WHAT IS NEW IN
GASTROENTEROLOGY AND HEPATOLOGY

Editors:
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Alina Popescu

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FOREWORD

In this book, professors Ioan Sporea and Alina Popescu from the Medical University of Timişoara have put together important contributions to highlight the enormous progress that has been made in gastroenterology and hepatology in recent years. With an outstanding faculty, the state-of-the-art in diagnosis, management, and treatment of digestive diseases is illustrated. In 33 chapters relating to the most interesting and pressing issues in the field, the reader is informed about current optimal practice and standards of care in gastroenterology and hepatology. The spectrum of subjects goes from pulmonary manifestations of gastroesophageal reflux disease and management of Barrett‘s oesophagus to neuroendocrine tumours and hepatocellular carcinoma. Screening for the most common tumour in the digestive tract, colon cancer, and postpolypectomy care to prevent interval cancer are as important as is the management of liver disease caused by viral hepatitis. The very modern times in our field are represented by the use of telemedicine in hepatology and artificial intelligence to improve diagnostic accuracy in endoscopy. Many high-quality endoscopic pictures and sonographic images highlight the remarkable technical progress with these techniques. When I was a fellow in gastroenterology many years ago, the only thing we had at patient conferences was radiographs after administering barium sulphate: barium swallow, upper GI-series, as we called it, small bowel follow-through, and barium enema. Look also at the capsule endoscopy in this book, and you will see that we have come a long way! Congratulations to the editors and authors for demonstrating this progress so impressively!

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PREFACE

Knowledge in medicine is a very dynamic process due to the continuing progress in this field. New developments influence research, but also the clinical practice. Hence the continuous need for improvement in the field in which we work is required. Gastroenterology and hepatology, as part of internal medicine, are very dynamic fields of medicine, with numerous innovations, in the last 20-30 years at least. Starting with clinical medicine and continuing with endoscopy, interventional endoscopy or ultrasound and ending with precision medicine, with proteomics or metabolomics, the future of medicine seems to be here.

This book aims to bring to the readers' attention the latest advances in gastroenterology and hepatology. The book offers a variety of topics in the field of gastroenterology and hepatology, approached in a structured, clear and comprehensive fashion, but also with practical applications. The invited authors are the best in this field, all members of a Society older than 60 years (Romanian Society of Gastroenterology and Hepatology). The book's was designed in such a way that every invited author must contribute with his/her best topic in the field of gastro/hepato!

Topics such as eosinophilic esophagitis, bariatric surgery, Barrett esophagus, neuroendocrine tumors, inflammatory bowel diseases, intestinal microbiota, videocapsule endoscopy, endoscopic ultrasound, *etc.*, in the field of gastroenterology, as well as liver elastography, alcoholic liver diseases and non-alcoholic fatty liver disease, HBV and HCV chronic liver diseases, contrast enhanced ultrasound (CEUS), *etc.* in the field of hepatology, recommend this book to all those interested in these fields, either specialists, or researchers or fellows in training and even students. The hot topics of precision medicine, artificial intelligence, the "omics" cascade, telemedicine are also included in this book.

In the end, after finishing the book, we hope that you have enjoyed the time spent reading what is new and "hot" in the field of gastroenterology and hepatology. If you liked it, please recommend this e-book to a friend!

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CHAPTER 1

What's New in Extra-digestive Gastroesophageal Reflux Disease?

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Abstract: Gastroesophageal reflux disease (GERD) is a highly prevalent complex chronic condition. The most extensive prospective and multicenter cohort study conducted in Europe has estimated that one-third of the patients with GERD may exhibit extra-esophageal symptoms. The Montreal Consensus recognized chronic cough, chronic laryngitis, bronchial asthma and tooth erosions as extra-digestive manifestations of GERD. The experts also considered that manifestations such as recurrent otitis media, idiopathic pulmonary fibrosis, sinusitis or pharyngitis are likely to be associated with GERD.

The traditional techniques used in the diagnosis of typical GERD are less useful for the diagnosis of extra-digestive GERD. No single testing methodology exists to definitively identify reflux as the etiology for the suspected extra-esophageal symptoms. The PPI trial is the first diagnostic but also a therapeutic step, while evaluation through esophageal impedance-pH monitoring currently represents the gold-standard for diagnosis.

Despite extensive work, extra-digestive GERD remains incompletely understood.

