aim of this study is to evaluate the profile of the epidemiologic factors of VHC infection.

Methods: We included 242 patients, with chronic viral C hepatitis (CVH), admitted in our hospital between 2004–2006. When taken the history, the patients have been questioned regarding the possible risk factors.

Results: The risk factors of the VHC infection were identified in 61.57% of the subjects.
The profile of the risk factors was dominated by the surgical procedures (51.24%) and by the blood transfusions (22.73%). The professional risk and the presence of acute hepatitis nonA nonB weighted a lot less (4.55%, and 4.96%). Other factors include family factors (1.68%) or hemodialyse (0.41%). The dentistry treatments of little extent were included in the transmission without identifiable risk factors.
Out of a total of 179 surgical procedures, the most frequent were the obstetric-gynecology (30.17%), appendicectomy (17.77%) and colecystectomy (11.73%). Part of these procedures (22.58%), especially the obstetric-gynecology ones, having needed blood transfusions.
The transfusions have been significantly associated with the feminine gender, most of them being done before 1995.

Discussion/Conclusion: The epidemiologic history revealed the presence of risk factors in about 2/3 of the patients, out of which the most frequent were surgical procedures (51.24%) or blood transfusions (22.73%). The most frequent were the obstetrics-gynecology procedures, appendicectomies and colecystectomies.
The transfusions have been significantly associated with the feminine gender, most of which were given before the donor testing was available.
Chronic hepatitis C with normal or increased transaminases

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Introduction: The clinical aspect of chronic hepatitis has particularities depending on etiology or evolutive stage. The aim of this study is to evaluate the biochemical profile and the relationship between with other characteristics.

Methods: We included 242 patients with chronic viral C hepatitis admitted in our hospital between 2004–2006, diagnosed on clinical, virological and morphological (Ishak score) criteria.

Results: Most of the patients presented high levels of AST or ALT, but the increase of ALT was higher (86.78% vs. 77.27%, p = 0.006). Number of patients with normal AST was significantly higher than those with normal ALT (22.7% vs. 13.2%, p = 0.006).

Patients with high levels ALT or AST had mean age higher than those with normal transaminases. Increased ALT was predominant in male subjects (p = 0.019), while high AST showed no significance (p = 0.906).

No significant associations could be observed between AST and ALT levels and the viral load. Suggestive correlations were obtained between the necroinflammatory index and Ishak fibrosis and AST and ALT levels (p < 0.001).

Patients with normal AST/ALT presented more frequently mild hepatitis (81.8% and 78.1%, respectively) and mild fibrosis (F1) (58.2% and 46.9%) than moderate hepatitis (18.2% and 21.9%, p = 0.000) or severe fibrosis (F3–F4) (23.7% and 31.3%). Patients with increased AST or ALT levels has more often moderate/severe necroinflammatory lesions and severe fibrosis, when referred to mild fibrosis forms (p = 0.000).

Discussion/Conclusion: The predominant clinical forms were the ones presenting elevated AST and/or ALT.

The AST or ALT levels correlates with the Ishak necroinflammatory activity and the fibrosis. The patients' normal AST or ALT levels present mainly mild/minimal hepatitis lesions and mild, as well as moderate/severe fibrosis changes.
Hepatic encephalopathy and free fatty acids composition in sera of patients with liver cirrhosis

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Introduction: Liver cirrhosis is associated with a decrease in plasma levels of polyunsaturated fatty acids (PUFA). Neurons are particularly enriched in docosahexaenoic acid (DHA, 22:6n-3). The deficiency of DHA may be related to the impaired neural function. The aim of this study was to assess the free fatty acids composition in sera of cirrhotic patients according to encephalopathy occurrence.

Methods: 25 patients with liver cirrhosis were studied (8 had a low-grade, 7 had II and higher-grade encephalopathy, 10 had no signs of encephalopathy). Control group consisted of healthy volunteers. Daily dietary intake was analyzed. The free fatty acids composition in sera has been analyzed by gas chromatography.

Results: The presence of encephalopathy (grade II or above) has been shown to be associated with increase of content of oleic, linoleic and arachidonic acid. We were not able to detect any significant differences in DHA content in sera of cirrhotic group. The daily PUFAs intake of our patients with neurological complications was lower than in the rest studied groups.

Discussion/Conclusion: We have noticed rather increased content DHA in free fraction, but its percentage in sera of cirrhotic patients decreased successively with liver function worsening. However patients with encephalopathy still had higher content of DHA in sera then healthy group. Studies of PUFA synthesis have shown that, neurons are unable to carry out fatty acid desaturation and thus are dependent upon endothelial and astrocytes its synthesis. Though, they have more DHA in sera it is possible that there is a tissue deficiency.
Suppository 5-ASA treatment to maintain remission in ulcerative proctitis: Continuous, intermittent or no treatment

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Introduction: Topical 5-ASA is effective and safe both for the induction and the maintenance of remission in ulcerative colitis located solely in rectum. Suppository treatment is a good option in terms of tolerance when compared with enemas. To date, during remission, the knowledge about the natural history of ulcerative proctitis without treatment is very limited. In this study, we compared intermittent or continuous suppository 5-ASA treatments with the option of no treatment in the maintenance of remission in ulcerative proctitis.

Methods: A total of 30 patients with ulcerative proctitis consisted of 22 patients in the treatment arm (mean age: 42.7 ± 11.7) and 8 patients without treatment who quitted the medications after remission was achieved (mean age: 49 ± 10) were randomized to take 5-ASA suppositories in a dose of 2 x 250 mg whether on a daily (11 patients, mean age: 38 ± 10) or twice in a week basis. (11 patients, mean age: 47 ± 10) Relapse rates and durations of remission were compared between groups for the first 12 months and follow up period

Results: At the end of first 12 months follow up period, relapse rates in the group without treatment were significantly higher and durations of remission were also significantly shorter than those under treatment whether on daily or twice in a week basis (p < 0.05). In the long term follow up period, there was no difference between the groups with or without treatment in terms of relapse rates and durations of remission (p = 0.27).

Discussion/Conclusion: Intermittent suppository treatment on a twice in a week basis is as effective as continuous treatment in the maintenance of remission in ulcerative proctitis for the first 12 months and longer. The durations of remission of Patients without treatment were the same as in the patients with treatment after first 12 months.
How to determine low risk patients for rebleeding and mortality after acute upper gastrointestinal non-variceal bleeding?

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**Introduction:** Endoscopic sclerotherapy is effective in securing hemostasis for bleeding lesions, but bleeding reoccurs in 10% to 30% and 4% to 14% of the pts die after acute non-variceal upper gastrointestinal bleeding (UGIB). The need for hospitalization and its duration for all the bleeding pts is still a controversial question. Aim was to create the simple scoring system able to determine low risk pts for rebleeding and mortality after successful endoscopic sclerotherapy.

**Methods:** Prospective study included 315 pts with acute non-variceal UGIB. Gastroscopy with successful sclerotherapy was performed within 12 hours after the admission. We investigated the episode of rebleeding and death during the initial hospitalization, and analyzed the following parameters: age, gender, drug intake, shock, bleeding stigmata, location of bleeding lesion and comorbidity.

**Results:** Rebleeding occurred in 53 pts (16.8%) and was determined by shock, bleeding stigmata and comorbidity. Eleven pts (3.5%) died and shock, rebleeding and comorbidity were all independent, statistically significant predictors of pts’ mortality. The numerical scores for determination of different risk levels for rebleeding and mortality have been developed using the significant predictors of rebleeding and death. The score values for rebleeding ranged from 3 to 9 and pts with values ≤ 4 had low risk of rebleeding; score values for mortality risk ranged from 3 to 8 and the values ≤ 5 revealed negligible risk of death.

**Discussion/Conclusion:** Following the successful initial endoscopic sclerotherapy, these scores can help to identify up to 26% of acute non-variceal UGIB pts with low risk of rebleeding and negligible risk of death, so they can be treated as outpatients.
Acute upper gastrointestinal non-variceal bleeding – How to determine low risk patients for rebleeding and mortality after endoscopic sclerotherapy?

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Introduction: Successful endoscopic sclerotherapy is effective in securing hemostasis for bleeding lesions and remains the first line and only needed therapy for most of the patients (pts), but bleeding reoccurs in 10% to 30%, and 4% to 14% of the pts die after acute non-variceal upper gastrointestinal bleeding (UGIB). The need for hospitalization and its duration for all the bleeding pts is still a controversial question.

Aim: To create the simple scoring system able to determine low risk pts for rebleeding and mortality by establishing the relative importance of risk factors for rebleeding and mortality after successful endoscopic sclerotherapy of acute non-variceal UGIB.

Patients and methods: Prospective study included 315 pts who where admitted to hospital because of acute non-variceal UGIB. All of them underwent gastroscopy with successful sclerotherapy within 12 hours after the admission. We investigated the episode of rebleeding and death during the initial hospitalization, and analyzed the following parameters: age, gender, drug intake, shock, bleeding stigmata, location of bleeding lesion and comorbidity.

Results: Rebleeding occurred in 53 pts (16.8%) and was determined by shock, bleeding stigmata and comorbidity. Eleven pts (3.5%) died and shock, rebleeding and comorbidity were all independent, statistically significant predictors of pts’ mortality. The numerical scores for determination of pts with different risk levels for rebleeding and mortality have been developed using the significant predictors of rebleeding and death. The score values for rebleeding ranged from 3 to 9 and pts with values ≤ 4 had low risk of rebleeding; score values for mortality risk ranged from 3 to 8 and the values ≤ 5 revealed negligible risk of death.

Conclusions: Following the successful initial endoscopic sclerotherapy, these scores can help to identify up to 26% of acute non-variceal UGIB pts with low risk of rebleeding and negligible risk of death, so they can be treated as outpatients.

Key words: Bleeding, endoscopic sclerotherapy, rebleeding, death, risk factors, scoring system
Ulcerative colitis in children under 1 year of age

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Introduction: Although ulcerative colitis (UC) can affect both adults and children, the disease is quite rare in individuals under 1 year of age. We observed 5 children with UC from 2 to 12 months of age.

Methods: All infants underwent clinical examination, full blood count, biochemistry and immunology, gastric and bowel endoscopy and histology.

Results: UC presented in infants at the age of 4 ± 3.2 months with diarrhea and rectal bleeding. Abdominal pain was noted in one child and wasn’t associated with bowel openings. Extrabowel symptoms included mild anemia in 3 infants and transient alanine aminotransferase elevation in 2. Leucocytosis with neutrophilia was registered in 3, trombocytosis in 4 and erythrocytes sedimentation rate rise in 2 cases. Stool assay showed occult bleeding and a big number of leucocytes. Immune changes were minimal: blood protein, globulins fractions, immunoglobulins were normal in most cases, circulating immune complexes were slightly elevated, autoantibodies (pANCA, ASCA, AMA) were negative. Colonoscopy revealed pancolitis in all the infants with edematous, erythematous and friable mucosa with loss of vascular pattern, surface erosions and ulcerations, expressed lymphoid hyperplasia. The distinguishing histological features were multiple erosions, submucous and muscular edema, diffuse infiltration with lymphocytes predominance and large amount of eosinophiles in all bowel portions.

Discussion/Conclusion: UC in infants usually manifests with diarrhea and rectal bleeding and affects the whole colon. Immune answer is slightly marked; this can be the consequence of immune system immaturity in infancy.
Multichannel electrogastrography discerns changes in the human gastric myoelectrical activity evoked by afferent vagal stimulation through an oral exposure to a sour or a salty taste

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Introduction: It is conceivable that among other control mechanisms the sense of taste may contribute to the regulation of the gastric pacer. In the study a hypothesis was tested if sensory stimulation with a salty or a sour taste would affect the interdigestive gastric myoelectrical activity (GMA) in humans.

Methods: Eighteen healthy volunteers (10 F, 8 M) were subjected on two separate days to four-channel electrogastrographic recordings divided into consecutive 35-min periods: (i) basal fasted, (ii) a stimulation epoch while a subject was chewing an agar cube soaked with a taste-delivering substance (sodium chloride for the salty taste, citric acid for the sour taste), (iii) a post-stimulatory (recovery) epoch. The amount of Sodium chloride or citric acid within the cube was adjusted taking into account the individually established taste thresholds which were established on two separate examination sessions. An electrocardiogram was simultaneously registered for the purpose of the heart rate variability (HRV) analysis.

Results: Exposure to the salty taste increased both the power of the low frequency (LF: 0.04–0.15 Hz) band and the low to high frequency (LF/HF) power ratio of the power spectrum-analyzed HRV data. The sour taste did not affect the HRV. During the stimulation and the recovery epoch either in the case of the salty or the sour taste a statistically significant augmentation in the relative time share of tachygastria within the multichannel electrogastrogram was observed. Exposure to the salty taste resulted in a statistically significant decrease in the fraction of the coupled gastric slow waves. Moreover, the time share of bradygastria rose slightly but statistically significantly in response to the stimulation with the salty taste. On the other hand, the sour taste elicited a significant decline in the dominant power of the gastric slow waves.

Conclusions: (i) Oral exposure to a salty taste elicits a sympathetic arousal reflected by an increase in the LF power and the LF/HF power ratio, whereas a sour taste does not change the balance between the parasympathetic and the sympathetic constituent of the autonomous nervous system; (ii) The increment in tachygastria appears to be an unspecific phenomenon because it was evoked by stimulation with either the salty or the sour taste; (iii) The inhibitory effect on the GMA of the exposure to the sour taste is reflected by a dumping of the dominant power, whereas the stimulation with the salty taste is followed by an uncoupling of the gastric slow waves and an increase in bradygastria.
Cytokine profile of patients with overlap syndrome (OS) at autoimmune liver diseases

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Introduction: Research of a level serum cytokines at patients with OS at autoimmune liver diseases is represented actual for reception of new data about pathogenesis of OS.

Aim: An estimation of a level of the cores anti-inflammatory (IL-4, IL-10) and proinflammatory (IL-12, TNFα and INFγ) cytokines at patients with OS (combination of primary biliary cirrhosis (PBC) and autoimmune hepatitis (AIH).

Materials and methods: 20 patients have been included in research, middle age 55.25 ± 11.8 years. The diagnosis of OS was established on the basis of a clinical picture, laboratory parameters. At 15 patients the diagnosis was established by liver biopsy. Control group practically healthy 10 persons have made, group of comparison – 20 patients with PBS.

Results: Level IL-4 (7.78 ± 1.79 pg/ml) and IL-10 (83.96 ± 25.75 pg/ml) at patients with OS authentically did not differ from parameters of control group (p = 0.56, p = 0.49, respectively) and parameters of group of comparison (p = 0.81, p = 0.93, respectively). Level IL-12 (180.51 ± 62.3 pg/ml), TNFα (22.5 ± 4.3 pg/ml), IFNγ (251.5 ± 214.6 pg/ml) in the basic group authentically exceeded corresponding parameters of control group (p = 0.01, p = 0.002, p = 0.015). In group of comparison lower maintenance IL-12 (p = 0.002), maintenance TNFα is noted and IFNγ authentically does not differ from parameters of the basic group (p = 0.36, p = 0.38).

Conclusion: The raised secretion proinflammatory cytokines (IL-12, TNFα, IFNγ) at patients with OS possibly reflects activation T-lymphocytes or monocytes/macrophages.

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Enterosorbents in complex treatment of endotoxicosis at chronic colon diseases in children

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Gut endotoxicosis caused by penetration of bacterial and metabolic toxins from chime on the background of increasing permeability of gut wall is of great importance in pathogenesis of chronic colon diseases. It is accompanied by disturbance of regulating homeostasis system with the following disturbances of organs and systems of toxication.

Introduction: Endotoxicosis expressions depended on the character of pathological changes in colon and on condition of organs of detoxication, first of all the condition of liver.

Methods: We observed 95 children at the age from 5 to 15 years old with chronic colon diseases: 55 of them with its anomalous development (dolichocolon, dolichosigma), 15 patients with non-specific ulcer colitis (NUC), 25 patients with chronic nonulcer colitis and dyskinesia of colon.

To obtain accurate diagnostics of the degree and phase of development of endotoxicosis we defined quantitative and qualitative changes of metabolic status by LMMWP (low and medium molecular weight peptides) and OP (oligopeptides), determined in some mediums: blood plasma, erythrocytes, urine.

Results: Correlation between the extent of affection, expression of symptoms with the degree and the stage of endotoxicosis. The most prominent endotoxicosis was observed in children with NUC with extraintestinal manifestations the predominant of which was liver dysfunction.

Therefore, the therapeutic complex was added natural lignin enterosorbent-polyphepan, which besides binding in gastrointestinal tract exogenous and endogenous toxic substances, rendered stimulating effect on reparation of ulcer defects, exerting positive influence on composition of gut microflora.

Discussion/Conclusion: Positive dynamics of laboratory-instrumental parameters in usage of complex therapy with inclusions of enterosorbent-polyphepan showed remarkable improvement of clinical conditions in comparison with control group of children.
Diet relationship with colorectal cancers; an ecological study in Romania

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Introduction: Diet may play an important role in the risk of colorectal carcinoma and identification of risk as well of protective factors represents an important approach in cancer prevention.

Methods: The incidence rate of colon, rectum and anus cancers from 7 regions of Romania was calculated using the cancer registry. The investigation included 10 years (1994–2003), taking in consideration the mean value of this period. Data concerning the population food intake derived from dietary surveys performed by the Romanian National Institute of Statistics in 2001, 2002 and 2003. Correlation and regression analysis was used to examine the association of dietary intake with incidence rates.

Results: A strong and positive association was observed for colonic cancer and the intake of: coffee, tea and cocoa (r = 0.77, p = 0.042), lipid (r = 0.77, p = 0.043), mainly vegetal lipids (r = 0.80, p = 0.032) and a borderline value for statistical significance was found for margarine intake (r = 0.73, p = 0.06) and sweets (r = 0.74, p = 0.066). A potential protective effect can be attributed to wine intake (r = -0.75, p = 0.03) and to vegetal proteins (r = -0.82, p = 0.024). Cancer of rectum and anus showed both a strong positive correlation with the intake of: red meat (r = 0.76, p = 0.048), processed meat (r = 0.87, p = 0.012), margarine (r = 0.97, p = 0.0004), butter (r = 0.76, p = 0.049), sweets (r = 0.93, p = 0.003), beverages (r = 0.97, p = 0.0003), coffee, tea, cocoa (r = 0.94, p = 0.002), as well as with lipids (r = 0.92, p = 0.004), mainly vegetal (r = 0.71, p = 0.076). Reversed correlations were reported for the recto-anal cancer and the consumption of: fish (r = -0.8, p = 0.032), cheese (r = -0.9, p = 0.006), wine (r = -0.85, p = 0.015), vegetal proteins (r = -0.89, p = 0.007) and carbohydrates (r = -0.82, p = 0.025).

Discussion/Conclusion: One can observe the need for reducing the dietary intake of margarine, red meat, processed meat and sweets as well as the beneficial effects of wine consumption.
Pro-inflammatory cytokines (IL1β, TNFα) and anti-inflammatory cytokine IL4 of gastric juice in children with chronic gastroduodenitis

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The authors examined 49 patients with chronic gastroduodenitis and 14 healthy children in the age 4–7 years old as control group in order to study role of cytokines in chronic gastroduodenitis. The implemented study let as to indicate clinical – immunological parallels of forming and diagnosis of chronic gastroduodenitis in children.

Introduction: Now, the problem of chronic gastroduodenitis in children from 4 to 7 years of age is very important and actual. There are many children have got changes in mucous membrane of stomach. However, mechanisms of development of inflammation are not quite investigated. Role of cytokines is not investigated too. Treatment often is not effective.

Methods: 49 patients with chronic gastroduodenitis and 14 healthy children in the age 4-7 years old as control group were examined. Levels of cytokines (IL1β, TNFα and IL4) were measured in gastric juice. The children were divided into 2 groups: 1st group received only traditional treatment; the second was administered probiotic “Evita” in addition to the traditional therapy.

Results: Patients with chronic gastroduodenitis had increased level of pro-inflammatory cytokines (IL1β, TNFα) and anti-inflammatory cytokine IL4 compared with those in normal controls. They showed positive correlation between cytokines level and phase of disease and activity of gastritis. The significant increase of TNFα and IL4 take place in case of gastroduodenitis which is associated with Helicobacter pylori. The increase of IL1β and IL4 take place in case of gastroduodenitis which is associated with food allergy. After the traditional therapy pro-inflammatory cytokines (IL1β, TNFα) levels decreased slightly and insignificantly. Patients received probiotic “Evita” demonstrated more fast improvement of clinical manifestations of the disease and significant decrease of pro-inflammatory cytokines (IL1β, TNFα) levels.