Keywords: Extra-digestive manifestations, Esophageal impedance-pH monitor ing, Gastroesophageal reflux disease, Proton pomp inhibitors.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a chronic complex clinical condition, which is also recurrent, multi-factorial, with a risk of complications and significant morbidity. It has become undoubtedly one of the most commonly diagnosed diseases by the gastroenterologists in specialized ambulatory care, being one of the most common diseases of modern civilization.

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GERD is defined by 2006 Montreal Consensus as a condition that develops when the gastric content is refluxing into the esophagus and causes troublesome symptoms and/or complications [1]. Typical GERD is characterized by esophageal symptoms such as regurgitation and heartburn, but in some categories of patients, extra-esophageal manifestations are recognized as a form of GERD.

GERD with extra-digestive manifestations continues to represent a controversial issue in terms of epidemiology, diagnosis and treatment, for both gastroenterologists and ear-nose-throat (ENT) surgeons, pneumologists and dentists. Despite several papers published regarding this subject, extra-digestive GERD still remains incompletely understood [1].

The Montreal Consensus recognized chronic cough, chronic laryngitis, bronchial asthma and tooth erosions as extra-digestive manifestations of GERD. The experts also considered that manifestations such as recurrent otitis media, idiopathic pulmonary fibrosis, sinusitis or pharyngitis are likely to be associated with GERD [1, 2].

Epidemiological studies report different prevalence data, based on different methodology and heterogeneous study's design. Moreover, the prevalence of extra-digestive GERD is hard to establish due to the difficulty of confirming the diagnosis. Thus, the diagnosis of GERD-related extra-esophageal manifestations requires a good collaboration between specialists, to exclude other causes [3].

The most extensive prospective, multicenter cohort study conducted in Europe has estimated that one-third of patients with GERD may present extra-esophageal symptoms [4]. Chest pain (14.5%), chronic cough (13%), laryngeal manifestations (10.4%) and bronchial asthma (4.8%), were the commonest conditions associated with GERD. Another large study on extra-digestive GERD conducted in the US showed that non-cardiac chest pain (23.1%) and the respiratory symptoms (pneumonia 23.6%, bronchitis 14.0%, asthma 9.3%) were the most frequent manifestations recorded, followed by ENT symptoms (hoarseness 14.8%, globus sensation 7.0%) [5]. In Romania, there are very few studies on the epidemiology of GERD with extra-digestive manifestations. Angelescu *et al.* [6] reported a prevalence of 31.1% for extra-digestive manifestations in patients with GERD. Dental erosions were found in 76.3% of patients, non-cardiac chest pain in 55.5% of patients, while chronic cough was identified in 44.5% of patients and chronic laryngitis in 22.7% of GERD patients.

There are two possible main mechanisms involved in the pathophysiology of extra-digestive GERD: the direct mechanism – the direct injury of the esophageal and laryngopharyngeal mucosa due to gastro-duodenal contents, with or without

airway microaspiration (the reflux theory) and the indirect mechanism–vagal-mediated tracheobronchial reflex, caused by acidification of the distal esophagus (the reflex theory). The reflux of gastroduodenal contents into the esophagus and hypopharynx may be classified as: high reflux (reflux crosses the esophagus and causes ENT or respiratory manifestations, either by direct pharyngo-laryngeal stimulation or aspiration) or distally reflux (occurs by reflex mechanism) [7].

Majority of the papers published on extra-digestive GERD are related to ENT and respiratory manifestations.

The diagnosis of reflux disease and the establishment of a clear relationship between reflux and extra-esophageal symptoms have proven to be very challenging. This is difficult to achieve because typical GERD symptomatology may be lacking in these patients. The presence of classical GERD symptoms in a patient with extra-digestive manifestations may suggest the diagnosis of GERD, but does not establish a certain causal relationship.

Unfortunately, the diagnostic methods currently available in clinical practice have serious limitations. The traditional techniques used in the diagnosis of typical GERD are less useful for the diagnosis of extra-digestive GERD. No single testing methodology exists to identify reflux definitively as the etiology for the suspected extra-esophageal symptoms. An association between clinical presentation, diagnostic test results and response to therapy is needed in order to determine if the reflux is the cause for the extra-esophageal manifestations or not [3].