Discussion/Conclusion: The implemented study let as to indicate clinical – immunological parallels of forming and diagnosis of chronic gastroduodenitis in children.
Effect of ursodeoxycholic acid in patients with non-alcoholic steatohepatitis

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Introduction: Non-alcoholic steatohepatitis (NASH) is a liver disease, associated with oxidative stress and with metabolic disorders – obesity, type 2 diabetes mellitus, insulin resistance, fatty liver, hyperlipidemia. The treatment requires correction of metabolic changes by diet and drugs, but is still unclear. The data of the efficacy of ursodeoxycholic acid (UDCA) in the treatment of NASH are controversial and its beneficial effect is not confirmed.

Aim: To investigate the effect of UDCA in patients with NASH.

Material and methods: The study presented 39 patients with NASH – 15 males and 24 females, divided in 3 groups: 1st – with elevated ALAT and ASAT only (cytolytic enzymes), 2nd – with both cytolysis and cholestasis, 3rd – with hyperlipidemia. Other reasons for chronic hepatitis were excluded (HBV, HCV, autoimmune hepatitis, alfa-1-antitrypsin deficiency, Wilson’s disease). Diabetes mellitus type 2 was found in 10 cases. In some patients BMI was abnormal. Ultrasound examination showed fatty liver in different degrees. Liver biopsy was performed in 11 patients. All patients were treated with UDCA (Ursofalk®) in dose 10–15 mg/kg/24 h and with antioxidants for 4 weeks. In cases with hyperlipidemia Lipanthyl (micronised fenofibrate) was added. All patients went on low-calorie diet. They were followed up for 2–3 months.

Results: Biochemical parameters of cytolysis and cholestasis in all groups significantly decreased after the treatment. Serum lipids reduced to normal too. No side effects were observed.

Discussion/Conclusion: Our study manifested the favourable effect of UDCA in patients with NASH. It is safe and effective agent in complex treatment with antioxidants and hypolipidemic drugs to improve liver function. Our results show expressed hepatoprotective action of UDCA. It could be useful in the management of NASH and we recommended UDCA as mandatory drug in the therapeutic strategy of this disease.
Introduction: The aim was to evaluate the precipitants factors of hepatic encephalopathy (HE) and to investigate the possible role of Helicobacter pylori (HP) infection, as a risk factor for development HE, in patients with hepatic cirrhosis.

Methods: We studied 156 patients with cirrhosis (36 cases Child-Pugh A, 52 Child-Pugh B, 68 Child-Pugh C). The diagnosis was based on clinical findings, biochemical liver tests, imagistical (US, CT, endoscopy) examination. The patients with HE were divided in: group A composed of 24 patients with HP infection and group B consists of 17 patients without HP infection. All patients was treated with low protein diet, neomicin, lactulose and amino acid solution and patients with HP was treated with additional specific therapy (40 mg omeprazole, 2000 mg amoxicillin, 500 mg clarithromycin, daily for two weeks). We determined plasma ammonia level, psychometric tests and serum HP antibodies IgG for each patients with HE, before and 8 weeks after therapy. Plasma ammonia levels, at baseline and after treatment, were analyses using the Chi-Square tests, and Pearson correlation coefficient.

Results: The incidence of HE was 26.28% (41 cases): 8.33% at patients with Child A, 23.07% in Child B and 38.23% in Child C cirrhosis. A higher percentage of HE (65.85%, 27 cases) was observed in patients with alcohol drinking history. The causes that determined encephalopathy was: gastrointestinal bleeding (11 cases), massive paracentesis (3 cases), diuretic therapy (10 cases), infection (2 cases), high protein diet (11 cases), unknown factors (4 cases).

The psychometric tests were positive in 63.41% of patients with HE. Plasma ammonia levels in Child-Pugh B and C was significantly higher. In B group, the ammonia concentration was reduced to the normal after the treatment and in a group was significantly reduced after HP eradication. There was no significant difference of EH forms in HP-positive and HP-negative patients. Blood ammonia concentration was correlated with Child-Pugh score (r = 0.61) and alcohol consumption level (r = 0.497).

Discussion/Conclusion: Plasma ammonia level was higher at patients with advanced cirrhosis. HP infection is not considered to be the factor determining EH.
Ursodeoxycholic acid versus simvastatinum in the treatment of nonalcoholic steatohepatitis

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Introduction: The aim of this study was to evaluate and compare the efficiency and safety of ursodeoxycholic acid (UDCA) versus simvastatinum in the treatment of non-alcoholic steatohepatitis (NASH).

Methods: We included in this study 33 patients with NASH and obesity. We excluded patients with viral or autoimmune hepatitis, diabetes mellitus or drug abuse. The diagnosis of liver steatosis was based on the correlation of histologic, imagistic and clinical findings. Liver biopsy was performed before and after therapy.

A group composed of 18 normolipidemic cases, treated with UDCA (13–15 mg/kg/day) and B group consist of 15 hyperlipidemic cases which received simvastatinum (20 mg/day) for six months. We evaluated liver function tests, serum lipids and BMI at the beginning of therapy, after 3 and 6 months.

Results: A number of 20 patients had elevated serum aminotransferases, but 13 had normal level. Lipid profile was abnormal in B group patients: 7 cases with hypercholesterolemia, 4 cases with hypertriglycerideremia and 4 with both. In A group, mean value of serum ALT-level was decreased from 88.3 ± 21.7 U/l at baseline, to 52.12 ± 17.5 U/l at 3 months. In B group, serum ALT was reduced (in mean with 19.3 ± 7.2 U/l) after 3 months and cholesterolemia was significantly improvement in 8 cases (72.7%). In 2 cases we need increased simvastatinum dose at 40 mg/day.

Histopathologic and sonographic examinations was relieved improvement the steatosis grade in A group patients (15 cases, 83.3%). Comparatively, in B group, the response rate was 73.3%.

In the therapy period, we could not establish a correlation between the values of serum aminotransferases and others parameters, but multivariate analysis showed that the BMI > 28 kg/qm and elevation of serum ALT were associated with steatosis grade. Patients which associated UCDA therapy with low caloric diet, had a good and rapid response.

Discussion/Conclusion: UCDA in association with low caloric diet still remains first line therapy at patients with NASH and obesity.
Severe gastroesophageal reflux with esophagitis has a deleterious effect on pulmonary functional parameters in asthmatic patients

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Introduction: The aim of the study was to estimate if gastroesophageal reflux can contribute to deterioration of pulmonary functional parameters in asthmatic patients with stable mild-to moderate asthma taking only inhalatory therapy.

Methods: One hundred twenty nine non-smoker patients (69 males/60 females) were selected to participate. Any oral therapy, including corticoids, aminophyllin and antacids was forbidden during the study period of three weeks. In all patients GERD was assessed clinically by administrating a reflux questionnaire (ReQuestTM) and endoscopically. Only 45 subjects (34.88%) from the study group did not meet any criteria for GERD, being classified as controls, while the rest had at least clinical symptoms of reflux disease. From those patients, 59 (45.73%) had non-erosive reflux disease, while 25 (19.37%) presented various degrees of erosive esophagitis extended from A to D (LA classification). Pulmonary functional assessment consisted in all subjects in three matinal determinations of peak expiratory flow rate (PEFR) and forced expiratory volume in 1 s (FEV1) performed every week at the same time.

Results: Mean values for PEFR were higher in controls than in GERD patients (341.58 ± 15.73 vs. 310.13 ± 12.33 L/min) but without statistical significance (p = 0.151) while FEV1 was significantly lower in GERD patients than in controls (1.09 ± 0.27 vs. 1.33 ± 0.43 L/s, p = 0.043). Meanwhile, in GERD group, both PEFR (269.32 ± 13.51 vs. 214.58 ± 14.38 L/min, p = 0.032) and FEV1 (1.14 ± 0.16 vs. 0.97 ± 0.27, p = 0.021) were higher in subjects with non-erosive reflux disease than in those with reflux esophagitis (all grades included).

Discussion/Conclusion: GERD certainly contributes to impairment of pulmonary function in asthmatic patients. Even it may be considered as a secondary factor, severe reflux with esophagitis can significantly diminish functional parameters like FEV1 in asthma, raising the question whether acid-lowering agents cannot be useful in this condition.
Celiac disease is associated with the changes in claudins 3 and 4 expression in duodenal epithelium

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Introduction: Claudins constitute a 24-member family of tight junction proteins that differentially regulate paracellular permeability. It is well known that intestinal permeability is increased in celiac disease (CD), but mechanisms of this alteration are not well understood. The aim of the study was to clarify whether CD is associated with a change in claudins 3 and 4 expression in duodenal mucosa cells.

Methods: Claudins 3 and 4 were assessed immunohistochemically in duodenal biopsy specimens from 6 untreated CD patients (Marsh III C) and 6 controls. In 3 CD patients duodenal biopsy specimens were repeatedly assessed after 1 year of the keeping to strict gluten-free diet.

Results: Claudin 3 was strongly expressed in the normal duodenal epithelium without an obvious gradient along the crypt-to-villus axis. Claudin 4 was preferentially expressed in the villus top region, whilst absent or barely detectable in crypt cells. In 5 CD patients, claudin 3 was only weakly expressed in crypt cells but there was no change in its expression in villous epithelium. Claudin 4 was weakly detectable or absent in 4 CD patients. In repeatedly obtained specimens histological recovery occurred (to Marsh I – 2 cases, to Marsh 0 – 1 case) in association with normalization of claudin 4 but not claudin 3 expression.

Discussion/Conclusion: CD is associated with the changes in claudins 3 and 4 expression, some of which seem to be reversible. Further investigations are needed to assess their role in intestinal barrier dysfunction and pathogenesis of CD.
Chronic alcoholic hepatitis and scavengers for reactive oxygen species

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Introduction: The aim of our study was to determine reduced glutathione (GSH) and superoxide dismutase (SOD) levels in chronic alcoholic hepatitis (CAH) patients, correlated with E vitamin administration, in vitro experiment.

Methods: Were investigated 5 normal peoples and 32 patients with CAH histological diagnosed, without HBs antigen or anti-C antibodies in sera, with increased value of gama-GT, and with an alcohol intake more than 80 g/day, for more than 10 years. In blood samples were determined SOD activity (by NBT technique) and GSH (by DTNB method). The antioxidant capacity was performed in basal conditions and after 30 minutes of pre-incubation of 2 ml heparined blood with 0.2 ml E vitamin solution.

Results: In CAH patients, in basal conditions SOD (7.514 ± 1.323 U/ml) and GSH values (584.45 ± 65.01 microM/ml) were greater than in control group (SOD= 5.592 ± 0.754 U/ml and GSH = 537.14 ± 26.52 microM/ml).

Discussion/Conclusion: E vitamin is an effective free radicals scavenger in CAH patients emphasized by the increased levels of SOD (16.02 ± 1.92 U/ml) and GSH (1108 ± 50.73 microM/ml) after blood pre-incubation with E vitamin, more than in control group. In CAH patients the oxidative stress was more intense than in healthy persons. These results sustained the importance of E vitamin supplementation in CAH patients.
Biochemical and morphologic changes in liver after autologic transplantation haematopoietic stem cells (1st step of clinical investigation)

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The possibility of haematopoietic stem cells (HSC) to stimulate the liver regeneration was shown in rats and after partial hepatectomy in human. Our research was made in Stem Cell Bank of Kazan medical university and is devoted to investigation of influence of HSC on course of alcoholic hepatitis. We study 3 patients with moderate and severe chronic alcoholic hepatitis (HAI 12–14) with cirrhosis (class A), increased levels of ALT, AST, GGTP and decreased prothrombin level. The stimulation of HSC leaving from bone marrow to blood was done by Neupogen. Mononuclear cells were separated by Cell Sorter MSC+. Twenty ml of cell’s concentrate were introduced into celiac trunk of each patient.

Preliminary results of study let conclude that transplantation of autologic HSC into celiac trunk of alcoholic hepatitis + cirrhosis patients is safe and effective procedure. In one month after injection of HSC the patients feels was better, ALT, AST, GGTP decreased, prothrombin increased. HAI is reduced on 2–3 points (because of diminished portal inflammation and intralobular necrosis). Immunohistochemical staining of liver specimens reveals significant reduction of hepatocyte’s proliferation and alpha-SMA+ myofibroblast number in liver parenchyma. The level of perisinusoidal fibrosis also decreased, and therefore the expression of CD34 disappeared from endothelial sinusoidal cells and these cells acquired phenotype that is typical for liver sinusoids.
The expression of E-cadherin-catenin complex in patients with advanced gastric cancer: Role in formation of metastasis

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Introduction: E-cadherin-catenin complex plays an important role in process of cell adhesion. Our aim was to evaluate the expression of E-cadherin and β-catenin in advanced gastric cancer in comparison with selected clinico-pathological parameters.

Methods: Formalin-fixed, paraffin-embedded tissue specimens were immunohistochemically stained with monoclonal antibodies E-cadherin and β-catenin (Novocastra).

Results: We have not observed statistical significant correlation between expression of E-cadherin, β-catenin and Lauren’s classification, histological differentiation. However, we found association between expression of β-catenin in main mass of tumor and in lymph node metastasis and localization of tumor. Also the depth of invasion was correlated with positive expression of β-catenin in main mass. A statistically significant association was observed between expression of E-cadherin and β-catenin in main mass of tumor and presence of lymph node metastasis. We have observed strong correlation between expression of E-cadherin in main mass of tumor and expression of β-catenin in main mass of tumor. We have found strong correlation between expression of these two proteins in lymph node metastasis.

Conclusion: Our results may suggest that E-cadherin-catenin complex is a factor of metastasis and disease progression in gastric cancer.

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Quality of life after laparoscopic treatment of gastroesophageal reflux disease

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Introduction: Surgical management of gastro-esophageal reflux disease (GERD) has evolved over the last three decades, introduction of laparoscopy being a real improvement in its management. The aim of our prospective study is to evaluate quality of life in patients with GERD underwent to laparoscopic management.

Patients and methods: We included in our study, between January 2002 and December 2005, 46 patients in which we achieved Nissen fundoplication (23 patients) and anterior valve (23 patients). Quality of life before surgery and in the first and fourth postoperative months was evaluated using the Short Form 36 general health questionnaire (SF36) and Illness Behavior Questionnaire.

Results: We discovered an important improvement (over 95%) in regurgitation, pyrozis and dysphagia in the first month after surgery and also a decrease of incidence of gas bloating four months after. In patients where we achieved anterior valve we reported significant improvements in eight of nine SF36 scales compared with Nissen fundoplication in which we observed improvements in five of nine at first postoperative evaluation. At four months after surgery we reported mostly similar improvements for both procedures.

Conclusions:
1. Laparoscopic fundoplication is an effective and valuable surgical operation in controlling symptoms of GERD and improving quality of life.
2. Anterior valve offer a better improvement of quality of life on short time compared with Nissen fundoplication but later follow up of these procedures was similar.

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Long-term outcomes of laparoscopic antireflux surgery for gastroesophageal reflux disease

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Introduction: Gastro-esophageal reflux disease (GERD), increasing esophageal exposure to gastric juice, can be due to a mechanically defective lower esophageal sphincter, inefficient esophageal clearance of refluxed gastric contents, and abnormalities of the gastric reservoir that augment physiologic reflux. Surgical therapy, with its new advances, minimally invasive surgery, has been recommended as it is more effective than medical therapy in the short term, but there is little data on the effectiveness of surgery long-term. The aim of our study is to evaluate GERD symptoms after laparoscopic anti-reflux surgery.

Patients and methods: We evaluated 62 patients in which we achieved a laparoscopic anti-reflux procedure (23 in patients Nissen fundoplication and in 39 Toupet), after a median follow-up of 28 months (15–62 months) in terms of symptoms, need for medication and esophageal acid exposure. We used Wilcoxon signed rank test to assess symptoms scores before and after surgery, a chi-square test for dichotomous variables and a paired Student’s t-test to assess the pH monitoring and manometry results. Significance was accepted at a p value less than 0.05.

Results: After surgery we discovered a significant improvement in GERD symptoms (heartburn, sore throat, cough, hoarseness, dyspnea and wheezing (84% of patients appreciate results as excellent or good) and also a significant reduction in necessary of antacid medication. Presence of abnormal reflux in the pharynx was the single predicting factor for surgical outcome.

Conclusions:
1. Laparoscopic anti-reflux surgical procedures provide a durable improvement in GERD-related symptoms;
2. Pharyngeal pH monitoring identifies those patients more likely to benefit from surgery.

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Epidemiology of paediatric inflammatory bowel disease (IBD) in Lower Silesia district (Poland): 1986–2005

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Introduction: The incidence of IBD, especially of Crohn’s disease (CD) in children seems to be rising.

The aims of the study were: 1. The delineation the trend in incidence of IBD in children < 18 years of age in the Lower Silesia district in the period of 1986–2005 (retrospective analysis); 2. The assessment of paediatric IBD incidence in the same region in the years 1998–2000 (prospective analysis).

Methods: 1. All children admitted to our Department between 1986–2005 who met the criteria of IBD (ulcerative colitis – UC, CD or indeterminate colitis – IC) were included. The clinical features and epidemiological data were analyzed.
2. Paediatricians from all departments in analysed district sent to us questionnaires if they had diagnosed a new case of IBD.

Results: 277 cases of IBD (UC – 155, CD – 55 and IC – 67) were recognized in the period of 1986–2005. The incidence rate (period of 1998–2000) was 2.28 new cases of UC and 0.38 cases of CD/100,000 children/year. An increase in incidence of IBD, especially of CD was observed. The year 2005 was the first year with equal number of new cases of UC and CD. A higher UC and CD morbidity rate was observed in boys and in large cities. Seasonality of the onset and exacerbations of IBD (September-March) was observed.

Discussion/Conclusion: 1. The incidence of IBD, especially of CD in children of Lower Silesia district (Poland) showed an increasing trend during the 20-year period.
Etiological factors in hepatocellular carcinoma

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In order to assess etiological factors included in pathogenesis of hepatocellular carcinoma (HCC) we investigated 67 patients with established diagnosis of HCC.

We found 22 patients (32.8%) with hepatitis B viral infection, 23 patients (34.4%) with hepatitis C viral infection, 10 patients (14.9%) had infection with both viruses, and 12 patients (17.9%) had no viral infection. There were no intravenous drug abusers. The history of blood transfusions had 7 patients (10.4%) – only one of them with hepatitis B viral infection. Also 7 patients (10.4%) had history of previous surgical interventions – 2 of them were HBsAg-positive, and 3 patients were anti-HCV-positive.

Significant alcohol consumption (> 80 g/l) was found in 32 (47.7%) patients. HBsAg-positive were 10 (31.25%) patients, 15 (46.87%) patients were anti-HCV-positive, 4 (12.55%) patients had infection with both viruses, and 3 (9.37%) patients had no viral infection.

In 22 (66.66%) patients with HCV infection and 7 (21.87%) HBsAg-positive patients liver cirrhosis was revealed.

The majority of patients were male – 56 (83.58%). Only 3 (4.47%) patients were < 40 years old, 15 (22.38%) were 40 to 60 years old, and 48 (71.64%) were > 60 years of age.

The data suggest that the most significant etiological factors in development of HCC are hepatitis B and C viruses, especially in association with alcohol. Alcohol consumption, gender and age are also important independent factors in etiology of this cancer.
Surgical treatment of Crohn's disease complications – Our experience

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Background: In Slovenia the incidence of Crohn’s disease (CD) has been in significant increase for the last two decades. Surgical treatment of CD is only symptomatic. It is indicated in case of complications endangering patient’s life, in septic complications, in chronic bowel obstruction, in enteric fistulas and in the therapy resistant extraintestinal manifestations of CD.

Patients and methods: From January 1999 to December 2006 179 patients were operated for CD. There were 101 female and 78 male patients, aged from 18 to 82 years (mean 36 years). 136 patients underwent only one operation, 43 patients had 2 to 5 subsequent operations in this 7-year period. The most common procedure was ileocecal resections (67 patients, six of them laparoscopic assisted). Resection of the ileum was performed in 66 patients, resection of colon in 48 patients and resection of previous anastomosis in 33 patients. Subtotal and total colectomy was performed in 8 and 5 patients, respectively. Proctocolectomy was performed in 3 cases and abdominoperineal excision of rectum in 16 cases. Procedures without resections were: duodenojejunostomy (2 x), ileostomy (4 x), strictureplasty (11 x), dilatation of stenosis (3 x) and endorectal advancement flap (2 x).

In 13 cases of perianal fistula only incisions were performed and in 16 cases of perianal fistulas without major CD involvement of rectum only fistulotomy was made.

Results: Dehiscence of strictureplasty occurred in one patient and anastomotic leak in three patients. Abdominoperineal excision of rectum in patients previously treated with colostomy was performed in 16 patients and in one patient with concurrent rectal carcinoma. Three patients with CD died after operative procedure, due to septic complications and peritonitis.

Conclusion: Surgical treatment of CD is only symptomatic where organ preserving surgery is recommended. For perineal manifestation of conservative procedures are indicated.
Water load in contrast to a liquid caloric test meal disorganizes the multichannel electrogastrogram in humans

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Introduction: The multichannel variety of electrogastrography, introduced by Chen et al. (Am J Physiol Gastro intest Liver Physiol 1999; 277: G424), remains a novelty and there is a need for research on a standardization of this method. The current study was devoted to a comparison of multichannel electrogastrograms obtained after intake of comparable volumes of an acaloric liquid load or a liquid caloric test meal.

Methods: Eighteen healthy volunteers (9 F, 9 M), free from Helicobacter pylori infection, were examined. On two separate days in randomized order they drank 400 ml of still mineral water or ingested 400 g of yoghurt (378 kcal) as a liquid caloric test meal. The gastric myoelectrical activity (GMA) was registered for 30 min during the interdigestive state and subsequently during 90 min of the fed period by means of a four-channel electrogastrographic system. The obtained electrogastrograms were analyzed with the use of the Polygram Net™ EGG 311224 software (Medtronic, USA).

Results: A drink of 400 ml water at room temperature evoked a statistically significant decrease in the relative time occupied by normogastria – from 81.3% during the fasted state to 75.5% (p = 0.044), 74.2% (p = 0.0091) and 71.2% (p = 0.00027) within the consecutive sub-periods: 1–30 min, 31–60 min and 61–90 min. Ingestion of the liquid caloric test meal did not elicit any significant change in the relative time share of normogastria. The liquid acaloric load did not affect the dominant frequency (DF) or the dominant power (DP) of the GMA. The postprandial evolution of the DF and DP observed after ingestion of the liquid caloric test meal was suggestive of an incremental trend of those parameters in response to the meal stimulation; the respective shifts proved, however, statistically not significant. Intake of 400 ml of the liquid acaloric load brought about a statistically significant decrease in the average percentage of slow wave coupling (APSWC) from 80.7% during the interdigestive state to 74.6% (p = 0.042), 74.7% (p = 0.049) and 70.3% (p = 0.00032) within the consecutive sub-periods: 1–30 min, 31–60 min and 61–90 min. A similar but weaker trend as concerns the effect on the APSWC was observed also after ingestion of the liquid caloric test meal. It failed, however, to gain a proof of statistical significance.

Conclusions: Intake of 400 ml of a liquid acaloric load decreases the rate of coupling of the gastric slow waves registered with the use of a multichannel electrogastro-graphic recording. Such a phenomenon does not occur after ingestion of a liquid caloric test meal.
Rifampicin ameliorates TNBS colitis in rats and improves the bioavailability of talinolol which was decreased during colitis

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Background and purpose: Purpose of this study was to investigate any possible relationship between the therapeutic efficacy of rifampicin in 2,4,6-trinitrobenzene sulfonic acid (TNBS) induced colitis of the rat and its P-glycoprotein (P-gp) inducing effect. P-gp inducing effect was studied indirectly by investigating the bioavailability of talinolol, a P-gp ligand, during colitis and after treatment with rifampicin.

Experimental approach: Three groups of rats were used for the in vivo bioavailability, in situ intestinal perfusion, and mucosal permeability studies. Each group was subdivided to control, colitis, rifampicin (15 mg kg⁻¹ d⁻¹, 14 d), and rifampicin + colitis groups. To determine the bioavailability of talinolol, blood samples were taken for 8 h. In in situ intestinal perfusion studies, intestinal segments were perfused with Tyrode solution containing talinolol. Talinolol levels were determined using the HPLC method. Mucosal permeability was determined by blood-to-lumen clearance of ⁵¹Cr-EDTA. At the end of the studies, rats were sacrificed and after macroscopic investigation, intestinal tissue samples were stored for biochemical and histochemical analysis.

Results: Rifampicin prevented the morphologic changes, oxidative damage and inflammation induced by colitis, decreasing the MDA, luminol and lucigenin, MPO and TNF-α levels, and increasing GSH levels significantly. Bioavailability decreased significantly in the colitis group but was back to control values following treatment, but intestinal effective permeability values were lower than the control group. Mucosal permeability was not changed.

Conclusion: Chronic treatment with oral rifampicin ameliorates TNBS colitis in rats. This effect may be related to its antibacterial effect as well as pregnane X receptor inducing property.
**Helicobacter pylori infection in peptic ulcer bleeding – Culture and rapid urease testing**

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**Introduction**: We evaluated the prevalence, density of colonization and susceptibility of *H. pylori* during the emergency endoscopy for peptic ulcer hemorrhage.

**Methods**: 110 patients – 81 males (mean 57.3; SD ± 15.9); 29 females, (mean 63.6; SD ± 12) were tested with culture, 104 of them additionally with rapid urease test (RUT) for *H. pylori*. One antral and one corporal biopsy were transported in Stuart medium, stained directly by Gram and cultured on selective and non-selective media for *H. pylori* for 7–10 days. The isolates of culture positive patients were compared with isolates from 292 *H. pylori* positive untreated dyspeptics without ulcers (controls). Density of colonization was evaluated using semiquantitative scale ranged 1 to 4 in 98 patients, 292 controls. Susceptibility of *H. pylori* was tested by limited agar dilution method in 74 patients, 236 controls.

**Results**: Positive for culture were 98/110, for RUT for *H. pylori* – 92/104 patients. Positive for both tests were 80.8% (84/104), negative for both tests for *H. pylori* – 4/104 patients.

Highly colonized (3+ and 4+) were 50% of patients vs. 36.3% of controls (n = 390, p < 0.015).

The primary resistance of *H. pylori* to metronidazole was 13.7% vs. 26.2% (n = 310, p < 0.041), to clarithromycin 25.7% vs. 17% (n = 315, p > 0.13), to amoxicillin 1.4% vs. 0.8% and to tetracycline 1.5% vs. 5% compared to controls.

**Discussion/Conclusion**: Patients with previous attempt for eradication of *H. pylori*, acid suppression or antimicrobials for the preceding month were not included. 33 patients reported NSAID use. Rapid urease test and culture for *H. pylori* were sensitive in these conditions despite bleeding. Most of our patients are highly colonized with *H. pylori*, which susceptibility patterns imply further investigations.
The clinical significance of bile duct sludge – Is it different from bile duct stones?

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Background: Some patients with suspected common bile duct (CBD) stones are found to have sludge, and no stones. While sludge in the gallbladder is a precursor of gallbladder stones, the significance of bile duct sludge (BDS) is poorly defined.

The aims of this study were to compare BDS to bile duct stones in terms of frequency, associated risk factors, and clinical outcome following endoscopic therapy.

Methods: Two-hundred and twenty eight patients who underwent therapeutic ERCP for suspected choledocholithiasis were included. The patients were divided into two groups: patients with BDS but no stones on ERCP and patients with CBD stones. The presence of risk factors for bile duct stones (age, periampullary diverticulum, ductal dilatation or angulation, past open cholecystectomy) were assessed at ERCP. Follow-up data (36 ± 19 months) were obtained from medical records and by patient questioning.

Results: BDS occurred in 14% (31/228) of patients and was more common in females. After endoscopic clearance CBD stones recurred in 17% (33/197) of patients with CBD stones, and in 16% (5/31) of patients with BDS (p = 0.99). CBD dilatation was less common in the sludge group. The other known risk factors for recurrent CBD stones: (age, past open cholecystectomy, bile duct angulation, and the presence of a peripampillary diverticulum) were not statistically different between the groups.

Conclusions: These findings indicate that the clinical significance of symptomatic BDS is similar to that of CBD stones. BDS seems to be an early stage of choledocholithiasis.
Polypectomy for all colorectal polyps or follow-up?

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Objective: There is controversy whether all colorectal polyps on colonoscopy should be removed whenever detected. This study evaluated the histopathologic characteristics of colorectal polyps in Turkish patients, and further determined their relationship to age, gender, size and location. We aimed to determine the risk of having neoplasms in those with small polyps (≤ 5 mm) and emphasize the importance of removing.

Materials and methods: Of 4145 colonoscopies reviewed between July 2004 and June 2006, 791 polypectomy and 211 polyp biopsies were performed on 576 patients.

Results: Of the 1002 polyps histologically analyzed, 586 (58.5%) were non-neoplastic, 396 (39.5%) were neoplastic and 20 (2.0%) were missed data. Among the neoplastic polyps 311 (78.5%) were tubular, 41 (10.4%) were tubulovillous and 31 (7.8%) were villous, and 13 (3.3%) had malignant degeneration. 63% of the non-neoplastic polyps were hyperplastic and the remaining 37% were inflammatory polyps. Both neoplastic and non-neoplastic polyps located predominantly in the left colon (rectum, sigmoid, descending colon). With increasing size of polyps, the frequency of neoplasia increased. As 31.7% of the polyps < 5 mm was neoplastic, 82.4% of the polyps > 20 were neoplastic. There was no significant gender difference in distribution of either neoplastic or non-neoplastic polyps. The peak prevalence of polyps occurred in the same age group (50–70) in both neoplastic and non-neoplastic polyps.

Conclusion: With the aging of the population the number of colorectal cancer cases is likely to increase in the years ahead. Even small polyps seen during colonoscopy should be removed and subjected to histologic analysis because of the advisability of follow-up examinations of patient with neoplastic polyps.
The role of spasmolytics in treatment of chronic constipation in children

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Introduction: Recently the problem of prophylaxis and treatment of chronic constipation becoming more and more relevant. Unfortunately standard medication therapy of chronic constipation isn’t always effective.

Methods: The main cause of functional constipation in children is duskeness of large intestine. Colon manometry was used to define motility disorders in large intestine. According to results 96.6%, out of 30 children examined, has hypokinetics motility disorder, 64% out of them has it due to local tone rise of intestinal wall, which arise 15–30 minutes after food intake. Intestinal wall’s hypertone leaded to the deterioration of the index and time of motility with abrupt rise of intraluminal pressure. For spasm removal we used spasmolytics as well as standard therapy. Buscopan® was chosen due to its phytogenic and convenient form (available in tablets, liquid and suppositories.) Medication was prescribed according to age-specific dosage. The length of intake was 8–10 days.

Results: Under the influence of the complex therapy in 10 days we could observe the positive dynamic of clinical symptoms: sigmoid colon’s tone was approximately normal, lack of anal sphincter spasm, normal stool frequency. Control colon manometry showed that tone of intestinal wall declined from 0.096 ± 0.003 to 0.056 ± 0.004 (p < 0.01) coming close to healthy children’s index. Due to this decline the motility index of large intense increased from 15.3 ± 0.17 to 24.6 ± 0.15.

Discussion/Conclusion: As a result of study show, the Buscopan® in conjunction with standard therapy increase the effectiveness rate.
Anorectal pathology with functional abnormalities of dejection among children

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Introduction: Only 1/3 of patients with functional abnormalities of dejection do not have structural changes of anorectal zone. These children have not been ill for more than 3–4 months. Untreated anorectal processes result in the relapse of functional abnormalities among the half of the children.

Methods: Retrospective and current analysis of the clinic and the results of the laboratory-instrumental inspection among 400 children at the age of 2 till 17 with the diagnosis “functional abnormalities of dejection”.

Results: The patients kept under observation have the following dysfunctions – functional diarrhea (16%), transient delays of dejection (5%), functional constipation (71%), obstipational encopresis (4.25%), irritable intestines syndrome (3.75%). State of the anorectal zone: 36% have no pathologies, 58% have anal fissures, 4.5% have cryptit and papillitis, 2.5% have haemorroidal piles, 3.5% have rectal prolapse including the solitary ulcer of rectum – 1%. 5% of children had combined injury. Half of the children with anorectal changes, especially with the delays of dejection, showed the regress of the clinic of abnormalities of dejection which occurred simultaneously with the recommencement of complaints about the affection of the anus (pain, a feeling of a foreign matter, admixture of blood to the dejecture, “the fear of a chamber-pot”). This situation happened when the recommendations for the topical treatment were not maintained.

The checkup must include an active showing up of complaints, typical for the anorectal pathology, an examination of the anus, finger-examination of the anus and/or the proctoscopy. If there is an admixture of blood to the faeces the necessity of the sigmoidoscopy/colonoscopy’s conducting arises. The treatment of the anorectal affections must be conducted together with the correction of the motor, secretory and barrier function of the intestines. In the foreground there must be activities connected with the prevention of the traumatization of anus and the elimination of the pain reflex from the side of anus.

Discussion/Conclusion: Anorectal affections stimulate the relapses of the functional abnormalities of dejection by stirring up the conditioned and psychogenic mechanisms of pathogenesis. Diagnostics, treatment and prophylaxis of the anorectal complications are essential components of the complex diagnostics and the pathogenetic therapy of the functional abnormalities of dejection.
Gastroesophageal reflux disease among patients suffering from coronary artery disease

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Introduction: In recent years the increasing frequency of gastroesophageal reflux disease (GERD) occurrence has been observed. GERD may take the form of so-called ‘heart mask’ (i.e. chest pain) imitating ailments typical for the myocardial ischemia.

Aims: The aim of this work was to evaluate frequency of GERD occurrence and the oesophagitis among patients suffering from angiographically confirmed coronary artery disease. The patients mentioned above were ordered to undergo CABG.

Subjects and methods: 134 coronary artery disease (CAD) patients were observed. All patients underwent medical history, physical examination and gastrointestinal endoscopy.

Results: GERD symptoms were found in 46 patients diagnosed with CAD what constitutes 34% of the total number of patients (28.3% vs. 3.4%, p = 0.00006). It has to be mentioned that oesophagitis was found more often among patients suffering from GERD (i.e. among 24% of the total number of patients). According to the Los Angeles classification, type A of the reflux oesophagitis occurred more frequently than type B (A = 15.3%, B = 10.9%). The Barrett oesophagus had been observed among 5.5% of patients. Other complications of GERD had not been found. It is worth to emphasize that there was a significant statistical correlation between GERD, hiatal hernia, heart infarction and smoking.

Conclusions: Patients often suffer simultaneously from the oesophageal reflux disease and CAD. Such coexistence of those illnesses may result in the ambivalent character of ailments and lack of clinical improvement.
Non-invasive assessment of liver periportal fibrogenesis in chronic viral hepatitis

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Introduction: An increasing number of reliable noninvasive methods for assessment of liver fibrosis are now available. A very attractive application of serum markers would be not only to measure grading of fibrosis, but also to monitor actual fibrogenic activity and disease progression.

In chronic viral hepatitis the extension of fibrous septa is consequence of an increase in the deposition of ECM by fibrogenic cells with myofibroblast phenotype recruited at the interface between the fibrous septa and the parenchyma. Alpha-smooth muscle actin (SMA) is a specific marker for smooth muscle cell differentiation.

Aim:
1. To compare biochemical markers with alpha-SMA expression in periportal/periseptal zone
2. To determine the utility of a combination of serum markers for prediction of significant alpha-SMA expression in this zone

Methods: Routine liver function tests, albumin, hyaluronic acid (ELISA) and serum levels of alpha2-macroglobulin, haptoglobin, apolipoprotein A1, IgG (immunoturbidimetry) were compared with semi-quantitatively scored immunohistochemical expression of alpha-SMA in 71 patients with chronic viral hepatitis – 40 HBV and 31 HCV.

Statistical analyze was done by Spearman correlation test and by receiver operating characteristic curves.

Results: We find significant correlation (p < 0.01) between serum levels of Hyaluronic acid, AST, alpha2-macroglobulin, IgG, albumin, ALT and alpha-SMA expression in periportal/periseptal zone. GGT, total bilirubin, haptoglobin and apoA1 did not show significant correlation. We devised an index – GAMAGEN (IgG, albumin, alpha2-macroglobulin and AST) based on the most informative basic serum markers. The AUROC of GAMAGEN for predicting significant alpha-SMA expression in periportal/periseptal lobular zone is 0.871 ± 0.5. Using optimized cut-off values significant myofibroblast activity in periportal/periseptal zone could be predicted accurately in 90% of patients.

Discussion/Conclusion: Our study showed that a simple index based on biochemical markers can help to identify patients in danger of fibrotic progression.
On a refinement of a solid test meal to provide an optimum postprandial multichannel electrogastrogram

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Introduction: In the year 2000 the Federal Drug Administration in the USA approved electrogastrography as a test for patient evaluation [Parkman et al., Neurogastroenterol Motil 2003; 15: 89]. Nowadays research work has to be done so as to reveal potential advantages of multichannel electrogastrography over the 'classical' single channel approach. The study was aimed at a comparison of multichannel electrogastrograms recorded after induction of the postprandial pattern of the gastric myoelectrical activity (GMA) with two different solid test meals.

Methods: The examinations were attended by 18 healthy, Helicobacter pylori negative volunteers (9 F, 9 M). On two separate days they were offered in random order a pancake of 350 kcal energy content or a sandwich of scrambled eggs laid on a white bread roll (370 kcal); a drink of 200 ml water was allowed after either the meal. The GMA was registered for 30 min during the interdigestive state and next for 120 min of the fed period by means of a four-channel electrogastrographic system. The obtained electrogastrograms were subsequently analyzed with the use of the Polygram Net™ EGG 311224 software (Medtronic, USA).

Results: Ingestion of the scrambled eggs sandwich did not affect significantly the relative time occupied by normogastria within the multichannel electrogastrogram. On the other hand, after intake of the pancake normogastria increased during the first 30 min of the postprandial period when compared to the fasted state (86.3% vs. 77.4%) and the pertinent difference approached the level of statistical significance (p = 0.051). Both meals evoked an augmentation of the dominant frequency (DF). With the scrambled eggs sandwich the increase in DF was statistically significant during the second half an hour of the postprandial observation only. Whereas the pancake elicited a statistically significant increment in DF during three consecutive sub-periods: 1–30, 31–60, and 61–90 of the postprandial epoch. Induction of the postprandial pattern of the GMA by the two test meals was reflected by a marked increase in the dominant power (DP), which was statistically significant throughout the four consecutive 30-min observation periods. The net meal-induced increment in DP was, however, greater after ingestion of the pancake than with the scrambled eggs sandwich. The latter test meal elicited a slight and statistically not significant decrease in the average percentage of slow wave coupling (APSWC). An opposite trend was found with the pancake, the ingestion of which brought about an increase in the APSWC during the first half an hour of the postprandial observation (82.4% vs. 73.6% in the fasted state; p = 0.063).

Conclusion: From among the two solid meals of similar energy content the pancake offers, in comparison to the scrambled eggs sandwich, a more efficient stimulation of the postprandial pattern of the gastric myoelectrical activity which implies its choice as a test meal for a multichannel electrogastrographic examination.
The immune response to endogenic interferon (IFN) in chronic hepatitis (CH) and liver cirrhosis (LC)

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The purpose: to investigate the immune response to endogenic IFN – the concentration of serum antibodies against endogenic alpha-interferon (anti-IFNα) in CH and LC.

Methods: IFNα and anti-IFNα concentration was measured in 62 patients with CH, 56 – with LC and in 30 healthy controls by ELISA test. IFNα antiviral activity was evaluated in the cell culture highly sensitive to IFNα and cytolytic indicator virus. All patients didn’t receive IFN therapy.

Results: anti-IFNα concentration in controls was 15.4 ± 3.5 ng/ml, in CH patients – 19.9 ± 2.5 ng/ml, in LC – 29.17 ± 4.2 ng/ml. In 28% cases the anti-IFNα concentration in CH patients, and 43% – in LC was increased in comparison to the controls (p < 0.05). In average antiviral activity and concentration of IFNα in controls were 6.1 ± 2.5 IU/ml and 5.3 ± 2.21 pg/ml. In CH & LC patients the IFNα concentration was increased (p < 0.001) in comparison to the controls (18.7 ± 1.94 pg/ml in CH and 14.6 ± 2.5 pg/ml in LC). In CH patients the antiviral activity of IFNα was increased in higher scale than in LC (23.78 ± 1.4 IU/ml and 15.2 ± 2.1 IU/ml accordingly).

The conclusion: Anti-IFNα level in CH and LC depends on a measure of progressing of the diseases. Thus the ratio between IFN active fraction and its total quantity changes in the part of the patients due to the growth of inactivated forms. One of the reasons of decreasing of IFNα antiviral activity in CH and LC is raising the concentration of its autoantibodies.
Morphological response of the gastric and duodenal mucosa in children with food allergy, Helicobacter pylori infection and Giardia lamblia infestation

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A constant contact of the gastro-intestinal tract with food antigens and frequently with viral, bacterial or parasitic pathogens, may lead eventually to the inflammation of the mucosa. Numerous cells of various biological functions whose activation result in the release of many biological mediators are involved in this process. These biological compounds are a proof of developing inflammation including allergic one and are responsible for a morphological and functional damage to the mucosa with accompanying clinical symptoms.