When extra-digestive reflux is suspected in a patient who also experiences heartburn and/or regurgitation, most guidelines recommend the therapeutic test with double-dose proton pump inhibitors (PPI) for a period of at least 3 months, as long as there are no warning signs [8, 9]. If the therapeutic test is positive (amelioration or disappearance of digestive and extra-digestive symptoms), most likely GERD is the etiopathogenic substrate for the extra-digestive manifestation. Non-responsive PPI patients should be further investigated to confirm or refute the diagnosis of GERD. However, there are also other authors who recommend abandoning this diagnostic test as studies showed a sensitivity and a specificity of 54-92% and 67-86%, respectively [10]. Unlike other GERD diagnostic methods, the therapeutic test is relatively simple, non-invasive and cost-effective.

Upper digestive endoscopy (UDE) has long been the main diagnostic test in GERD. Nowadays endoscopy is recommended when alarm signs are present, in non-responders to PPI patients, in patients with long-lasting extra-esophageal symptoms or screening in patients with high risk for developing complications,

CHAPTER 2

Optical Diagnosis in Barrett Esophagus and Related Neoplasia

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Abstract: The detection of high grade dysplasia and esophageal adenocarcinoma with improved survival rates is the aim of optical diagnosis in BE. Advanced imaging technologies improve the characterization of dysplastic BE by mucosal visualization and enhancement of the fine structural and microvascular details (mucosal and vascular pattern) and may guide targeted biopsies for the detection of dysplasia during surveillance of patients with previously non-dysplastic BE.

Keywords: Barrett esophagus, Dysplasia, Esophageal adenocarcinoma, Optical diagnosis.

INTRODUCTION

Barrett's esophagus (BE) is a well-known pre-malignant lesion of esophageal adenocarcinoma (EAC). Even though there is an increased risk of developing EAC in patients with BE, the absolute risk remains low [1, 2]. However BE is found in the majority of patients with EAC, but only 5% of the patients with EAC had a prior diagnosis of BE [3], showing that unfortunately most cancers are diagnosed outside of surveillance programs.

Surveillance of patients with confirmed BE is recommended by all guidelines and largely applied. The Seattle protocol, consisting of target biopsies of visible lesions and four-quadrant forceps biopsies at every 2 cm, is accepted as the standard for surveillance in BE, although difficulties resulting from this procedure are well known by endoscopists.

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The recognition of dysplastic BE offers the possibility to intervene at an early stage of EAC with improving the survival rate and reducing mortality. The efforts should be undertaken to better identify the patients at risk of developing EAC.

The Rationale of Optical Diagnosis in BE

Optical diagnosis in BE endeavors to enhance survival outcomes by catching high-grade dysplasia and esophageal adenocarcinoma. Surveillance in patients with previously non-dysplastic BE can now be expanded to include targeted biopsies, that could uncover dysplasia [4 - 6]. Furthermore, this new technology allows the practitioner to examine visually the fine mucosal and vascular details of BE with dysplasia [4 - 6]. Real time optical diagnosis allows taking therapeutic decisions if dysplastic lesions are diagnosed.

Optical diagnosis in BE is a complex, time consuming procedure that requires training and expertise and a continuous contact with an expert high-volume center.

Pre-adoption Requirement to Start Optical Diagnosis in BE

• Quality measures: To ensure a basic standard of endoscopic quality in optical diagnosis, it is recommended that the ESGE (European Society of Gastroenterological Endoscopy) and UEG (United European Gastroenterology) key performance measures for upper gastrointestinal tract endoscopy to be adopted. In accordance with this, the best practice is an inspection time of at least 1 minute/cm of the circumferential extent of Barrett's epithelium, in order to inspect and describe the mucosal and vascular pattern.
• The size and extent of Barrett epithelium have to be done by using Prague C& M criteria, which assess the circumference (C) and maximum (M) extent of the Barrett epithelium endoscopically visualized, above the gastroesophageal junction. Barrett islands have to be reported separately.
• High definition - white light endoscopy (HD-WLE) equipment has become a routine part of the practice of most endoscopists and should be a "must", when the optical diagnosis of BE is addressed.
• There are two ESGE-required instruction modules for endoscopists wishing to perform optical diagnosis in BE patients for the purposes of early detection of neoplasia:
-BORN ["Barrett's Esophagus-Related Neoplasia" (BORN)] for high- definition white-light endoscopy or Chedgy instruction in utilizing acetic acid for chromoendoscopy [6].
ESGE recommends the use of validated classification systems to support the use of optical diagnosis with advanced endoscopic imaging and chromoendoscopy.
Stages of Optical Diagnosis in BE.