The aim of the study was to evaluate morphologically the gastric and duodenal mucosa in children with food allergy, Helicobacter pylori infection and Giardia lamblia infestation

Material and methods: The study included 93 children and adolescents who underwent gastroscopy due to chronic or recurring dyspeptic symptoms. Patients were divided into 4 groups based on clinical symptoms and current complex diagnostics. Group I – 48 children (51.6%) with food allergy (FA), aged 4.6 to 18 years (mean age 10.6 ± 3.6 years). Group II – 18 children (19.3%) infected with Helicobacter pylori (Hp), aged 5.0 to 18 years old (mean age 12.8 ± 4.1 years). Group III – 12 children (12.9%) infested with Giardia lamblia (G), aged 4.5 to 15.2 years (mean age 10.7 ± 3.5 years). Group IV – 15 children (16.1%) aged 4.9 to 14.9 years (mean age 10.1 ± 3.2 years) with functional dyspeptic symptoms, but with food allergy, H. pylori infection and Giardia lamblia infestation excluded. The gastric mucosa was estimated histologically according to the Sydney System. The mucus taken from the duodenum by means of the brush swab technique, was placed in the fluid ACD at 6.8 pH and centrifuged. Then the smear was taken and stained by the Giemsa and H-E method. The presence of lamblia trophozoites and cysts was assessed in a light microscope of Zeiss firm (magnification 400 x). The duodenal mucosa was evaluated according to the Marsh scale.

Results: In children with food allergy, the normal antral mucosa was found in 43.7%, the mucosa in the norm border in 35.4% of the examined and chronic inflammation in 20.8% of children. Chronic inflammation was revealed in 100% of children infected with H. pylori. The normal antral mucosa was observed in 75% of the examined; changes were from the norm border in 38.1% of children, whereas chronic inflammation was found in 14.3% of the examined. The evaluation of antral mucosa inflammation activity in the study groups according to the Sydney System proved a statistical significance (p < 0.001). The highest percentage of follicles in the antrum was observed in children with H. pylori infection (61.1%), whereas it equaled 4.1% of the examined in children with food allergy. The evaluation of the corpus mucosa
showed chronic inflammation in 16.6% of children with food allergy; changes from the norm border in 37.5%, whereas the normal corpus mucosa in 45.8% of children. Chronic corpus inflammation was observed in 100% of children with H. pylori infection. In group infested with G. lamblia, 75% of the examined had the normal mucosa and changes from the norm border were reported in 16.6% of the examined, whereas chronic inflammation was observed in 8.3% of the infected. The activity of corpus mucosa inflammation was proved statistically significant (p < 0.001). The highest percentage of inflammatory changes was revealed in children infected with H. pylori infection (83.3%), in 58.3% of the infested with G. lamblia and in 35.4% of children with food allergy. Follicle atrophy was found in 12.4% of children with food allergy and in 8.3% of the infested with Giardia lamblia.

**Conclusion**: Inflammatory changes in the gastric and duodenal mucosa were differentiated with regard to a cause factor. The greatest inflammatory changes were reported in children with H. pylori infection.
Nephrolithiasis and risk of calculus in children with chronic alimentary tract diseases

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Introduction: Nephrolithiasis is a disease of a complex, often systemic and not entirely unambiguous etiopathologic mechanism, the effect of which is concrement crystallization in the urinary system. The aim of the study was the estimation of frequency of occurrence of calculosis and states of concrement crystallization risk in the urinary system in children with chronic alimentary tract diseases.

Methods: Examination was conducted on 75 children aged 4 to 18 with chronic alimentary tract diseases including 31 (41.3%) children with chronic gastric and duodenal mucosa inflammation coexisting with H. pylori infection, 25 (33%) intestinal malabsorption syndrome coexisting with hipodisaccharidemia, 19 (25%) with ulcerating inflammation of large intestine. In all children in general examinations of urine, erythrocyturia and increased excretion of crystalloids was diagnosed.

Results: In 32 (42%) examined children the family interview revealed the occurrences of urinary system calculus, in 54 (72%) children occurrences of states of risk of oxalate-calcium concrement crystallization were revealed and in 66 (88%) children a decreased elimination of Mg ions with urine was observed. In group of 9 (12%) children with diagnosed gastric and duodenal mucosa inflammation coexisting with H. pylori infection (short disease history) crystallization risks in the urinary system were not observed. In the control group in 2 (2.6%) children the risk of phosphor concrement crystallization was observed (p < 0.01).

Discussion/Conclusion: Chronic alimentary tract diseases influence the occurrence of states of risk of concrement crystallization in the urinary tract.
The role and therapeutic influence of probiotics on the pouch mucosa inflammation in patients with ulcerative colitis

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Introduction: Ulcerative colitis (UC) is the most common disease, treated with the restorative proctocolectomy procedure. This relatively new method still requires post-operational follow-up, because of several complications. Pouchitis – non specific inflammation of the restored anal pouch – is a frequently observed complication in patients who underwent this procedure. There are many theses explaining the etiologic of pouchitis. One of them explains the development of pouchitis as active pathogenic microbial process, which probably takes place in the restored part of intestine. Bearing the above in mind, one of the potential anti-pathogenic drugs which can decrease inflammatory process are probiotics. The aim of the study was to estimate the role and therapeutic influence of probiotics on the pouch mucosa inflammation in patients with ulcerative colitis.

Methods: Up to now the complete research had been performed on 16 patients (out of the assumed group of 40) after proctocolectomy procedure. These patients were included into examination – 8 cases and a control group – 8 cases. All patients took identically-looking placebo and probiotic preparations. The examined group was given probiotic – Trilac. The control group obtained placebo. The complete evaluation of pouchitis consisted of endoscopic, clinical and histological factors – modified PDAI scale (pouchitis disease activity index). Each patient was examined four times in the period of three months.

Results: No significant differences of pouchitis process activity – PDAI scale were detected in patients between Trilac and placebo intake (ns). A statistically significant decrease of bowel openings per day were observed in the group intaking study medication – Trilac in dose 6 capsules/day in adverse to the control group – obtaining placebo (p < 0.02)

Discussion/Conclusion: Probiotics in the therapy of the pouchitis improve the quality of life of the patients and reduce the number of stool per 24 h. They should be a part of pharmacological treatment of pouchitis.
The use of ursodeoxycholic acid in treatment of chronic alcoholic hepatitis and hepatitis B virus

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Introduction: The association of the hepatitis B virus (HBV) at patients with chronic alcoholic hepatitis represents a risk factor, producing clinical cholestatic forms, thus influencing the evolution and prognosis of this disease.

Methods: The authors have included in this study 28 patients with chronic alcoholic hepatitis and HBV hospitalized in the Clinic of Infectious Diseases Timisoara. The positive diagnosis was established on clinical, epidemiological and biological elements (blood cell identification, erythrocyte sedimentation rate, glycemia, amylasemia, amylasuria, ALT, AST, BD, BT, BI, gamma-GT, summary urine exam, electrophoresis, Ab IgM HAV, Ab IgM HBc, Ab HCV, Ag HBs, etc.), along with abdominal echography examination. All patients presented cholestatic syndrome (total bilirubine > 10 mg/dl) and followed treatment with: ursodeoxycholic acid (UDCA), 10 mg/kg/day, for 4 weeks, glucoses 5%, B group vitamins, vit. C and digestive enzymes. The clinico-biological modifications before and after the treatment were registered in the personal patient file.

Results: After 20 days of treatment with UDCA the jaundice disappeared at 20 patients (71.42%) and ALT and AST have been normalized at 15 patients (53.57%); Gamma-GT decreased with 50% at 22 patients (78.57%); the hepatic symptoms and the fatigue syndrome disappeared after the first week of treatment. Side effects were minor and transitory, 5 patients (17.85%) with diarrhea, 2 patients (7.14%) with nausea.

Discussion/Conclusion: UDCA therapy (Ursofalk®) improves the biochemical-hepatical tests at patients with chronic alcoholic hepatitis and HBV, having benefic effects upon the clinical evolution and prognosis of this disease.
Overview of patients with inflammatory bowel disease treated for at Izola General Hospital

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Introduction: The aim of this study was to outline some demographic and clinical characteristics of our patients with IBD.

Methods: Descriptive univariate analysis of main demographic (age, sex) and clinical (age at diagnosis, type and duration of disease, location, extraintestinal manifestations, complications, medical therapy, operations) characteristics of 156 patients referred to our department.

Results: 80 of patients are males (51%), 76 females (49%). 100 (64%) have CD, 50 (32%) UC, 6 (4%) indeterminate colitis. Mean age at diagnosis was 41.5 ± 14.0 years, mean duration of disease is 8.3 ± 5.1 years. The most frequent localization of CD is colon, followed by terminal ileum. Proctitis, leftsided colitis and pancolitis are nearly equally presented in patients with UC. 31 of patients (20%) have extraintestinal manifestations of disease. Overall, 15 of patients (15%) with CD had undergone surgery during the course of disease (because of stenosis 9, fistula 3). Mean time from diagnosis to surgery in CD patients was 5.6 ± 4.3 years. None of patients with UC had surgery. Currently, 78 of patients (78%) with CD are taking mesalazine, 19 (19%) azathioprine and 1 methotrexate as maintenance therapy. Among patients with UC, 49 (98%) are taking mesalazine, 1 (2%) azathioprine as maintenance therapy.

Discussion/Conclusion: IBD affects people of all ages, often young people. CD most frequently affects colon, in UC proctitis, leftsided colitis and pancolitis are equally distributed. A high number of patients have extraintestinal manifestations, predominantly entheropatic arthritis. Surgery plays an integral role in the treatment of CD, both to control symptoms and treat complications.
Study regarding the prevalence of chronic C hepatitis and its association with metabolic syndrome (a multicenter study on groups of hospitalized patients)

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**Introduction**: Chronic C hepatitis is still a public health problem in Europe. It is often associating with liver steatosis. Our aim was to study the prevalence of the chronic C hepatitis and its association with the metabolic syndrome (MS), in Transylvania, were, as it is known, predominates genotype 1 of the C virus. We have used a multicenter study on groups of hospitalized patients.

**Methods**: We have studied all the walking patients which were hospitalized during September 15th–October 31st, 2006 in the Internal Medicine Departments of the County Clinical Hospitals from Brasov, Oradea and Sibiu, to whom we have performed an abdominal ultrasonographic examination. At them, we have analyzed the next parameters: the presence of the HBs antigen, the presence of the anti-VHC antibodies, the presence of the components of the metabolic syndrome, the ultrasonographic liver parameters, biochemical liver tests, the level of glycemia, cholesterol, triglycerides, HDL-cholesterol and the APRI score. We have studied the possible association between chronic C hepatitis and MS and the clinical, biological and imagistic particularities which this association involves. The results were statistically analyzed using the relative risk (RR) and t Student Test.

**Results**: From all the 693 patients which were studied, 36 (5.19%) were infected with C hepatic virus. Among these, 18 (50%) had a liver hyperechogenicity. Only one of those with a liver normoechoegenicity had MS, comparing with those with liver hyperechogenicity were 5 (27.78%) presented MS (RR = 5). 29 patients presented chronic C hepatitis and 7 had a latent infection with C virus. The average value for the glycemic level and the APRI score were higher at the patients with chronic C hepatitis and MS, comparing with those which had only MS, but the differences weren't statistically significant.

**Discussion/Conclusion**: Our study suggests that about a half from the patients infected with C hepatitis virus have liver steatosis, and, among these, over a quarter have MS, a condition which compromises the answer to the antiviral therapy.

**Acknowledge**: This study belongs to a complex research grant which is financed by the Research and Education Minister from Romania, to whom we are deeply grateful.
Study regarding the prevalence and the characteristics of the nonalcoholic fatty liver disease (multicenter study on groups of hospitalized patients)

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Introduction: NAFLD is associating with the metabolic syndrome (MS), which constitutes a public health problem in many developed countries. We proposed ourselves to study the prevalence and the particularities of this disease in Transylvania, by a multicenter study on groups of hospitalized patients.

Methods: We have studied all the walking patients which were hospitalized during 15 September 15th–October 31st, 2006 in the Internal Medicine Departments of the County Clinical Hospitals from Brasov, Oradea and Sibiu, to whom we have performed an abdominal ultrasonographic examination. At them, we have analyzed the next parameters: the presence of the entities which constitute the MS, ultrasonographic liver parameters, biochemical liver tests, the level of glycemia, cholesterol, triglycerides, HDL-cholesterol, and the APRI score. We have studied the possible association between NAFLD and MS and the clinical, biological and imagistic particularities which this association involves. The results were statistically analyzed using the relative risk (RR) and t Student Test.

Results: Among the 623 patients which were studied, 256 had a liver hyperechogenicity, and 75 from these had also hepatic cytolysis. NAFLD was present at 183 patients (26.41%). From these, 149 (21.5%) presented liver steatosis (LS) and 34 (4.91%) presented NASH. Among the patients with LS, 77 had MS, and from those with NASH 17 had MS (RR = 1.039). At the patients with NASH and MS, the average value for the triglycerides was significantly higher (p < 0.005) and the value for the APRI score was also significantly higher (p < 0.01) comparing with the patients with LS and MS. The average value for the glycemia and HDL-cholesterol level did not varied in a statistically significant way.

Discussion/Conclusion: NAFLD is a frequent disease in the hospitals from Transylvania, and it is associating in about half of the cases with MS. The association between NASH and MS is characterized by higher values for the triglycerides and a more advanced liver fibrosis.

Acknowledge: This study belongs to a complex research grant which is financed by the Research and Education Minister from Romania, to whom we are deeply grateful.
Recognition and modelling of hepatic tumors from ultrasound images based on textural properties

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Introduction: Non-invasive image based detection of diseases is one of the most important issues in the nowadays research of biomedical images, because it prevents from some problems that could be generated by the invasive techniques. Texture is a fundamental visual property of the tissue providing a lot of information concerning its pathological state. The purpose of this paper is to analyse some textural features, determined through computerized methods, and to establish which of them are relevant in order to do non-invasive tumour recognition.

Methods: For features extraction, we use the Gray Level Cooccurrence Matrix (GLCM) and the corresponding second order statistics, the autocorrelation index, edge-based statistics, as well as the Hurst fractal index. Then, Bayesian Networks are used in order to establish which of the computed parameters best characterize tumours, and also the most probable intervals of values for these parameters that are specific for tumour tissue are determined.

Results: Applying Bayesian Networks for classification, the recognition rate was 76.66%. The same method revealed that the most relevant parameters, that had the major influence on the decision, were GLCM energy and entropy. From the experiments also resulted that the Hurst fractal index has increased values for diffuse hepatocarcinoma (approx. 0.50) than for normal tissue or other liver diseases.

Discussion/Conclusion: The high influence of entropy, as well as the increased values of the Hurst coefficient demonstrate the complex structure in grey levels for tumours areas, in accordance with the complex structure of the tumour tissue.
Serum hemoglobin determination as predictive marker for renal complications in hepatic cirrhosis associated with ascitis

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Introduction: Mortality in hepatic cirrhosis is influenced by complications development. Anemia is determined by complex mechanism, but its presence and severity influence negative the evolution of the disease.

Aim of study: Evaluating the predictive role of the serum hemoglobin determination and others predictive parameters in the early diagnosis of the possible renal complication in hepatic cirrhosis evolution.

Material and methods: We studied a group of 487 patients with hepatic cirrhosis with ascites followed over 5 a years period. Statistically, the majority was male patients (73.5% men comparative 26.5% woman); mean age was 57.05 ± 7.54 years. The research protocol contained a clinical, biological and a complete imagistic evaluation of the liver and portal system, the ascitic fluid analysis and especially tests for the evaluation of the systemic haemodinamic changes and of the renal function (Holter monitoring of medium blood pressure and cardiac frequency, urea and creatinin quantification, seric and urinar ionogram, creatinin clearance and water diuresis). We determined hemoglobin serum levels at least once a year.

Results and discussions: During the study period of 5 years, a number of 82 patients, meaning 10.5%, developed hepatorenal syndrome. Statistically the predictive parameters helpful for early diagnosis of the hepatorenal syndrome were: creatinin clearance, water diuresis, protein’s level of the ascitic fluid, medium blood pressure, urinar sodium and serum hemoglobin. The patients developing renal complications presented lower levels of hemoglobin than those of the reference group (without complications). The evaluation of these parameters has to be done in dynamic, following a good schedule.

Conclusions: Severe anemia at a cirrhotic patient without obvious causes such as infection, hemorrhage and neoplasia can be considered as an obvious risk factor for the development of the hepatorenal syndrome. This is probably due to its implication along with hypoxia in the development of haemodynamic dysfunction in hepatic cirrhosis. Determination and the treatment of anemia can be important features for early diagnosis and to prevent the renal complications in hepatic cirrhosis.
The study of the efficacy UDCA (ursodeoxycholic acid) therapy in cholestatic disorders in patients with chronic viral hepatitis C

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Introduction: UDCA improves biochemical tests in a number of cholestatic disorders. The inclusion of the Ursofalk® in the complex therapy of the patients with cholestatic forms of the chronic viral hepatitis C gives the possibility of obtaining positive results in the treatment.

Aim of study: Our study sets as an objective to investigate UDCA effect in cholestatic disorders in patients with chronic viral hepatitis C.

Patients and methods: A prospective study was carried out, including 84 patients with chronic viral hepatitis C. All patients had biochemical evidence of impaired liver function with bilirubin > 25 µmol/l, serum alkaline phosphatase > 150 IU/l, serum alanine aminotransferase > 100 IU/l and/or serum gamma-glutamyl transpeptidase > 40 U/l at entry to the study. Patients were randomized: 44 patients to receive UDCA (15 mg/Kgc/day) and 40 patients to receive placebo for 12 weeks. All the patients received the association peginterferon alfa-2a plus ribavirin (antiviral therapy). The monitoring was made by monthly dosage of alkaline phosphatase (PA), gamma glutamyl transpeptidase (GGT), bilirubin, aminotransferases (ALT) and seric gammaglobulins. Paired Student's t-test was used to assess changes in the liver function tests during the observation period.

Results and discussion: At 3 months from the beginning of therapy: For test group the cholestatic syndrome was remitted, while in the other group this was not observed. It was noted also, the amelioration of citolitic syndrome in UDCA treated patients (decreasing with 2.5 x initial values at 54% patients). The improvement in the liver biochemistry was evident after 8 weeks of treatment with UDCA.

Conclusions: UDCA improves biochemical tests in a number of cholestatic disorders and may have a beneficial effect on disease activity in chronic viral hepatitis C especially if cholestasis is present. UDCA had a good tolerance for the patients in these cases.
Loss of efficacy of infliximab or metastatic Crohn's disease? – Case report

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Background: In the last decade biologic therapy considerably changed treatment and prognosis of patients with severe Crohn's disease. The first among these drugs is chimeric monoclonal antibody against tumor necrosis factor alpha (TNF-α) named infliximab (Remicade®). (1) Due to its murine region it is highly immunogenic. Formation of secondary antibodies to infliximab (ATI) is known to be related to loss or reduction of clinical response to the drug. We present the course of disease and dilemma considering infliximab therapy in our patient with Crohn's disease.

Case report: 22-year-old male patient was diagnosed with Crohn's disease at the age of 15. Stomach, terminal ileum and colon were affected. Due to refractory and steroid-dependent Crohn's disease the patient's pediatrician started treatment with infliximab in October 2004. After three-dose induction regimen (at weeks 0.2 and 6) he has been administered infusions (dosage 5 mg/kg body weight) of the drug every 8 weeks and continued with concomitant treatment with immunosuppressive agent azathioprine. Nevertheless after 22 weeks of maintenance therapy with infliximab enterocutaneous perianal fistulas and pyoderma gangrenosum developed necessitating intravenous corticosteroid therapy. Although we continued biologic treatment the disease progressed and a perirectal abscess formed which had to be treated surgically. Considering course of disease we speculate that our patient has metastatic Crohn's disease, but we also suspect reduction of efficacy of infliximab due to presence of ATI formation.

Discussion and conclusions: Infliximab is efficient in treating patients with severe Crohn's disease. A single intravenous infusion induced remission in 25 to 48% of patients with refractory disease and a series of three induction infusions closed 38 to 55% of fistulas. (2) A similar positive effect was first observed in our patient with steroid-dependent Crohn's disease. Formation of ATI reduces the clinical effect or shortenes the duration of response to infliximab. (1,2) Maintenance infusions (3), concomitant use of immunosuppressives (2) and intravenous hydrocortisone premedication (4) were shown to prevent ATI formation. Despite maintenance therapy and concurrent administration of azathioprine our patient experienced disease progression. We speculate that our patient has metastatic Crohn's disease but reduction of efficacy of infliximab due to presence of ATI is also feasible. We shortened the interval between infusions to 6 weeks and are eagerly awaiting a novel therapeutic option, less immunogenic, fully humanized anti-TNF-α antibody adalimumab (Humira®). (5)
Literature:


Key words: Crohn's disease, biologic therapy, infliximab, treatment efficacy
Impairment of cardiovagal autonomic function in patients with chronic hepatitis C

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Introduction: Patients infected with hepatitis C virus (HCV) may have neurological complications such as peripheral neuropathies and neurocognitive cerebral dysfunction, often complicated with cryoglobulinaemia. Autonomic neuropathies are common in cholestatic and in toxic liver diseases, with or without liver cirrhosis. It is not known, whether HCV can cause autonomic neurological dysfunction.

Methods and results: Autonomic function was assessed by baroreflex sensitivity (BRS) and heart rate variability (HRV) indices of 21 HCV-PCR-positive patients before antiviral treatment and 36 healthy, age matched controls. R-R interval was derived from ECG, continuous radial artery pressure was measured simultaneously by applanation tonometry.

Three BRS and three HRV indices were decreased in HCV group compared to controls (p < 0.05): BRS spontaneous sequence (SeqU = 7.4 ± 3.5 vs. 10.3 ± 6.5, SeqD = 7.1 ± 3.1 vs. 10.8 ± 7.4), frequency-domain (LFalpha = 7.2 ± 3.6 vs. 10.5 ± 7.4) indices, and HRV time-domain (pNN50 = 3.4 ± 6.3 vs. 10.3 ± 16.8), frequency-domain (VLF = 183.3 ± 98.6 vs. 431.0 ± 392.1, LF = 183.3 ± 98.6 vs. 267.1 ± 248.1) indices. No differences were found in systolic, diastolic blood pressure and heart rate between the groups. There was no difference in autonomic indeces between subgroups of HCV patients with cryoglobulinaemia (n = 6) and without cryoglobulinaemia (n = 15).

Conclusion: We found decreased cardiovagal autonomic function in HCV infected patients. Although there was no clinical sign of cardiovascular malfunction, the autonomic dysfunction is known to associate with higher risk of cardiovascular mortality, and it may play role in progression of hyperdynamic systemic and splanchnic circulation in liver cirrhosis. The autonomic neuropathy seems to be independent from the presence of cryoglobulins. The mechanism of HCV caused autonomic dysfunction needs further investigation.
Ulcerative colitis – The role of the angiogenesis in pathology of the disease

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The aim of the study: The aim of our work was the evaluation of the changes of the blood vessels of large intestine mucosa, as one of the crucial factors in the development and the course of ulcerative colitis.

Method: The samples of large bowel mucosa were taken from the resected large bowel from 36 patients operated on ulcerative colitis. The histological and ultrastructural examination, using routine techniques, was done in all cases. The controlled group consisted of 12 patient operated on the large intestine cancer. The samples were taken from the proximal cutting line, free from tumorous changes.

Results: In the samples taken from the patients with ulcerative colitis, numerous disorders of the blood vessels have been acknowledged: incorrect routs of the vessels, erythroragia, thrombosis, in the lumen of the some venous vessels, and the increase of the surface of the blood vessels sections in the comparison with the controlled group. In the electron-microscope pictures among patients with ulcerative colitis, we discovered focal leakage of the base membrane and changes of the ultrastructure of the endothelial cells. The observed changes, not found in the control group, were especially intensive among patients with chronic (long-term) disease.

Conclusion: The observed changes constitute one of the elements of the generalised ulcerative process taking place in the large intestine area. The degree of these changes correlates with the clinical course of the illness. Patients with long period of duration of ulcerative colitis have had more intensive changes in blood vessels net. The question: to what extend are the observed changes the cause or to what extend are they the results of the ulcerative process remains unanswered.
Palliative treatment of the metastatic tumours of the liver with TNF-α intratumoral injection

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Introduction: Metastatic tumours amount to 80% of neoplastic lesions of the liver. Half of the tumours proves to be irresectable after careful evaluation. Therefore, palliative procedures have been introduced in order to prolong the life-span and improve the quality of life of the patients. The authors report preliminary results of treatment of irresectable metastatic liver tumours with (Tumour Necrosis Factor) injected directly into the tumour. TNF-α is a major cytokine consisted of 157 amino acids. The mediator is released in vivo by activated macrophages showing antyneoplastic activity among others.

Methods: Seven patients were treated with TNF-α in the 3rd Department of Surgery in Poznań in 1998. The criteria of irresectability included: extensive anatomical lesions (the number of lesions – 3 cases, the size of tumour – 1 case), bilateral hilar vascular involvement (1 case). General poor condition was a contraindication for TNF-α treatment in two cases. TNF-α (1 mg) was given during laparotomy in four cases and percutaneously under computer tomography control in three cases. Mild flu-like symptoms occurred in 5 cases and usually subsided after 48 hours.

Results: All the patients remain under continuous surveillance and CT scanning is performed every third month. Regression of the tumour diameter has been observed in two patients whereas the diameter remained unchanged in four cases. One patient died due to disseminated malignant process.

Discussion/Conclusion: TNF-α injection into the liver tumors seems to be the interesting and helpful procedure for palliative treatment of the liver malignant tumors.
Correlations between Helicobacter pylori (Hp) eradication and gastroesophageal reflux disease (GERD)

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Background: The effect of Helicobacter pylori eradication on the development of gastroesophageal reflux disease is controversial. There are some studies suggesting that Helicobacter pylori eradication is associated with an increase in the incidence and severity of gastroesophageal reflux disease (GERD).

Aims: We aimed to investigate the evolution of clinical and endoscopic aspects in GERD after Helicobacter pylori eradication.

Methods: We have included in our study a number of 142 patients diagnosed with GERD between 2004–2005 on clinical and endoscopic criteria. Clinically, the patients accused epigastric pain, acid regurgitation and heartburn. Patients selection was based on the endoscopic aspects (gastritis, Los Angeles grade A to C esophagitis) and the positive rapid urease test for HP. We excluded from this study the patients found with gastric or duodenal ulcer, or NSAID induced ulcer. The patients with GERD and negative for Helicobacter pylori were included in the control group.

Results: From the 142 patients included in this study, 76 patients were positive for HP and 66 patients were negative for HP. From 76 HP positive patients, 38 patients had I\textsuperscript{st} grade esophagitis, 30 patients had II\textsuperscript{nd} grade esophagitis and 8 patients had III\textsuperscript{rd} grade esophagitis. From the control group, 36 patients had I\textsuperscript{st} grade esophagitis, 28 patients had II\textsuperscript{nd} grade esophagitis and 2 patients had III\textsuperscript{rd} grade esophagitis. Helicobacter pylori positive patients received the triple therapy for HP eradication (proton pump inhibitors and 2 antibiotics: clarithromycin and amoxycillin) and the control group received only proton pump inhibitors therapy. In the HP positive group we obtained an eradication at 69 cases (90%). From this group of patients, clinical and endoscopic signs of esophagitis persisted at 92% (70 cases). In the control group, the patients showed no symptoms and endoscopically, only 8 cases presented esophagitis (7 cases I\textsuperscript{st} grade esophagitis and 1 case II\textsuperscript{nd} grade esophagitis).

Conclusions: Helicobacter pylori eradication does not have a considerable influence on clinical and endoscopic aspects of the reflux esophagitis in the absence of antisecretory therapy. Proton pump inhibitors therapy has a positive effect on the clinical and endoscopic evolution of GERD.
Portal vein thrombosis: Clinical and evolutive aspects, prognostic and treatment strategies

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Introduction: Portal vein thrombosis has an approximately 7.9% frequency in patients with portal hypertension. The etiology can be established in about 75% of cases. The prognostic is critical in patients with liver cirrhosis, where mortality can reach 25% in the first 5–6 years.

Aims: To evaluate the prognostic, the evolution and the therapeutic options according to etiology.

Methods: This is a 4 years retrospective study which evaluate 35 patients, diagnosed with portal system thrombosis. Besides usual explorations, there were used also Doppler echography, computer tomograph, nuclear magnetic resonance and arteriography.

Results/Discussions: The etiology of the 35 studied cases was: hepatoma – 19 cases; liver cirrhosis – 5 cases; pancreatitis – 2 cases; protein C deficit – 3 cases; hemolytic anemia – 2 cases; oral contraceptives use associated with lupus anticoagulant – 1 case; lupus anticoagulant – 2 cases; genital tumor with hepatic metastasis – 1 case.
Main clinical signs were: ascites – 24 cases, hepatomegaly – 20 cases, jaundice – 18 cases, hypersplenism – 21 cases, hepatic encephalopathy – 4 cases, acute pancreatitis – 2 cases.
From the 19 hepatoma cases, the majority had an unfavorable and slowly evolution, with ascites and weak therapeutic response. At the end of the evaluation period there were reported 11 deaths from the 19 cases.
As treatment, the most frequent used were the anticoagulants (low molecular weight heparin), and less frequent, surgical shunt or TIPS (transjugular intrahepatic portal-systemic shunt) followed by warfarin.

Conclusions: The most frequent cause of portal vein thrombosis is hepatocellular carcinoma.
Anticoagulant treatment hadn’t the expected efficiency.
The prognostic remains unfavorable, with a high mortality rate.
Surgical treatment or TIPS are a better solution, but they are less used.
NASH or EBV hepatitis – How to deal with serology

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Introduction: Non-alcoholic fatty liver disease (NAFLD) is an important cause of liver-related morbidity but Epstein-Barr virus (EBV) is rarely related to chronic liver injury. Despite serology is standard diagnostic tool it reflects reactivation retrospectively. No criteria for EBV hepatitis are accepted.

Methods: To investigate parameters of cellular immunity in patients with chronic hepatitis and serologically reactivated EBV infection we studied 49 patients. All were HIV, HBV, HCV-negative, without autoimmune and genetic liver diseases or alcohol consumption. Thirty-five patients, aged 37.2 (SD 10.89) were supposed to have EBV-related liver disease. Fourteen patients, aged 38.3 (SD 7.11) were referred to NAFLD subgroup and compared to 15 NAFLD patients without EBV-reactivation. Immunophenotyping of circulating and in vitro EBV-peptide stimulated T-cells was performed using flow cytometry.

Results: No significant difference in serum ALT-value was found (119.5 ± 53.3, 140.2 ± 46.3, 109.6 ± 41.2 respectively). The absolute numbers and percentages of T-, B-, NK-cells were within the reference ranges. The fine subset analysis of CD4 and CD8 T-cells revealed a significant decrease of naïve (CCR7+CD45RA+, CD27+CD28+) CD8 T-cells (p < 0.001), increased percentage of memory (CCR7-CD45RA-) (p < 0.01) and terminally differentiated CD28-CD27- CD8 T-cells (p < 0.01). An increased number of CD38 molecules on CD8+ T-cells, reflecting a low-level viral replication (p < 0.05) was detected in EBV-presumed hepatitis group, and also significant percentage of circulating EBV-specific CD8+ T-cells as compared to EBV+ healthy controls. Neither circulating EBV-specific CD8+ T-cells, nor increased CD38 expression was found in the NAFLD-group.

Discussion/Conclusion: EBV serology alone could be misleading. Determination of circulating EBV-specific CD8 T-cells and CD38 quantitative expression may help the diagnosis of EBV-presumed hepatitis.
Anxiety at colonoscopy

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Introduction: Colonoscopy is a very useful examination that can produce anxiety due to potential findings, embarrassment and possibility of discomfort or pain during the procedure. Patients undergoing ultrasonographic examination of the abdomen have the same concern about the findings, but there is no embarrassment about the procedure or about the possibility of pain. The objective of this study is to evaluate patient anxiety associated with ambulatory colonoscopy and ultrasonography.

Methods: 30 consecutive outpatients referred for diagnostic lower endoscopy and 30 consecutive outpatients referred for ultrasonographic examination of the abdomen were evaluated. Anxiety was rated immediately before the procedures using the State-Trait Anxiety Index (STAI) form. Because the patients were not admitted in the hospital and the majority had come alone, the colonoscopy was performed with no sedation.

Results: The STAI scores in patients undergoing colonoscopy were significantly higher in state anxiety (41.3) compared to the scores in patients undergoing ultrasonography (33.2), but the results did not differ significantly in case of trait anxiety (36.4 vs. 35.3).

Discussion/Conclusion: Diagnostic colonoscopy is associated with increases in state anxiety, whereas ultrasonographic examination of the abdomen has no such influence. This may be explained by the concern of embarrassment and the possibility of pain during the examination of the colon. Further studies are necessary to investigate the level of anxiety if the procedure is performed under sedation.
Cancer cell budding at the invasive margin in colon carcinoma is associated with beta3-tubulin expression

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Introduction: Tumor budding is defined as dedifferentiated cancer cells at the invasive margin and is known as an independent factor associated with poor prognosis in colorectal cancer. Cell locomotion, including cancer cell invasion, is closely associated with the dynamics of cytoskeletal structures. Tubulin is a constitutive molecule of microtubules, a major component of the cytoskeleton. Previous in vitro studies indicated that tubulin isotype composition may affect polymerization properties and dynamics of microtubules. Notably, the polymerization properties of the alfa-beta3 isotype are significantly different from the others. Hence, we investigated the possible association of tumor budding and beta3-tubulin expression in colon carcinoma.

Methods: Surgical specimens from 35 patients with colon carcinoma were retrieved. Immunohistochemistry was performed by using anti-beta3-tubulin antibody and anti-cytokeratin antibody AE1/AE3 to confirmed the presence of tumor budding.

Results: Tumor budding was identified in 29 patients (83%). Positive cytoplasmic staining of budding cells for beta3-tubulin was revealed in 27 tumors (77%) whilst positive staining of tumor cells in the central area was observed in 18 cases (51%). There was a significant association of beta3-tubulin expression in budding cells and the presence of tumor budding (p < 0.001). No correlation was found between beta3-tubulin expression in central area of tumor mass and in budding cells.

Discussion/Conclusion: These results indicate that beta3-tubulin expression is up-regulated in budding cells in colon cancer and beta3-tubulin could be implicated in the development of tumor budding. This is the first report of association between beta3-tubulin expression and cancer cell budding.
Surgical treatment for hydatid cysts in liver

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Introduction: The liver is the organ most frequently infected by hydatid disease and medical therapy alone is ineffective usually. The authors analyse the clinical data of the patients who were operated because of echinococcus cyst of the liver between 1992 and 2006.

Methods: 63 patients were operated in this period. Male and female ratio was 26/37. In 46 cases solitar cyst, 10 cases duplex cyst and in 7 patients multiple cyst removal were performed. The average size of the cysts were about 7.4 (1–18) cm. Anatomical resection was performed in 34 cases, pericystectomy in 17 cases, atipical resection in 4 cases, marsupilisation with omentoplasty in 4 cases and laparoscopic resection in 4 cases. To avoid the anaphylaxic shock we used hyperosmotical liquid (PAIR method).

Results: In the early postoperative period we lost 2 patients because of anaphylaxic shock end lung embolisation. We experienced other complications like fever in 9 cases and seroma in 3 cases. In follow-up control all of our patients were in good health. There was found reinfection in 1 patient.

Discussion/Conclusion: Complete surgical resection of hepatic hydatid disease should be attempted whenever possible. Authors suggest to perform pericystectomy in the case of echinococcus cyst of the liver with protecting the uninvolved tissue of the liver. In those cases when the cyst wall is quite thin and there is a chance for its rupture we still advise hepatic resection to prevent severe complications such as anaphylactic shock or peritoneal bleeding. If it is possible we suggest the laparoscopic resection.
The liver function after partial resections of the gastrointestinal tract

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Introduction: The aim of our study was the valuation of metabolic function of liver after different types of gastrectomy or colectomy.

Methods: We compared biochemical parameters of blood (protein, aminotransferases, bilirubin, alkaline phosphatase, coagulation factors level) before and after surgery.
Our studied group consisted of 75 patients. 30 patients were operated for gastric cancer (without metastases), 30 for colon cancer (without metastases) and 15 (control group) operated for inquinal hernia.

Results: In first two groups we observed laboratory features of transition metabolic dysfunction of the liver. Biochemical abnormalities were small, the changes were more intensive at the patients after colectomy. In control group no changes were found.

Discussion/Conclusion: Gastrectomy or colectomy, effecting on digestion’s and absorption’s processes, disturb liver metabolism. Monitoring of the liver function and treatment of biochemical abnormalities should be an important component of patients’ follow-up after partial resection of the gastrointestinal tract. It is very important especially for patients, who had liver disease before operation.
The role of neuroticism in functional dyspepsia. The study of school-aged children

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Introduction: Functional dyspepsia (FD) is the most prevalent type of functional abdominal pains, which is observed in 20% of population. There have been identified dysmotilities and ENS and CNS disorders resulting in FD, while psychiatric trials suggest, the patients with FGID may present emotional disorders simultaneously, which may influence symptoms perception and even affect the effectiveness of medical treatment.

Defining relationship between emotional disorders and coexisting symptoms as well as their change during dyspepsia treatment might be helpful in establishing focused therapy strategies, including appropriate psychological interventions.

Aims:

1. To evaluate the neuroticism level in children with functional dyspepsia.
2. To reveal correlations of investigated psychometric parameters and experienced dyspeptic symptoms.
3. To assess the differences in manifest anxiety level and grade of denial in children with dysmotility-like and ulcer-like FD.
4. To assess the relationship between analysed psychosomatic factors and release of dyspeptic symptoms during the pharmacological therapy of functional dyspepsia.

Methods: A total of 66 children (43 females and 23 males aged 11–18 years were diagnosed with FD following the Rome II criteria. The control group consisted of 86 healthy volunteers (49 females and 38 males) aged 11–18 years who denied recurrent abdominal pain. In all children pain severity was measured with faces pain scale whereas severity of other dyspeptic symptoms (heartburn, epigastric burning, hunger pains, nausea, early satiety, feeling full long after food, sense of sucking, belching, and sleep disorders) were assessed with the created Dyspepsia Symptoms Questionnaire consistent with visual-analogue scales. Psychological evaluation was carried out using Children Manifest Anxiety Inventory “Ware you like?” by M. Choynowski and E. Skrzypek.

All patients received typical treatment for 4 weeks. After 8 weeks of drug prescription children were asked to refill the symptoms questionnaires. Healthy children were asked to fill all the questionnaires only once.

Results: The FD patients present higher scores in scales of neuroticism, which is particularly seen in female gender (score 17.73 vs. 11.59 in controls p < 0.001, 41.9% girls in FD group met a diagnostic outcome in this scale, vs. 8.2% in controls).
In the Lie Scale boys revealed strongly elevated scores (score 4.87 vs. 2.70 in controls $p < 0.001$; 39% boys with FD comparing to 3% in controls showed a diagnostic outcome). In patients with dysmotility-like FD almost half of girls and boys were diagnosed to neuroticism, while almost half of boys with ulcer-like FD met the diagnostic outcome in Lie Scale. Correlation analysis exposed the positive relationship between neuroticism in females and all experienced symptoms, while in boys only dysmotility symptoms was correlated to neuroticism. In the course of clinical observation it has been noted that during the therapy neuroticism was related to the heartburn increasing (both genders) and dysmotility symptoms (boys).
Favorable comparison of virtual colonoscopy with conventional colonoscopy in a community-hospital setting

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Introduction: Studies of virtual colonoscopy (VC) for colorectal cancer screening have thus far focused on university hospital settings. The purpose of this ongoing study is to evaluate the accuracy of VC compared to optical colonoscopy (OC) in average-risk, asymptomatic patients at a community hospital.

Methods: 41 asymptomatic patients underwent same-day VC followed by OC at a 100-bed community hospital. VC studies were performed on a multi-detector CT. OC was then performed segmentally, with the gastroenterologist initially unaware of the VC findings. Upon completion of the endoscopic evaluation, the endoscopist was unblinded to the VC result and, in cases of a discrepancy between the endoscopic interpretation and VC, repeat endoscopy of the colonic segment was performed. The final, unblinded OC data was used as the reference standard.

Results: For polyps greater than or equal to 5 mm (n = 7), VC had a sensitivity of 86%, a specificity of 75% and a negative predictive value (NPV) of 98%. For polyps greater than or equal to 6 mm (n = 4), the sensitivity was 100% with a specificity of 67% and NPV of 100%.

Discussion/Conclusion: Preliminary data from this ongoing study suggests that CT colonoscopy compares favorably with conventional colonoscopy as an accurate screening method for clinically relevant colorectal lesions.
Burden of colorectal cancer in Slovenia

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Colorectal cancer is currently the second most common malignant disease in Slovenia. Its incidence is constantly on the rise. Predicted incidence rate for 2006 are 71.3/100,000 for males and 52.4/100,000 for females, with approximate total number of cases 1200 for both sexes.