Fig. (1). Stages of optical diagnosis in BE.

Optical diagnosis in BE starts with the inspection of the entire Barrett epithelium. In order to detect any abnormality which might be in the dysplastic areas or even cancer, is mandatory to be aware and compare the appearance of these modifications with the normal view of Barret epithelium.

The *regular endoscopic view of Barret epithelium* is shown in Fig. (**2**) and the followings are the most common characteristics:

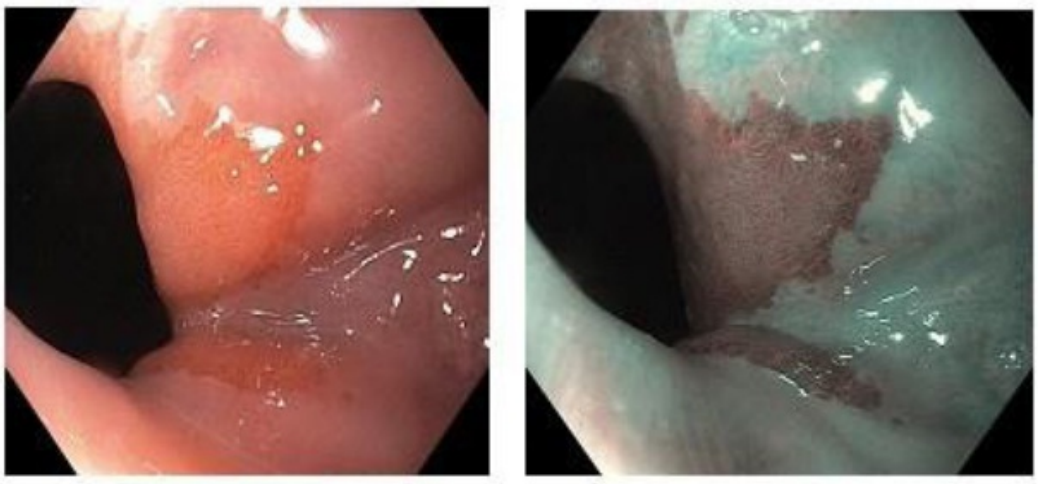

Fig. (2). Non-displastic Barrett epithelium: HD-WLE and NBI (narrow band image).

CHAPTER 3

Eosinophilic Gastrointestinal Disorders

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Abstract: Eosinophilic infiltration of the gut occurs unusually and its clinical relevance was only recently recognized. The medical conditions with eosinophilic infiltration are commonly named eosinophilic gastrointestinal disorders [EGID]. EGID is described as a gastrointestinal tract disorder with functional and morphological abnormalities due to a dense infiltration of eosinophils in the gastrointestinal wall. The cause could be an allergic reaction due to varied allergens, food or the environment. EGID is including eosinophilic esophagitis [EoE], eosinophilic gastroenteritis [EGE], and eosinophilic colitis [EC].

EGIDs pathophysiology is not yet fully understood, but histopathology is characterized by degranulation and an excessive number of eosinophils. A role in the pathophysiology of EGIDs is played by a hypersensitive reaction. Diagnosing EGIDs is quite challenging. It can be described as a combination of eosinophilic invasion of one or more organs from the GI tract with non-specific GI symptoms. The gold standard for EGIDs diagnosis is the histology of gastrointestinal mucosal biopsy, an overabundance of eosinophils being the principal diagnostic criterion without a known cause.

The treatment for EGID is not well defined yet, because of the limited prospective controlled studies performed. The treatment is an empiric one and is administrated according to the severity of the symptoms and it is represented by diet, corticosteroids, and steroid agents.

Keywords: Eosinophilic colitis, Eosinophilic esophagitis, Eosinophilic gastroenteritis, Eosinophilic gastrointestinal disorders, Hypersensitive reaction.

INTRODUCTION

The largest surface in the body, with an important number of immune cells, is represented by the gastrointestinal (GI) tract, an organ system that fulfills many important roles, including the oral tolerance and absorption of nutrients [1]. Eosinophils are normally present in most parts of the gastrointestinal tract, they

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may be quite numerous, except at the esophagus level, where they are not present in physiological states [2, 3]. Eosinophils can be present in chronic diseases that appear and disappear, from months to years as well as in any inflammatory condition present for days to weeks. A raised number of eosinophils are also found in auto-immune gastritis, gastroesophageal reflux disease, inflammatory bowel disease, radiation enteritis, collagen vascular disease, neoplasm and many other disorders, and even in the absence of a specific disease which is not quite common. They can be distinguished by the presence of many neutrophils and an association of inflammation. Most of these entities show a mix, between-neutrophil-rich, inflammation and other features, which allow their distinction [2]. Eosinophilic infiltration of the gut, uncommonly appears even in the lack of aforementioned cause. The disorder with eosinophilic infiltration is commonly named eosinophilic gastrointestinal disorders (EGID), formed by eosinophilic esophagitis (EoE), eosinophilic gastroenteritis (EGE), eosinophilic colitis (EC) [3, 4].

EGID is described as a gastrointestinal tract with functional and morphological abnormalities, due to a dense infiltration of eosinophils in the gastrointestinal tissue. The cause could be an allergic reaction due to varied allergens, food or the environment [5].

EGIDs is present at both sexes, more common at males (3:2), is present at different ages, including children. The Caucasian population is most affected, but it can affect all races and ethnic backgrounds [3, 6]. EGIDs are rare disorders, EoE is the most common disorder from EGID, with a prevalence of 10-57 per 100,000, compared to those found outside of the esophagus like EC, EGE or EG which are 2.1-5.1 cases per 100,000 [7].

EOSINOPHILIC ESOPHAGITIS (EOE)

Introduction

A great interest in the last years has been raised by EoE, which is an immune-mediated disease, that is characterized by infiltration of eosinophils at the esophagus level, causing esophageal dysfunction. Now EoE represents an important differential diagnosis when patient symptoms are gastroesophageal reflux, dysphagia and food impaction [8, 9]. One of the strongest risk factors for developing EoE is the gender, male being the most affected gender showing 3:1 male to female predominance [8, 10].

Epidemiology

For the first time a patient with EoE was mentioned in a report in 1978 [11], and it

was accepted as a distinct clinical entity in the early 1990s [12, 13]. Although, initially it was a rare case report, but in the last few years, its prevalence and incidence have considerably expanded, and it became a common condition found in any gastroenterology clinic or emergency room [14]. The expansion of the cases of EoE could have two explanations, one is a real increase of the incidence, and the other could be due to an improved recognition [15].

The incidence in European countries is between 2.1-7.4 cases per 100,000 inhabitants [16, 17], the prevalence is between 13.8-44.6 cases per 100,000 inhabitants [18, 19]. EoE can affect any age, from patients at 1 year old, to patients at 98 years old [20], with a higher prevalence in adults [14], and the highest prevalence at 30-40 years of age [21].

The incidence and prevalence of EGID is increasing due to endoscopic detection, although in the United States it is still categorized as a rare disease with < 200,000 people affected.

The approximate prevalence is 1 to 2,000, with 150,000 cases in the US and more than 1 billion $ being the estimated expenditures for EoE, from a total of 18,1 billion $ spent annually for esophageal disorders. This represents a colossal number for a rare disease, being comparable with the cost for more common diseases [22, 23]. One of the modifications that appear is the esophageal remodeling, with functional damage and stricture development, being progressive in its natural course. The duration of untreated disease are associated with the prevalence of esophageal strictures [24, 25].

Pathophysiology

The mechanism of EoE has still not been entirely clarified, due to the fact that is a new disease described in the literature, but in the last few years, there has been a progression in the understanding of EoE pathophysiology [26, 27]. It was described as a genetic predisposition, where a patient with a food allergy, with GERD, a possible disturbance of the microbiota or epithelial barrier favors allergens to infiltrate the epithelium and trigger the receptors and the inflammatory cells, like eosinophils to activate [28]. Due to its response to dietary therapy, EoE is correlated with food antigen-driven hypersensitivity, being triggered by different foods like milk, combined sometimes with eggs, soy or wheat and resulting in 15% of cases serious IgE mediated reactions like anaphylaxis or mild reactions as urticaria. It was described that almost half of the patients with EoE, diagnose positive for food antigens from serum testing and to skin prick testing [29, 30]. Also EoE patients present aeroallergen hypersensitivity or a known history of respiratory allergy [31].