EUROCARE-3, a European study on cancer patients diagnosed during 1990–1994, has shown poorer survival of Slovenian colorectal cancer patients in comparison with the most developed European countries. This called for a detailed analysis. Data on patients operated on in 1997 in all of Slovenian hospitals, gathered by Cancer Registry of Slovenia for the aforementioned study, served as a starting point for the analysis. Higher stages of disease at diagnosis and lower resection rates were found to be the main cause for poorer survival of Slovenian patients. The study also revealed high rates of abdominoperineal resections with rectal cancer patients. The differences were substantial among the different institutions regarding the surgical treatment of patients and also their survival. KC Ljubljana showed the best results, with highest resection rates, lowest rates of abdominoperineal resections and best survival. Efforts are being made for years in KC Ljubljana towards improving surgical treatment on national level by organizing surgical symposiums and publishing scientific guidelines. The goal is to achieve a high standard of surgery in all institutions involved in treatment of colorectal cancer patients. Results are being monitored with special clinical surveys, which are conducted every five years. According to surveys from 2000 and 2005 improvement has been achieved. The resection rates of tumors rose in the last years, perioperative mortality remained acceptably low and a substantial decrease of abdominoperineal excisions has been noticed. Improvement of surgical treatment, as detected in clinical surveys, is confirmed by improvement in survival, as detected by the Cancer registry of Slovenia. According to Cancer registry data, the relative 5-year survival of males with colonic cancer (ICD code C18) improved from 42% during 1993–1997 to 51% during 1998–2002 and with rectal cancer together with cancer of the rectosigmoidal junction (ICD code C19-20) from 40% to 48%. Relative 5-year survival of females with colonic cancer improved from 45% to 54% in the same period, with rectal cancer together with cancer of the rectosigmoidal junction from 43% to 47%.

On one hand, prognosis of Slovenian colorectal cancer patients treated in 2007 is already much better compared to ten years ago. With further improvement of surgical treatment efforts must also be made towards achieving higher standards of non-surgical treatment. On the other hand, the implementation of strategies for earlier diagnosis could substantially reduce the mortality of colorectal patients in Slovenia.
Pelvic ileal pouch – Our experiences

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Background: Total proctocolectomy with distal mucosectomy and ilealpouch-anal anastomosis (IPAA) is a surgical option for patients with ulcerative colitis (UC) and familial adenomatous polyposis (FAP), curing the disease and avoiding body mutilation with a permanent ileostomy.

Patients and methods: In the 22-year period, from January 1st 1985 to December 31st 2006, 53 patients underwent total proctocolectomy with or without distal mucosectomy and IPAA; 30 patients had UC (14 males, 16 females) and 23 FAP (12 males, 11 females).

4 patients had one stage procedure (TCP, IPAA without diverting ileostomy), 43 two stage procedure (TCP, IPAA with diverting loop ileostomy; closure of ileostomy) and 6 three stage procedure (TC, closure of the rectum stump and terminal ileostomy; proctectomy, IPAA and diverting ileostomy; closure of ileostomy).

Results: There were no postoperative mortality (0/53 operations). One reoperation – diverting ileostomy – 5 days after first operation, due to leak of ilealpouch anastomosis and peritonitis in one patient with one stage procedure (1/4 operated patients) was necessary. As a rule, the diverting ileostomy was closed 6 to 8 weeks after the operation, when X-ray examination proved complete healing of ilealpouch-anal anastomosis. In 3 patients with partial leak of ileoanal anastomosis diverting ileostomy was retained longer, to 4 to 6 months after the first operation. In the same patients developing relative stenosis dilating of ileoanal anastomosis was required. In one female patient – with preoperative diagnosis of UC and definitive pathohistological diagnosis Crohn’s disease – the removal of pelvic pouch and definitive terminal ileostomy was necessary one year after the first operation (two stage procedure). In our patients the frequency of bowel action varies from 4 to 14 in 24 h (average 6.4). All patients are satisfied with their quality of life.

Conclusion: In accordance with literature, in the last 20 years our own results prove that ileal pelvic pouch offer patients undergoing total coloproctectomy the best body integrity and quality of life.
Incidence of rectal cancer in Slovenia is constantly on the rise. Rectal cancer is still more common in males than females. In the last decade the incidence of rectal cancer together with cancer of the rectosigmoidal junction (ICD code C19-20) increased from 26.1/100,000 to 32.7/100,000 in year 2006 with males and from 196/100,000 to 229/100,000 in year 2006 with females.

Poorer survival of Slovenian patients with colorectal cancer has been shown by an international study (EUROCARE-3), which compared survival of cancer patients of different European countries diagnosed during 1990–1994. Reasons for poorer survival have tried to be identified in a study on all Slovenian colorectal cancer patients diagnosed in 1997. All the aspects of treatment of our patients, with special focus on surgical treatment and survival, have been analyzed. Higher stages of disease at diagnosis and lower resection rates were found to be the main cause for poorer survival of our patients. The study surprisingly revealed high rates of abdominoperineal resections with rectal cancer patients, on average 23% nationwide, with some institutions showing even much higher rates. The differences were substantial among the different institutions regarding the surgical treatment of patients and also their survival. KC Ljubljana showed the best results, with highest resection rates, lowest rates of abdominoperineal resections and best survival. Efforts are being made for years in KC Ljubljana towards improving surgical treatment on national level by organizing surgical symposiums and publishing scientific guidelines. The goal is to achieve a high standard of surgery in all institutions involved in treatment of rectal cancer patients. Results are being monitored with special clinical surveys, which are conducted every five years. According to surveys from 2000 and 2005 improvement has been achieved. The resection rates of tumors rose in the last years, with acceptable perioperative mortality. The rate of abdominoperineal resections decreased and reached 17.3% in 2005. With more experience in laparoscopic surgery and encouraging results from abroad laparoscopic procedures in selected rectal cancer patients have been introduced. Improvement of surgical treatment, as detected in our clinical surveys, is confirmed by improvement in survival, as detected by the Cancer registry of Slovenia. According to Cancer registry data, the relative 5-year survival of males with rectal cancer together with cancer of the rectosigmoidal junction improved from 40% during 1993–1997 to 48% during 1998–2002. Relative 5-year survival of females in the same period improved from 43% to 47%.

It is well known that neoadjuvant and adjuvant forms of treatment contribute to the overall survival of rectal cancer patients. With further improvement of surgical treatment, efforts must also be made towards achieving high standards of nonsurgical treatment. For more precise evaluation of all aspects of treatment another population study would be necessary in the years to come.
NASH and the metabolic syndrome at the patients from Southern Transylvania

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Introduction: Nonalcoholic steatohepatitis (NASH) is integrated in the entity named Nonalcoholic Fatty Liver Disease (NAFDL). The association with the metabolic syndrome is now well known. We attempted to study the prevalence, the risk factors and the association of this disease with the metabolic syndrome in Southern Transylvania.

Methods: We have analyzed the clinical, biological and imagistic parameters at all the patients which were hospitalized in the Medical II Department from the County Clinical Hospital from Sibiu, during 15 of September–31 of October 2006, to whom we have performed an abdominal ultrasonography. We have studied the association between NASH and the metabolic syndrome (MS). The results were statistically analyzed using the relative risk (RR) and the “t” Student test. Patients with elevated liver aminotransaminases, negative serologic markers of viral or autoimmune hepatitis and no alcohol intake were considered to have NASH.

Results: From the 530 patients which were studied, at 45 (8.49%) we have put the diagnosis of NASH. There were statistically significant differences between the patients with NASH and those without NASH, regarding: the level of aminotransaminases TGO (p = 0.011), TGP (p = 0.032), alkaline phosphatasis (p = 0.000227), glicemic level (p = 0.0032), BMI (p = 0.0092), triglycerides level (p = 0.024). The differences were not significant regarding the APRI score of fibrosis (p = 0.4475), the cholesterol level (p = 0.492), the total bilirubin level (p = 0.076). The steatosis was severe at 18.75% from the patients, moderate at 53% and mild at 28.12%. The FORNS index was 4.0590 at the patients without NASH, and 6.683 at with those with NASH, a difference which is very significant (p = 0.000192), which means that the patients with NASH have an advanced fibrosis. The relative risk of developing NASH at the patients with diabetes mellitus comparing with those without this disease was 1.03, at the patients with obesity (BMI > 30 kg/m²) was 2.33 and at the patients with dislipidemia was 1.125.

Discussion/Conclusion: Our study suggests that about 8.5% from the hospitalized patients in a medical clinic have NASH. At them, the noninvasive markers of liver fibrosis show an advanced fibrosis. They have higher values of aminotransaminases, triglycerides, glycaemia and alkaline phosphatasis than those without NASH. The patients with a BMI > 30 kg/m² have a twice higher risk to develop NASH. The patients with dyslipidemia and diabetes mellitus develop more often NASH.

This study belongs to a complex research grant which is supported by the Ministry of Research from Romania.
The role of *Helicobacter pylori* infection and use of non-steroidal anti-inflammatory drugs in the pathogenesis of peptic ulcer bleeding

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**Introduction**: Non-steroidal anti-inflammatory drugs (NSAIDs) are known to be associated with the pathogenesis of peptic ulcer (PU) bleeding. There are controversial reports concerning the effects of *Helicobacter pylori* (*H. pylori*) infection per se in the pathogenesis of PU bleeding, as well as concerning the mutual effects of these two risk factors.

**Methods**: This study investigated presence of *H. pylori* infection in 213 patients with bleeding PU and 88 patients with non-bleeding PU, and the role of *H. pylori* infection in pathogenesis of PU bleeding without and with the use of NSAIDs. The presence of *H. pylori* was established by histopathologic analysis of the gastric mucosa biopsy samples taken by esophagogastroduodenoscopy, whereas a standardized questionnaire was used to collect information about the use of NSAIDs. Risk assessment was done using univariate logistic analysis, Odds ratio with 95% confidence interval.

**Results**: *H. pylori* was detected in 66.19% of patients with PU bleeding and in 56.82% of patients without PU bleeding. 66% of patients of the study group were taking NSAIDs, as well as 42% of patients of the control group. *H. pylori* infection was associated with the use of NSAIDs in 45.53% of patients of the study group, and in 18.18% of patients of the control group. The risk of ulcer bleeding was significant in patients using NSAIDs: OR = 2.68 (1.69–4.26); p = 0.00003.

**Discussion/Conclusion**: *H. pylori* infection per se does not increase the risk of ulcer bleeding: OR = 1.49 (0.89–2.47); p = 0.125; however, if associated with the use of NSAIDs, it has a synergic effect: OR = 3.63 (1.59–8.35); p = 0.0023. Eradication of *H. pylori* is recommended prior to initiation of NSAIDs, as well as continuous use of proton-pump inhibitors.
Persistence of HCV RNA in peripheral blood mononuclear cell is associated with decreased level of serum LDL cholesterol

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Introduction: Serum lipid metabolism seems to be influenced by changing in hepatocellular function connected with chronic hepatitis C and also by IFN treatment for hepatitis. In the same time hepatitis C virus replication occurs in the lipid rafts and seems to be dependent on intracellular cholesterol level. Although IFN therapy clears chronic hepatitis C infection in approximately 30% of cases, some patients, who respond to IFN therapy with HCV RNA elimination from sera, can preserve HCV genome in peripheral blood mononuclear cells.

Aim: Analyze the correlation between the responsiveness of chronic hepatitis C patients to IFN therapy and the cholesterol and triglyceride status in sera and in PBMC.

Methods: HCV RNA, LDL, HDL cholesterol and TAG were determined in 67 sera samples from patients after IFN-alpha therapy. HCV RNA and cholesterol level were evaluated in corresponding PBMC samples. cDNA was synthesized in RT reaction (Improm, Promega, random primers) from RNA isolated from all PBMC samples and used for analysis of HMG-CoA reductase, LDL receptor, SREBSP-1 and PPAR expression.

Results: HCV RNA determination was the basis of following groups selection: responders (R) where HCV RNA were eliminated in sera and PBMC, partial responders (RP) where HCV RNA was eliminated only from sera and no responders (NR). HCV RNA elimination from sera was correlated with significantly higher level of serum LDL cholesterol and triglyceride. Persistence of HCV RNA in PBMC was accompanied by low level of LDL cholesterol and low expression of LDL receptor. Comparison of R, PR and NR groups showed that the lowest level of LDL cholesterol was characteristic for non-responsiveness to IFN therapy, the medium value for partial responders and the highest for responders.

Conclusions: LDL cholesterol concentration is significantly higher in patients with chronic hepatitis C who responded to IFN therapy by elimination HCV RNA from both sera and PBMC.
Autoimmune disorders in chronic B and C hepatitis

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Introduction: The present study was carried out to evaluate the prevalence of autoimmune disorders (autoantibodies) in chronic hepatitis B and C.

Methods: Consecutive 35 patients with chronic hepatitis type C (HCV), 18 with chronic hepatitis B (HBV), suspected to be AIH, and 17 normal control patients were screened for antinuclear antibodies (ANA), antismooth muscle antibodies (ASMA), antimitochondrial antibody (AMA), anti-liver kidney microsomal antibodies (anti-LKM-1) and anti-gastric parietal cell (APC) by indirect immunofluorescence test, using tissue sections of rat stomach, kidney and liver-kit Trinity biotech.

Results: We found autoantibodies at 69% of HCV patients, 15% with chronic HBV, while prevalence in the control group was 5%. The incidence of serum ANA, SMA, RF was significantly higher in HCV than that at HBV patients and control group. We detected SMA in higher titer (> 1:160) in chronic active C hepatitis and at intermediate titers (1:40, 1:80) in B hepatitis. The ANA titres greater than 1:80 were found more frequently at the patients with HCV towards those with HBV and were missing in the control group. MA were observed in 2.8% of chronic C hepatitis patients and were missing in HBV patients.

Discussion/Conclusion: The prevalences and the titers of anti-tissue autoantibodies were significantly higher at chronic viral hepatitis C patients than at patients with chronic hepatitis B.
Primary biliary cirrhosis – Overlap syndrome with autoimmune hepatitis in current practice

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Introduction: Some patients with primary biliary cirrhosis (PBC) may have in their evolution a more “hepatitic” picture; they could be included in the diagnosis of overlap syndrome with autoimmune hepatitis (OLS PBC-AIH).

Aim: to evaluate the frequency, characteristics and evolution of these cases in our practice.

Methods: We included all patients diagnosed and followed in our unit with PBC between July 2000–June 2006, with ≥ 3 presentations. We reevaluated the histology when the pattern of disease changed, and a score for AIH (IAHG 1999) was calculated for every patient.

Results: In these period were diagnosed, treated and followed 105 cases with PBC (median age at diagnosis 49.6 ± 7.8 years): 97 females (92.38%), 8 males (7.62%); 19 patients (18.09%) were diagnosed with OLS with AIH: M/F: 1/18, all of them with “probable AIH”. The univariate analysis showed that the diagnosis of OLS was associated statistically significant with: age at diagnosis > 40 years (p = 0.037), aminotransferases values > 5 ULN (p = 0.00022), GGT values < 2 ULN (p = 0.0019), antibodies anti small muscle antigen positive (p = 0.0002) and the presence of interface hepatitis (p = 0.015). We did not observed statistically significant differences between patients with PBC and with OLS regarding: female gender (p = 0.65), presence of hypercholesterolemia (p = 0.63) and response of cholestasis to UDCA (p = 0.81) The multivariate analysis: the predictive factors associated with the presence of an OLS in CBP patients are: GGT < 2 ULN, interface hepatitis and the presence of antibodies to SMA.

Discussion/Conclusion: The OLS with AIH is not infrequently between patients with PBC. We may think about in case of a patient with moderate cholestasis, ASMA positive and interface hepatitis on histological exam.
Primary sclerosing cholangitis (PSC) and autoimmune pancreatitis (AIP) in 13-years old boy with inflammatory bowel disease (IBD)

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Introduction: In the course of IBD, an occurrence of numerous extraintestinal symptoms is observed, among others, in liver and pancreas. Primary sclerosing cholangitis (PSC) is often observed in patients with IBD. The pancreatitis grounded in autoimmunological processes is a rarely diagnosed disease entity.

Case report: A case of a 13-years old boy with diagnosed allergy to grass pollen, referred to the Dept. of Pediatrics, Gastroenterology and Nutrition because of skin pruritus, frequent bloody stools, chronic abdominal pain and weakness was reported. The patient was diagnosed with IBD (colonoscopy, histopathological examination) concomitant with PSC (biochemical traits of cholestasis in serum, MRCP, liver biopsy) and AIP (increased activity of amylase and lipase in serum, increased concentration of IgG4, inflammatory alternations in pancreas observed in ultrasonography and MRCP). Because of clinical symptoms of mesalazine intolerance, ursodeoxycholic acid and prednisone were used in the therapy.

Conclusions: A simultaneous incidence of IBD with PSC and AIP is very rare. Concomitance of the above disease entities makes the therapy difficult and increases the danger of neoplastic transformation of the organs affected by the disease.
Ultrasound telescreening network for hepatocellular carcinoma. Preliminary data from Telehepascan Project

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Background: Hepatocellular carcinoma (HCC) is actively diagnosed in chronic liver diseases (CLD) patients through screening programs, using a sensitive and easily accepted method – ultrasonography (US) and AFP determination.

Aim: To test a new and improved tele-screening system for HCC using US image transmission and image analysis, wishing to: (a) early identify any suspicious focal liver lesion; (b) create a viable ultrasound tele-screening protocol for HCC; (c) create a health grid for CLD and HCC; (d) develop the system for risk identification based on an interactive, predictive analysis and pre-classification of US images.

Methods: The tele-sonography network consists in many internet connected ultrasound remote terminals situated in the GP’s office and a core located in a tertiary health care facility. A dedicated software recognizes, analyzes and pre-classifies the images on normal-abnormal principle. Only abnormal images will be furthermore analyzed by human experts. The system is designed as a Computer Aided Monitoring System (CAMS) helping the diagnosis procedures.

Results: US screening and surveillance protocols for patients with CLD were developed, according to clinical condition (chronic hepatitis ± focal liver lesions; cirrhosis ± focal liver lesions). 5 locations were identified, in remote areas of north Romania. A total number of 30,000 patients undergo US examination. A short training in US examination of the liver and HCC screening was given to medical professionals (doctors and/or nurses)

Conclusion: Screening for HCC using telesonography may become a valuable tool for better understanding of the disease and provide new evidences in large series of patients.

(grant PCD-M1–CEEX nr 3/2005 from the Romanian Ministry of Education and Scientific Research)
Obstructions of the portal venous system (OPVS) in adults: Clinical epidemiology and relationship with liver cirrhosis

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Background: OPVS (thrombosis and tumour vascular invasion) are considered common situations. Although it was previously demonstrated to have a low incidence both in general population and in liver cirrhosis patients, no coherent evidence is currently available, especially in European populations.

Aim: To assess the incidence, the clinical background and complications of OPVS and also its relationship with liver cirrhosis (LC).

Methods: 416 necropsy records were studied retrospectively between 2001 and 2005. Localization, clinical conditions, and potential risk factors were taken into account. DRG entries were used to appreciate the real prevalence in general population.

Results: OPVS was observed in 30 patients (7.21%) and LC was demonstrated in only 7 of them (23%). Other causes of OPVS were: intra-abdominal infections (10 cases – 33.33%); cancers (9 cases – 30%); post-operative status (2 cases – 6.66%); mieloproliferative disease (1 case – 3.33%); antiphospholipid syndrome (1 case – 3.33%). The most common localization of OPVS was the main PV (73.33% of cases), but all other sites of the portal venous system were affected. In the subgroup of patients with both LC and OPVS the most common cause of liver disease was ethanol intake (57.14%), while VHB and VHC infections were found more rarely. In 5 of 7 cases no other cause of death besides liver disease could be found. No association with HCC was found. In this group, and all of the patients presented a micronodular type of cirrhosis (p = 0.00).

Conclusion: OPVS is not a rare condition in general population. It may complicate liver cirrhosis quite often, especially the micro-nodular one.
Optimizing the outcome for patients with colorectal cancer; patients of UMC Ljubljana

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Background: In Slovenia the incidence of colorectal cancer is growing rapidly. In 1998 1022 new cases were registered. Our study compares results of two groups of patients with colorectal cancer.

Patients and methods: In the period from 1.1.1991 to 31.12.2000 1478 patients with a colorectal carcinoma underwent potentially curative resection. We divided them in two groups, one operated in the first 5-year and second in later 5-years period. 5-year survival was estimated with Kaplan-Meier statistical analysis. Patients who died within 30 days after the operation were censored. Differences in survival curves between both groups were assessed by the log rank test.

Results: We resected 1478 /1599 (92.4%) patients. There were 913 (61.7%) patients resected with colon cancer and 528 (35.8%) with rectal cancer and 37 (2.5%) with sinhronius tumors. R0 resection was performed in 1174 (79.4%) patients, R1 in 29 (2.0%), and R2 in 273 (18.5%) patients. Postoperative mortality rate in resected patients was 5.48% (81/1478), in the group with paliative operations was 17.35% (21/121). Overall five-year survival rate was 54.9% (56.18% for colon cancer and 52.4% for rectal cancer Five-year survival rate for the patients with radical resection (R0) was 66.54% for colon cancer and 59.47% for rectal cancer.

Conclusion: 5-year survival for R0-resected patients with colon cancer was in the last period from 1996 to 2000 statistically significantly better compared with the period from 1991 to 1995 (76% vs. 60%) in stage I (p = 0.04048) and in stage III (p = 0.01842). 5-years survival for R0-resected patients with rectal cancer was significantly better in the same period (63% vs. 55%) (p = 0.03627) in stage III (p = 0.01663).
Quantifying a relationship between lifestyle, age, gastric and colonic cancer

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Introduction: Aging is closely correlated with the nutrition factors, just like gastric and colonic cancer. Alimentation is correlated with the environment, culture and climate. The aim of this study was to estimate the correlation between the presence of gastric or colonic cancer, the patient's age and lifestyle.

Material and methods: Located at the University Hospital CF Timisoara, this study was made on 110 patients, from whom 38 had gastric cancer and 72 had colonic cancer. The lot had an age average of 54 years (age interval 23–85 years) and was studied for 12 months and was balanced in the gender repartition. All of the patients were investigated by the means of clinical and complex paraclinical exams.

Results: 59% of the patients had normal weight, 35% were overweighted and 6% underweighted. The lot ate too much meat and too many fats (65%) and they lacked fruits 61%, vegetables 53%, and diaries 51%. 49% of the patients lived in the rural area. Interestingly, 53% of the elderly patients had a hyper-caloric diet. Based on this statistic results we developed a prediction scheme and test it on every member of our lot, obtaining a medium accuracy of 89.7%.

Conclusion: The nutrition plays an important role especially at elderly persons in the initiation of gastric and colonic cancer.
Urgent resection of spontaneously ruptured liver tumours: Report of three cases

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Introduction: The rupture of the tumour is a potentially fatal complication of liver neoplasms. The authors present three cases of urgently operated ruptured liver tumours with different origins.

Methods:
Case 1: A 7 years old girl with a positive familiar anamnesis of hepatoblastoma was admitted with signs of severe abdominal bleeding. During the operation a ruptured tumour was removed from the 4th segment of the liver. Histology proved hepatoblastoma.
Case 2: A 51 years old female was admitted with DIC. The origin was an enormous ruptured hemangioma occupying the right hepatic lobe. After an unsuccessful chemoembolisation an urgent right lobectomy was performed.
Case 3: A 65 years old male was planned to undergo staging laparoscopy due undetermined neoplasm of the liver suspected to be HCC. During laparoscopy we detected the rupture of the tumour of the left lobe. After conversion a left lobectomy was performed.

Results: The 7 years old girl received chemotherapy. After 27 months she is free of recurrence. The 51 years old female died after 8 months due to the rupture of lung hemangiomas. The 65 years old male died 13 months after the resection because of recurrence of the HCC.

Discussion/Conclusion: In certain cases when the chemoembolisation is not successful and delayed operation is not affordable urgent liver resection is the treatment of choice. It can result a good survival rate comparable to those undergoing elective surgery although the complication rate is higher and the recurrence of the disease is more common.
Non-recorded alcohol consumption – Cause of high mortality on cirrhosis?

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Alcohol consumption and its increasing trend is a worldwide problem. Over the last 50 years it has increased in one third of European countries, Slovakia included, four times. After 1990 the alcohol consumption increased in most of East-European countries, but in Slovakia it has paradoxical decreased to 9.5 l in 2003. Is it true or not? Position of Slovakia in alcohol consumption decreased from 5th place to 11th place in Europe, but in mortality on cirrhosis it remained at the same 5th level. Mortality from chronic liver diseases has increased 10 times in men and 4 times in women within the last 40 years. It remains at the same level till now. But, the recorded alcohol consumption doesn’t correlate with mortality on liver cirrhosis in the past 10 years. The most reliable explanation is the increase of non-recorded home-produced alcohol, especially spirits. To achieve a further decrease of alcohol consumption in Slovakia, the following health care measures should be taken:

1) in the field of primary prevention – to elucidate and provide insight into the notions of "risk consumption", "real consequences of alcohol intake", "healthy risk" at individual and general population level;

2) in the field of secondary prevention to achieve at the stage of minimal functional lesion
   - early detection of alcohol liver diseases - recognizing subjects at risk
   - improvement of patient compliance
   - improvement of cooperation between outpatient and inpatient departments.

Thanks for statistical dates to Office of Statistics of Slovak Republik, Office of Health Statistics of Slovakia and Office of WHO.

This work was supported by VEGA 1/2295/05.
Salmonelosis – Cause of venoocclusive disease?

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A 34-year-old woman was admitted to hospital for ascites, weakness, jaundice, nausea, vomitus, anorexia and fever in the last 2 months after episode of diarrhoe. Laboratory parameters showed leukemoid reaction with leukocytosis, high thrombocytemia, moderate hypocoagulative state with high hyperbilirubinemia. There was 100 times elevation of transaminases with 10 times elevation of cholestatic enzymes at admission with gradually decrease to 10 times of normal limit, slight hyperamylasemia, hypoproteinemia and hyperammonia. Virologic examination was negative. Salmonelosis and uroinfection were found. Hepatomegaly and ascites with slow portal vein flow, nonvisualisation of hepatic veins, slight splenomegaly and cholelithiasis were found on ultrasonography. CT found hepatosplenomegaly with massive infiltrative inflammatory or neoplastic process, ascites, fluidothorax, retroperitoneal and intraperitoneal lymphadenopathy and suspicion on ovarian tumor. Esophageal varices P.II. were found with following hematemesis. Ascites was positive for Acinetobacter with repeatedly negative cytologic examination. Because of suspicion on gynecologic or urologic malignancy (under CT, US, positive CA 125, CA 19-9, B2M, NSE) there was non considered treatment with liver transplantation. Recurrent torpid hematemesis occurred and the patient died. Pathologic examination showed acute flebithis of small hepatic veins. Cavography could not be done for the severe hypocoagulative state. Nonvisualisation of hepatic veins is often present in liver cirrhosis. Inflammation of hepatic veins and disseminated intravascular coagulation caused their thrombosis. The cause of inflammation could be salmonelosis with bacterial peritonitis. Liver transplantation could be the only therapeutic option.

This work was supported by VEGA 1/2295/05.
Heparin II cofactor deficiency – Cause of portal vein thrombosis

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Background: Heparin II cofactor deficiency is a rare cause of portal vein thrombosis. Firstly it was described in 1985. Positive family history of thrombosis with episodes of recurrent venous thromboembolism before age of 40 is usually present.

Case report: A 25-year-old man with family history of thrombosis and recurrent esophageal bleeding was examined. Portal vein thrombosis together with splenic vein thrombosis were found on color Doppler ultrasound. Surgery or inflammatory abdominal process were excluded. Levels of activated proteins C and S, coagulation inhibitors (protein C and S, antithrombin III, heparin II cofactor), homocystein, plasminogen, factors II, VII, XII were measured, as well as DNA analysis of factor II and V were performed. A reduced level of heparin II cofactor antigen and decreased activity of heparin II cofactor were found.

Conclusion: A heparin II cofactor deficiency was found to be the cause of portal and splenic vein thrombosis with symptomatic portal hypertension. The examination of coagulation inhibitors should be involved in all patients with portal vein thrombosis of unknown origin. In 1/3 of patients with portal vein thrombosis the hematological origin, especially hereditary thrombofilic state is the most common cause.

This work was supported by VEGA 1/2295/05.
Unusual source of obscure lower gastrointestinal bleed – Splenic artery pseudoaneurysm

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Introduction: Obscure lower gastrointestinal bleeding (OLGIB) is a recurrent bleeding the source of which remains undefined by routine endoscopic and contrast studies. Among these, pseudoaneurysmal bleeding may complicate up to 12% of chronic pancreatitis with pseudocysts. Typical presentation is a self-limited blood-loss followed by life-threatening exsanguination. Splenic artery aneurysms are a consequence of chronic pancreatitis and most commonly rupture into the peritoneal cavity, the pseudocyst itself or the upper gastrointestinal tract.

Methods: We present a case-report of OLGIB caused by rupture of a splenic artery pseudoaneurysm into the colon.

Results: The 43 year-old male with a history of chronic pancreatitis was readmitted for severe hematochezia, after he had undergone EGDS and colonoscopy for bleeding at another facility. After correction of his hemodynamic parameters he developed a mild episode of acute pancreatitis, after which repeated endoscopies, abdominal computerized tomography, ultrasound and radionuclide imaging failed to localize the bleeding, as did mesenterial angiography, that revealed a splenic artery pseudoaneurysm. Capsule endoscopy was planned, but hyperacute bleeding required urgent surgical intervention.
An inflammatory mass was found around the body and tail of the pancreas involving the colon and spleen with a 6 cm pseudoaneurysm of the splenic artery. Distal pancreatectomy with splenectomy and resection of the colon was carried out. Microscopic examination clearly showed a tract between the pseudoaneurysm and the colon.

Discussion/Conclusion: Histologic demonstration of a tract between the splenic artery pseudoaneurysm and the colon in a patient without a known pseudocyst in chronic pancreatitis is unprecedented in the literature.
Endoscopic stapled esophago-diverticulostomy versus open surgery in the treatment of Zenker diverticulum: What kind of operation would be chosen?

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Introduction: The authors analyse in a comparative study the indications, contraindications, early and late results of two types of operations (diverticula resection with crycopharyngeal myotomy and endoscopic stapled esophago-diverticulostomy) for the treatment of Zenker’s diverticulum.

Methods: In a five year period 10 patients (5 male, 5 female, mean age of 56.9 years) were operated for Zenker’s diverticulum. Six open and 4 endoscopic operation were indicated, although in one case the placement of the endoscope was unsuccesful. The indication of open surgery was a lateral positioned, was too small or large diverticulum and if endoscopic surgery was executed.

Results: The operative time was shorter in the endoscopic group then in the open surgery group (32.3 vs. 80.7 minutes). In the open surgery group (7 patients) saliva fistule caused by suture insufficiency occured in one case. The hospital stay was 8.1 days in the resected group while 4.7 in the endoscopic group. No recurrence was observed.

Discussion/Conclusion: The advantages of the endoscopic oesophago-diverticulostomy are the shorter operating time and hospital stay, less complication rate and its minimal invasivity. The authors suggest endoscopic oesophago-diverticulostomy as the choice of operation in case of Zenker’s diverticulum. The open surgery is indicated only if the diverticulum is in lateral position or if it is bigger than 8 cm. The technical contraindications of the endoscopic surgery are the short, rigid neck and limited mouth opening.
Immunohistochemical study of cell proliferation in H. pylori associated gastritis and premalignant gastric lesions

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Introduction: To investigate gastric mucosal cell proliferation with monoclonal antibody MIB 1 in gastritis and precancerous lesions.

Methods: Expression of Ki-67 antigen was immunohistochemically determined on paraffin-embedded specimens from normal gastric mucosa (n = 5), mucosa adjacent to gastric carcinoma (n = 15), chronic gastritis (n = 20), H. pylori-associated gastritis (n = 30), type III intestinal metaplasia (n = 15) and high-grade dysplasia (n = 20). The Ki-67 labelling index were counted in each zone and expressed as a percentage (KI LI = the number of Ki-67-positive cells/500 Ki-67-positive and -negative cells).

Results: In normal gastric mucosa, Ki-67 immunoreactivity was observed exclusively in the proliferative zone (KI LI = 46.5% ± 15.1). The proportion of Ki-67-positive cells was much greater in H. pylori gastritis (KI LI = 72.86% ± 8.6) with numerous positive nuclei in superficial zone (KI LI = 38.82% ± 13.9). KI LI in superficial zone was significantly higher in severe H. pylori colonization (44.46%) than in mild colonization (22.89%). In type III intestinal metaplasia was noticed an expansion of the proliferative compartment to the lower layer of mucosa (49.27% ± 17.4). In high-grade dysplasia was observed an expansion of the proliferative activity to the upper zone (63.38% ± 14.8).

Discussion/Conclusion: These results show different cell proliferation patterns, with significant differences in Ki-67 scores in each zone among various histologic lesions. Our data suggest that H. pylori can influence the rate of epithelial cell proliferation.
The neoplastic potential of ulcerative colitis-associated hyperplastic polyps

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Introduction: Colorectal cancer represents the major cause for mortality by malignant disease in ulcerative colitis (UC). The histological evidence of dysplasia was shown to be a strong indicator of underlying or associated cancer. Hyperplastic polyps may also develop in chronic UC, but the neoplastic potential of this polyps is unknown.

Aim: To evaluate and compare the neoplastic potential of UC-associated hyperplastic polyps with UC-associated dysplasia.

Methods: 20 hyperplastic polyps from patients with chronic UC and 26 colonic mucosal biopsies from patients with chronic UC with dysplasia (12 low-grade dysplasia and 14 high-grade dysplasia) were analyzed by immunohistochemistry for p53 (DO-7) and KI-67 (MIB-1). Lesions were considered p53-positive if at least 5% of nuclei in a high power field were positive for staining. We counted the numbers of KI-67 immunoreactive cells per 500 crypt cells.

Results: p53 mutations were present in 30% of UC patients with hyperplastic polyps and in 42.3% of patients with UC dysplasia (3 patients with low-grade dysplasia and 8 patients with high-grade dysplasia), respectively. MIB-1 labeling indices were significantly higher in high-grade dysplasia (65.7%) and hyperplastic polyps (49.7%) than in low-grade dysplasia (34.8%).

Discussion/Conclusion: This data suggest that chronic UC-associated hyperplastic polyps may have neoplastic potential and should be investigated further as a risk lesion for colorectal cancer development.
The effects of lanreotide and peginterferon alpha-2b therapies on hepatic fibrosis induced by bile duct ligation in rats

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Somatostatin receptors have been shown on hepatic stellate cells and somatostatin infusion has been shown to inhibit the stellate-cell activation. The antifibrotic effect of interferons is still debate. We aimed to test the effects of lanreotide and peginterferon, as the long active form of the drugs on bile-duct ligation (BDL) induced liver fibrosis in rats.

Material/Method: Seventy-five male Wistar rats were divided into 8 groups. First 4 groups were BDL operated and administered; lanreotide autogel (20 mg/kg/month), peginterferon alpha-2b (50 µg/kg/week), combination of both drugs and serum physiologic, intraperitoneally, respectively. Three sham operated groups and one control group were also given the same doses respectively. After one month of the study, liver enzymes and free radical tests were studied with commercial kits. Total liver collagen was determined by the method of Lopez de Leon and Rojkind. Liver slides were stained by Haemotoxylene/Eosin and Masson-Tricrom/Gomory reticulum staining.

Results: The tissue collagen levels, biochemical parameters (AST, ALT, alkaline phosphates) and free radicals (malondialdehyde, luminol, lucigenin) levels of the BDL groups were higher than the sham operated and control groups (all p < 0.001). In histopathological examination, BDL groups showed stage-3 fibrosis, while all the control groups were normal. None of the drugs could improve the liver fibrosis neither histologically, nor biochemically.

Conclusions: A monthly active somatostatin analogue, lanreotide and a weekly active interferon molecule, peginterferon alpha-2b and their combination therapies were not able to improve the BDL induced liver fibrosis in rats. Lanreotide and peginterferon did not have antifibrotic effects in the model; they are long active drugs, thought.
Hepatocyte apoptosis in NAFLD patients with elevated versus normal GGT

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Background and aim: Hepatocyte apoptosis is associated with the liver injury in non-alcoholic fatty liver disease (NAFLD). Increased gamma-glutamyl transferase (GGT) levels are frequently observed in NAFLD patients. Potential associations between GGT elevations, liver histology, apoptosis and disease severity in NAFLD are yet to be examined. We aimed to determine the hepatocyte apoptosis factors in NAFLD with normal and elevated GGT levels.

Methods: Fifty non-drinker patients (M/F = 24/26) with biopsy-proven NAFLD were studied. Immunohistochemistry was performed for activated caspase-3, caspase-8, NFκB and antiapoptotic Bcl-2 protein, tumor necrosis factor-alpha receptor (TNFr) and TNF-sRp55. Tissue caspase-3, caspase-8, NFκB and Bcl-2 were semiquantitavely evaluated using the 4-point scoring system.

Results: Twenty-five patients (M/F = 10/15) had normal GGT levels and the other 25 patients (M/F = 14/11) had GGT elevation more than two fold of upper-limit. In normal GGT group, NFκB, caspase-3, caspase-8, and Bcl-2 ± SD (according to the cell counts in %/high power field) were 29.8 ± 22.5, 30.7 ± 22.4, 22.2 ± 20, 4.1 ± 5.4 respectively. Patients with high GGT had significantly higher NFκB, caspase-3 and caspase-8, and Bcl-2 levels (54.5 ± 26, p = 0.002; 56 ± 27.2, p = 0.002; 47.9 ± 28, p = 0.001; 11.2 ± 12.3, p = 0.016, respectively). However, TNFr levels were not statistically different. The liver biopsies revealed NAFL in 21/50 (42%) and NASH in 29/50 (58%) patients. Although the steatosis grade and inflammation were not different, the fibrosis stage was significantly higher in high GGT group (p = 0.05). The patients with high-GGT had significantly higher ALT (p = 0.008), AST (p = 0.013) and ALP (p = 0.01) levels.

Conclusions: GGT elevation in NAFLD is not only a result of a cholestatic reaction but also a result of more severe disease with fibrosis in the majority of non-alcoholic steatohepatitis subgroup.
Non-invasive markers of liver fibrosis and other characteristics of alcoholic hepatitis

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Introduction: Alcoholic hepatitis continues to remain an important health problem as prevalence and clinical manifestations.

Methods: We have studied all the patients which were hospitalized during 15.09–31.10.2006 in the internal medicine departments from the Clinical County Hospitals from Brașov, Oradea and Sibiu, to whom the abdominal ultrasonography revealed a hyperechoegeneous liver. We have studied the prevalence of the alcoholic hepatitis and its clinical, biological and imagistic characteristics. The liver fibrosis was estimated by the next non-invasive markers: Forns index, APRI score and the platelets number. The results were statistically analyzed using the “t” Student test and the Pearson test of correlation.

Results: Among the 436 patients with hyperechoegeneous liver, 59 (13.5%) had alcoholic hepatitis. Other etiologies of the chronic hepatitis were: 52% NAFDL, 15% NASH, 10% viral C hepatitis, 4% drugs induced hepatitis, 3% viral B hepatitis, 2% autoimmune hepatitis, 0.45% liver cancer. We have formed 2 groups: group A with alcholoic hepatitis (n = 59) and group B with other etiology of liver disease (n = 377). There were statistically significant differences between the two groups regarding: age (p = 0.019), the grade of the posterior attenuation (p = 0.027), ASAT (p = 0.003), ALAT (p = 0.0053), total bilirubin (p = 0.03), direct bilirubin (p = 0.05), GGT (p = 0.002), cholesterol (p = 0.001), BMI (p = 0.037). The average for the Forns index was 4.9566 at the patients from group A and 5.1816 at those from group B (p = 0.246). The average for APRI score was 0.2951 at those from group A and 0.3731 at those from group B (p = 0.4002). At the patients with alcoholic hepatitis there is an inverse linear correlation between the number of platelets and the Forns index (r = -0.544) and between the number of platelets and the APRI score (r = -0.402).

Discussion/Conclusion: The patients with alcoholic hepatitis are generally younger; they have a BMI lower than the average; they have cholestasis and higher values of liver enzymes and cholesterol. The non-invasive markers of fibrosis do not differ significantly at those with alcoholic hepatitis comparing to those with other etiologies. The number of platelets can be an indicator for liver fibrosis at the patients with alcoholic hepatitis.

This study belongs to a complex research grant which is financed by the Research and Education Minister from Romania, to whom we are deeply grateful.
Gamma-glutamyltransferase in patients with metabolic syndrome and nonalcoholic fatty liver disease

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Introduction: Nonalcoholic fatty liver disease is closely associated with metabolic syndrome (MS). Elevated gamma-glutamyltransferase (GGT) level is a marker of liver injury, insulin resistance and visceral fat, especially hepatic steatosis. The aim of the study was to evaluate the association between the GGT levels with MS components and nonalcoholic fatty liver disease.

Methods: A total of 241 patients with MS (108 male; 133 female; mean age 53.76 ± 10.55 years) had liver steatosis on transabdominal ultrasound. Exclusion criteria: HCV or HBV infection, alcohol consumption > 20–30 g/day, hepatotoxic drugs. GGT was divided into five groups ≤ 19 U/l (n = 5), 20–29 U/l (n = 35), 30–39 U/l (n = 41), 40–49 U/l (n = 45), ≥ 50 U/l (n = 115). Each group was compared with age, weight, blood pressure, total cholesterol, HDL cholesterol, triglycerides, fasting plasma glucose, ALT, AST, alkaline phosphatase, white blood cells count (WBC), erythrocytes sedimentation rate (ESR).