CHAPTER 4

Postoperative Digestive Complications of Bariatric Surgery

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Abstract: Digestive complications of bariatric surgery are quite rare, especially those which are sever in nature, with a lower rate aftersleeve gastrectomy compared to Roux-en-Y gastric bypass. This chapter discusses the bleeding, anastomotic leaks, stenosis and ulceration, gastroesophageal reflux, bowel transit dysfunction, gallstones and complications related to adjustable gastric banding and other after bariatric surgeries.

Keywords: Bariatric surgery, Complications, Endoscopic treatment, Endoscopy, Gastric bypass, Obesity, Sleeve gastrectomy.

INTRODUCTION

Bariatric surgery is known for reducing the risks of medical and/or metabolic complications related to obesity such as diabetes and cardiovascular diseases or even cancers. The main surgical procedures include sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGB) or mini-gastric bypass, laparoscopic adjustable gastric banding (LAGB) and single anastomosis duodeno-ileal bypass with sleeve gastrectomy (SADI-S).

In the last seven years, in the USA,over 200,000 bariatric surgeries were performed, out of which61 percent sleeve gastrectomy, 17 percent gastric bypass, 1 percent gastric band, and 0.8 percent biliopancreatic diversion with duodenal switch. The remaining 15 percent were revisional procedures [1].

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Operating on obese patients is challenging, because of the anatomic and physiologic characteristics and comorbidities of obese patients. Adverse intraoperative complications (1 - 5% of cases) [2, 3] are serious, like myocardial infarction or pulmonary embolus. The postoperative severe complications are rarely seen, compared to open surgery (3.37% *vs*. 7.42%; $p<0.0001$) and they are more frequent in the case of RYGB (3.3%) than in SG or adjustable gastric banding (1%) [4].

Compared to the LAGB, SG has a higher rate of anastomotic/staple line leaks, fluid/electrolyte/nutrition problems, strictures, infection/fevers, pulmonary embolism, bleeding and events not otherwise specified. Compared to LRYGB, SG has a lower, but comparable rate of nearly all postoperative bariatric specific occurrences requiring readmission, reoperation or an intervention, except for a lower rate of stricture, intestinal obstruction, and anastomotic ulcer [5].

If the obese patients present already a significant comorbidity, like cirrhosis, the proportion of postoperative complications is higher. A meta-analysis on 18 studies and 471 patients with obesity and liver cirrhosis showed that the rate of complications was 22% (lower for SG of 10% compared to RYGB of 31%) with 0.08% intraoperative complications and 4.62% 90-days related mortality [6].

Table 1. The main complications related to bariatric surgery.

-	**Intraoperative Complications**	**Perioperative Immediate Complications**	**Postoperative Delayed Complications**
Cardiovascular	Myocardial infarction Deep vein thrombosis Pulmonary embolism		-
Digestive	Laparoscopic access related injuries Splenic or hepatic injuries Portal vein injury Bowel ischemia	Bleeding Stenosis Leaks Anastomosis ulcerations GERD	Stenosis Leaks Anastomosis ulcerations GERD Bowel transit dysfunction Internal hernias with bowel obstruction Gastric banding -slippage and erosion Gallstones
Other	Comorbidities related	Wound complications	Malnutrition Hypoglycemia Weight regain Recurrent port-site infection

Bleeding occurs usually during the first hours after surgery, although this is quite rare (1-4%) and occurs at the level of the staples line, in case of SG or at the level of gastro-jejunal anastomosis in case of RYGB. The diagnosis is based on tachycardia, oliguria and falling hemoglobin level and it can be produced into the

GI tract or peritoneum, usually at the level of staples or suture line. Endoscopy with haemoclips or bipolar coagulation isuseful, but OTSC (Over-The-Sco- e-Clip) or large volume injection can be applied, although the risk of anastomotic stenosis increases with this technique. In case of failure, full thickness re-suturing with monofilament sutures is used. The PPI (proton pump inhibitor) highdose intravenously is needed for decreasing the gastric acidity.