Results: Total cholesterol (r = 0.3421, p < 0.01), lower levels of HDL cholesterol (r = 0.7036, p < 0.01), triglycerides (r = 0.5653 p < 0.01), fasting plasma glucose (r = 0.1981, p = 0.02), AST (r = 0.3212, p < 0.01), ALT (r = 0.1891, p = 0.003), alkaline phosphatase (r = 0.5122, p < 0.01), ESR at 1 hour (r = 0.2315, p < 0.01), systolic and diastolic blood pressure (r, p = NS) showed a linear trend in relation with increasing serum GGT level. Additional significant associations between fasting plasma glucose and ESR (r = 0.2859, p < 0.01) and between triglycerides and ESR (r = 0.2653, p < 0.05) were found. WBC was not correlated with GGT (p > 0.05). 54.4% of type 2 diabetes vs. 44.8% of those with normal fasting glucose had elevated GGT (≥ 50 U/l) but no significant difference between GGTs means was found (p > 0.05). 76.5% of obese patients (BMI > 30 kg/m²) vs. 23.5% of overweight patients (BMI = 25–30 kg/m²) had elevated GGT (> 50 U/l) (p > 0.05). There were no significant correlations between ALAT and fasting plasma glucose.

Discussion/Conclusion: Increase in GGT activity was associated with components of MS and elevated aminotransferases. Increased values of GGT were more frequent in diabetes patients and also in obese patients.
Elements predicting variceal bleeding in cirrhotic patients

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Aim: To identify elements that can predict variceal bleeding in cirrhotic patients (Child-Pugh class, size of the varices, presence of red margins, etiology).

Material and method: This retrospective study included patients diagnosed with cirrhosis for a 3 years period (2003–2005) in the Department of Gastroenterology Timisoara, Romania. We studied 126 patients (66–52% men; 60–48% women, mean age 54.01 years). All patients underwent endoscopic evaluation of the degree of esophageal varices (EV), which were also classified using the scoring system developed by Snady et al. Severity of liver disease was assessed using the Child-Pugh classification: class A – 33 patients (26.1%), class B – 67 patients (53.1%), class C – 19 patients (15%).

Results: Mean Snady score for the batch we studied was 4.72 (patients in Child-Pugh A – 3.77 ± 0.89, Child-Pugh B – 4.82 ± 1.24, Child Pugh C – 5.57 ± 1.03). According to the EV degree, 7 (5%) patients had grade I, 60 (47%) grade II and 59 (46%) grade III. Patients with low Snady score rebled in 9.09% cases, those with medium score in 23.27% cases and those with high score in 66.66% of cases (these data are similar with those published by Snady et al.). The risk of variceal bleeding was also significantly related to the patient's Child-Pugh class (patients in Child-Pugh class A rebled in 3.63% cases, those in Child-Pugh class B rebled in 46.26% of cases and those in class C in 52.63% of cases).

Discussions/Conclusions: Routine use of a risk scoring system in variceal bleeding is extremely useful, allowing selection of cases with high risk. Size of esophageal varices (Snady score) is significantly related to the patient's Child-Pugh class (p < 0.001 – ES), the risk of rebleeding (p < 0.001 – ES), and ethanolic etiology (p < 0.0368 – S).
Outcome of patients with variceal bleeding undergoing banding and propranolol treatment

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Aim: Patients with esophageal varices (EV) have a 25–40% chance of first variceal bleeding within 2 years of follow-up in the absence of effective prophylactic treatment (propranolol and/or variceal band ligation). We studied the outcome of patients undergoing medical and endoscopic therapy.

Material and method: We studied 126 patients with EV admitted between 2003–2006 in the Department of Gastroenterology and Hepatology Timisoara (66–52% men, 60–48% women, mean age 54.01 ± 8.9 years). Upper GI endoscopy and band ligation (if needed) were performed in all patients.

Results/Discussions: Severity of liver disease was assessed using the Child-Pugh classification: class A – 33 patients (26.1%), class B – 67 patients (53.1%), class C – 19 patients (15%). 7 patients (5%) presented EV I st degree, 60 (47%) EV II nd degree and 59 (46%) EV III rd degree. The group of propranolol treated patients (n = 63 – 50%) received a mean dose of 45.43 ± 1.88 mg (class A: 44.24 ± 1.79 mg, class B: 45.45 ± 2.03 mg, class C: 45.71 ± 1.82 mg). Rebleeding occurred in 46.25% cases (an unacceptable high rate compared to literature data, p = 0.001558, VS), explained by lower doses administrated (p < 0.001 – ES). In the group of patients undergoing band ligation, a mean of 5.69 ± 1.56 bands were placed (class A: 4.93 ± 1.13, class B: 5.89 ± 2.49, class C: 6.26 ± 1.05). Rebleeding after banding occurred in 34.17% of cases (3.63% in class A, 46.26% in class B, 52.63% in class C). A mean of 4.7 ± 0.3, 3.2 ± 0.9 and 3.1 ± 0.9 bands were placed during the second, third and fourth session, respectively.

Conclusions: 1. Required propranolol dose and number of bands needed increases with severity of liver disease (p = 0.006554 – VS, and p = 0.0352 18 – S). 2. Fewer bands were required during subsequent sessions because of reduction in EV size (p < 0.001). 3. The risk of rebleeding after variceal bleeding increases with the Child-Pugh score (p = 0.000027 – ES).
Lesional aspects in chronic gastritis with and without duodenitis in patients with Helicobacter pylori infection

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Aim: to estimate the severity and histological characteristics of HP positive chronic gastritis patients with and without associated duodenitis.

Methods: Biopsies from gastric antrum and body were obtained from patients undergoing endoscopy for dyspepsia. Helicobacter pylori was diagnosed by gastric histology and serology. Severity of gastritis and density of the HP infection were graded according to the Sydney and Whitehead system.

Results: Of the 47 patients studied, 34% had chronic gastritis lesions without duodenitis on the endobioptically specimens. 75% out of this patients had infectious gastritis lesions (type B) HP-positive, with histological activity score 2 and 3. Non-specific diffuse duodenitis associated with chronic gastritis was found in 29% of cases. The incidence of HP infection in this group was 85.7%, with the activity score 1 and 2. Erosive duodenitis was correlated in all of the cases with the major score of activity in chronic gastritis patients HP+ and with the positive HP serology. High titres of serical antibodies to HP in patients with and without duodenitis was associated with follicular, lymphocitar and atrophic gastritis, where the presence of HP on gastric body mucosa was not detected.

Conclusion: The results suggest that HP positive patients with duodenitis have a more severe form of gastritis than those without associated duodenal inflammation.
Evidence for the role of gastric mucosa for the secretion of soluble triggering receptor expressed on myeloid cells (sTREM-1) in peptic ulcer disease

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Introduction: To investigate the implication of gastric mucosa for the secretion of sTREM-1 in peptic ulcer.

Methods: Seventy two patients were enrolled; 35 with duodenal, 21 with gastric ulcer and 16 with chronic gastritis without ulcer. Patients were endoscoped and gastric juice was aspirated. Patients with duodenal and gastric ulcer underwent a second endoscopy post-treatment. Biopsies were incubated in the absence/presence of endotoxin (LPS) or gastric juice. Supernatants were collected and sTREM-1 and TNFα were measured by enzyme immunoabsorbent assays. Scoring of gastritis was performed before and after treatment according to updated Sydney score.

Results: Patients with duodenal and gastric ulcer and those with chronic gastritis had similar scores of gastritis. sTREM-1 was greater in supernatants of tissue sampled from H. pylori-positive than from H. pylori-negative patients with gastric ulcer; it was also elevated compared to patients with chronic gastritis. Release of sTREM-1 was significantly decreases from mucosa sampled after treatment. Similar changes were not found for TNFα. Positive correlations were found between sTREM-1 of supernatants from patients with both duodenal and gastric ulcer before treatment and the degree of infiltration of neutrophils and monocytes.

Discussion/Conclusion: sTREM-1 secreted by the gastric mucosa is an independent mechanism connected to the pathogenesis of peptic ulcer. sTREM-1 was released in the presence of H. pylori from the inflamed gastric mucosa in the field of gastric ulcer.
MELD prioritization for patients with cirrhosis and small hepatocellular carcinoma has a positive impact in waiting time and recurrence free survival post liver transplantation

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Introduction: Selected patients with HCC can be cured by liver transplantation (LTx). Long waiting time may preclude transplantation.

Aim: To evaluate living donor LTx (LDLT) and MELD prioritization on pre- and post-LTx outcome of patients with cirrhosis and HCC.

Methods: 55 patients with small unresectable HCC (single nodule < 5 cms or up to 3 nodules < 3 cm) and normal chest and bone scan were listed for LTx between Jan 2001 and Sept 2006. Outcome was analyzed in 2 time periods: Jan 2001/June 2005 (Group A, all patients were offered the possibility of LDLT) and July 2005/Sept 2006 (Group B, all patients received a MELD score of 22 and additional points every 3 months in the waiting list). No differences in etiology and severity of cirrhosis were observed between groups. Results were also analyzed within Group A between patients with/without an available living donor.

Results:

<table>
<thead>
<tr>
<th></th>
<th>Waiting time (mo)</th>
<th>Died waiting or “drop out” from list</th>
<th>LDLT from inclusion</th>
<th>Recurrence-free survival from Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (n = 32)</td>
<td>24.3 ± 10.3</td>
<td>11/32 (34.3%)</td>
<td>7/32</td>
<td>19/32 (59.3%)</td>
</tr>
<tr>
<td>- with LD (n = 7)</td>
<td>6.8 ± 2.1</td>
<td>0/7 (0%)</td>
<td>7/7</td>
<td>6/7 (85.7%)</td>
</tr>
<tr>
<td>- without LD (n = 25)</td>
<td>27.8 ± 13.7*</td>
<td>11/25 (44%)</td>
<td>–</td>
<td>12/25 (48%)</td>
</tr>
<tr>
<td>B (n = 23)</td>
<td>2.8 ± 1.6*</td>
<td>2/23 (8.6%)</td>
<td>–</td>
<td>19/23 (82.6%)</td>
</tr>
</tbody>
</table>

*p < 0.05

Conclusion: LDLT is a good alternative for patients with small HCC and an adequate living donor, but low applicability results in a small impact in overall recurrence free survival. MELD prioritization has a high efficacy, resulting in short waiting time and high survival rates.
Evaluation of examinations used in diagnostic of lactose intolerance in children

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Introduction: The diagnosis of lactose intolerance is established on the basis of the clinical picture, determined concentration of glucose in the blood and/or the hydrogen breath test after the oral lactose load. The most valuable examination seems to be the determination of lactase activity in the intestinal biopsy. However, in literature there are only few studies comparing these diagnostic methods.

The aim of the study was the evaluation of sensitivity and specificity of the hydrogen breath test and the evaluation of glucose concentration in the blood after lactose load in comparison with lactase activity in the intestinal biopsy.

Material and methods: In 61 children we performed the hydrogen breath test, the oral lactose load test with determination of glucose concentration in the blood and we determined lactase activity in the intestinal biopsy.

Results: In 79% of the patients we observed a compatibility between the hydrogen breath test and lactase activity, in 16.6% the hydrogen breath test gave false positive results, and in 4.4% the results were false negative. In a majority of the patients with false positive results of the hydrogen breath test, lactase levels were at the low normal range. The oral lactose load test with the determination of glucose concentration in the blood was characterized by lower sensitivity and specificity. In over 20% it showed false positive results and in 10% false negative results.

Summary: With regard to a large number of false positive and negative results in the hydrogen breath test and the oral lactose load test with the determination of glucose concentration in the blood, in the case of diagnostic difficulties it seems reasonable to determine lactase activity in the intestinal biopsy.
The influence of chronic colitis on carcinogenesis in experimental studies on rats

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Background: The project is related to experimental oncology. The study of the adenoma-carcinoma sequence in an animal model of chronic colitis resembling human ulcerative colitis is essential to understand the pathogenesis of the process.

Aim of the study: The aim was to establish a model of chronic colitis to study the relationship between inflammation and cancer development as well as to elucidate the adenoma to carcinoma cascade demonstrated by the P53 and Ki67 makers and dysplastic lesions (high and low grade). Additionally, the metastatic affection of liver tissue was investigated.

Material and methods: An experimental model of colitis and carcinogenesis in 50 two months old Wistar rats was used. First colitis was induced using 4% acetic acid given by the rectal canulla and histologically proved. Than carcinogenesis in two groups of animals (healthy and with induced colitis) was studied. Azoxymethane was used as the carcinogen.

Results: Colonic adenocarcinoma developed in 30% of the colitis induced group and in 20% of the group without induced colitis but receiving the carcinogen. Dysplasia preceded the development of colonic adenocarcinoma. Ki67 and P53 positivity was an early sign of colonic malignancy in both dysplastic (mostly high grade) and carcinoma lesions. Liver tissue was affected by metastatic carcinoma only in those animals with chronic colitis.

Conclusions: Chronic colitis resembling human ulcerative colitis leads to the development of colonic adenocarcinoma. In the colitis-induced group the process of carcinogenesis was more frequent and expansive than in the healthy animals.
Surgically treated patients and extraintestinal manifestations of ulcerative colitis

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Background: Restorative proctocolectomy with ileal-J-pouch-anal anastomosis is currently the method of choice, considering surgical management of severe ulcerative colitis. Many research studies underlined the clinical relationship between ulcerative colitis and its extraintestinal manifestations. The most frequent disorders include a variety of joint involvement, primary sclerosing cholangitis, autoimmune hepatitis, dermatologic and gynecologic diseases.

Aim of the study: Retrospective analysis of the coexistence of extraintestinal manifestations in patients operated due to ulcerative colitis in our Department. The evaluation of clinical course of concomitant diseases was analyzed as well.

Patients and methods: 104 patients were operated between 1994 till 2006 due to ulcerative colitis in our Department. All of them underwent restorative proctocolectomy. The average was 40 years. Every patient was considered individually. The extraintestinal manifestations of ulcerative colitis were confronted in all suffered patients.

Results: Extraintestinal manifestations of ulcerative colitis were diagnosed in 36 patients (34.6%). In 16 patients (15.8%) temporo-mandibular joint involvement was diagnosed. In 10 (9.6%) patients peripheral arthritis. All symptoms in those groups decreased significantly after surgery. 5 (4.8%) patients developed large ovarian cysts treated surgically (cystis follicularis and endometriotica). In 3 (2.8%) primary sclerosing cholangitis was diagnosed. This group needs medical treatment after surgery. Dermatologic presentation like pyoderma gangraenosum was observed in 1 (1%). Symptoms ceased after surgery and cyclosporine treatment. In 1 (1%) patient severe disturbances of the coagulation-fibrinolysis system were diagnosed. After surgery symptoms ceased completely. All patients treated surgically in our Department remain under regular follow up examinations.

Conclusions:
1 Extraintestinal manifestations of ulcerative colitis are relatively common and diminish “the quality of life” in significant number of patients.
2 Symptoms of extraintestinal disorders decreased significantly after surgical treatment of ulcerative colitis excluding primary sclerosing cholangitis.
Type A behaviour pattern influences on symptoms severity and treatment response in children with functional dyspepsia

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Introduction: Functional dyspepsia (FD) is the most prevalent type of functional abdominal pains, which is observed in 20% of population. There have been identified several organic disorders resulting in FD, while psychiatric trials suggest, the patients with FGID may present behavioural disorders simultaneously, which may influence symptoms occurrence and affect the pharmacological treatment effectiveness. Defining relationship between common personality aspects: type A and/or type B behavioural patterns (TABP/TBBP) and coexisting symptoms as well as their change during FD treatment might be helpful in establishing focused therapy strategies, including appropriate psychological interventions.

Aims: To evaluate the grade of type A behaviour pattern (TABP) in children with FD. To reveal correlations of investigated psychometric parameters and experienced dyspeptic symptoms. To assess the differences in TABP in children with dysmotility-like and ulcer-like FD. To assess the relationship between analysed psychosomatic factors and release of FD symptoms during the pharmacological therapy.

Methods: A total of 66 children (43 females and 23 males aged 11–18 years were diagnosed with FD following the Rome II criteria. The control group consisted of 86 healthy volunteers (49 females and 38 males) aged 11–18 years who denied recurrent abdominal pain. In all children pain severity was measured with faces pain scale whereas severity of other dyspeptic symptoms (heartburn, epigastric burning, hunger pains, nausea, early satiety, feeling full long after food, sense of sucking, belching, and sleep disorders) were assessed with the created Dyspepsia Symptoms Questionnaire consistent with visual-analogue scales. Psychological evaluation was carried out using Type A/B Behaviour Scale for Children and Adolescents (TAB) by N. Ogińska-Bulik and Z. Juczyński.

All patients received typical treatment for 4 weeks. After 8 weeks of drug prescription children were asked to refill the symptoms questionnaires. Healthy children were asked to fill all the questionnaires only once.

Results: The general TABP scores were significantly decreased in FD group comparing to the controls (43.45 vs. 47.81, p = 0.0016), which was especially seen in boys. High scores corresponding to moderate and extreme TABP were diagnosed in 4.17% FD boys and in 29.73% male controls (comparing with 30.23% FD girls and 36.73% female controls), while in 66.7% FD boys (vs. 24.3% controls) and 37.2% FD girls (vs. 22.5% controls) met criteria of moderate and extreme TBBP. Comparing to the control group boys with ulcer-like FD revealed lowered scores of Total TABP (score 40.20 vs. 49.39 p < 0.001) as well as in all TABP subscales: competition, impatience, sense of time urgency and hostility.
Correlation analysis exposed the positive relationship between Total TABP as well as competition and hostility with dysmotility-like symptoms ("sense of sucking"), while sense of time urgency and total TABP correlated negatively to the measured pain.

In the course of clinical observation it has been noted that hostility was related to the most dyspeptic symptoms increasing during the therapy ($p < 0.037$).

The competition was conductive to the nausea release in boys, and to aggravation of the heartburn and filling full long after food in both genders. The sense of time urgency was related to belching intensifying.
Gastrointestinal stromal tumours – Rare disease in children or unrecognizable?

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Gastrointestinal stromal tumours have so far been diseases very rarely diagnosed in children.

We present a case report of two children who were admitted to Department of Paediatrics of Medical University of Silesia. We diagnosed gastrointestinal stromal tumours in these children. Clinical symptoms, the course of disease and the prognosis in these children are different.

A 15 year-old girl was admitted to hospital due to nausea, abdominal pain localized in the epigastrium and periodical vomiting. In the endoscopy of the upper part of the alimentary tract we found the submucosal tumour of the stomach, with diameter about 15 mm, localized in the subcardial region. The girl was operated, now for five years she has been observed in the outpatient clinic, she expresses no complaints, and the control endoscopy of the upper part of the alimentary tract does not show any abnormalities. Gastrointestinal stromal tumour with low mitotic index was diagnosed on the basis of the histopathological examination.

The other patient was admitted to hospital due to intensive haemorrhage from the upper part of the alimentary tract, with considerable anaemia. In the endoscopy of the upper part of the alimentary tract we found three tumours of the stomach, with diameter about 30 mm each, one with the ulceration and symptoms of active haemorrhage. The surgical operation was done in the urgent procedure. The gastrointestinal stromal tumour was diagnosed on the basis of histopathological examination. We are considering treatment with imatinib in this child with regard to the high mitotic index in the histopathological examination and the progression of the disease.

In present the description of these cases we would like to draw attention to rare diseases, especially in children – stromal tumours of the alimentary tract, their non-characteristic clinical picture, diagnostic problems (final diagnosis is often made not until during a surgical operation or in histopathological examination), controversial treatment and uncertain prognosis.
Thrombosis of the portal venous system

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Background: Thrombosis in the portal system causes a wide spectrum of clinical pictures. There are few published studies describing the clinical features and consequences of portal venous system thrombosis. We depicted to document the etiologies and the outcomes of each portal and splenic vein thrombosis and thrombosis of both veins.

Patients and methods: Ninety-five cases diagnosed as portal venous system between September 2001 and April 2006 were enrolled in this study. Demographics, clinical presentation, diagnostic investigation, management, morbidity and mortality were recorded in their follow-up.

Results: Of the 95 cases with portal venous system thrombosis, 35 had isolated portal vein (IPVT group) and 27 had isolated splenic vein thrombosis (ISVT group), and 33 patients had both portal and splenic vein thrombosis (PSVT group). The mean follow-up period after diagnosis of IPVT, ISVT and PSVT were 36, 31 and 32 months respectively. Abdominal pain and gastrointestinal bleeding are the most common symptoms at the presentation in both IPVT and PSVT groups, whereas, abdominal pain was the dominant symptom in ISVT group. Twenty-six of the 35 IPVT and 23 of 33 PSVT patients and 24 of 27 ISVT cases had no bleeding during the follow-up period. Eleven of 35 IPVT, 1 of 27 ISVT, and 5 of 33 PSVT cases developed portal biliopathy at the follow-up. There were 1, 11 and 1 deaths in IPVT, ISVT, and PSVT groups respectively.

Conclusion: The etiology of portal venous system thrombosis varies in portal and splenic veins. IPVT has a higher morbidity rate (bleeding and portal biliopathy), whereas, ISVT not associated with an underlying malignancy has a favourable prognosis.
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