Stenosis of the level of anastomosis, signalized by dysphagia, may occur at the level of proximal staple line in 4% of the cases with GS, and in 3-28% of cases with RYG [7]. Also, functional stenosis after GS can be identified: type 1 due to the twist of the gastric tube with the endoscopic appearance of an anti-reflux valve, while type 2 is owing to a spiral course of gastric stapling that winds around the stomach [8]. Treatment with several endoscopic balloon dilatation sessions should start 3-4 weeks after surgery, until the luminal diameter is 12-15 mm.

Anastomotic leaks are the most fearful complications and they occur usually in the first postoperative week or even after discharge. Up to 90% of SG leaks occur at the esophago-gastric junction [9] and rarely at the distal part of the staple line. Therefore, the patient must be followed-up carefully in the first 30 days after the operation. The rate of leaks varies between 0.8% to 6% [10 - 13]. The risk of leaks is higher in the case of RYGB (1.6%), than in case of SG (0.8%) [13]. The risks for fistula in case of SG are perigastric hematoma and/or twisting of the distal part of gastric remnant on 48h CT scan [14]. After SADI-S, some patients may develop a leak from the duodeno-ileal anastomosis or within the gastric tube. They occur usually in the proximal portion of the anastomosis because this region is exposed to high pressure with ingested liquids, gastric juice, bile and saliva in the most proximal portion of the staple line and alsothere is a relative obstruction in the mid body portion of the stomach as the narrow gastric sleeve traverses the incisura angularis.

They can be classified according to the time of occurrence as acute (<7 days), early (within 1 to 6 weeks), late (within 6 to 12 weeks) and chronic (> 12 weeks). The risk factors are advanced age, BMI>50, male gender, revisional surgery and obstructive sleep apnea.

Acute leaks are associated with severe abdominal pain or peritonitis, because of lack of time for localization. They are related to the misfiring of a stapler or inadequate suture technique.

In case of a delayed leak, the generalized peritonitis arerare, usually, they present an intraabdominal abscess localized by the omentum of neighboring organs and the patients present fever and pain irradiating in the shoulder. More likely the

CHAPTER 5

What is New in Gastro-Entero-Pancreatic Neuroendocrine Tumors

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Abstract: Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a group of heterogeneous malignancies that can occur anywhere in the digestive system, with a growing incidence over the past decade. For proper diagnosis and management, the grading and histological diagnosis have been revised recently. Thus, the WHO grading criteria have been updated in 2017 as well as the TNM staging for pancreatic NETs in 2018. To establish a correct diagnosis, a multimodal approach is required, including various biomarkers, endoscopic tumor biopsy and tumor imaging. Over the past decades, improved diagnostic techniques including endoscopic ultrasound and somatostatin receptor fusion imaging have gained ground and have assisted treatment decision making. Regarding the treatment strategy, the management implies taking into account the tumor stage and degree of tumor differentiation, as well as tumour growth and spread. Novel therapies such as molecular-targeted agents, tryptophan hydroxylase inhibitor and peptide receptor radionuclide therapy were recently approved by FDA, improving the prognosis for advanced GEP-NETs.

Keywords: Carcinoids, Diagnosis, Follow-up, Gastroentero pancreatic neuroendocrine tumor, GEP-NETs, Update.

INTRODUCTION

Neuroendocrine tumors (NETs) are a group of tumors originating from neuroendocrine cells, with various anatomic locations, such as gastrointestinal (GI) tract, pancreas, lungs, thymus and endocrine glands [1, 2]. Gastro-ente--pancreatic (GEP) NETs can occur anywhere in the digestive system, the GI tract representing the most common site for this type of tumor. Over the last decade, the incidence of GEP NETs increased, due to improved diagnostic techniques, which resulted in higher detection rate of gastric and rectal NETs. However, they

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are still considered rare tumors, accounting for 2% of all GI tumors. In general, the tumors are sporadic, but a variable number of NETs can also be encountered in some genetic syndromes such as multiple endocrine neoplasia (MEN) type 1, von Hippel-Lindau disease, von Recklinghausen disease (neurofibromatosis type 1) and tuberous sclerosis [1].

NETs have a wide variety of clinical presentations, depending on the type of hormone hypersecretion (see below). Furthermore, a constellation of symptoms, which are classically known as carcinoid syndrome (CS) has been described. Most often, CS occurs in primary tumors in the distal small intestine or proximal colon and is usually due to metastatic disease, especially liver metastases. The symptoms may vary, depending on the release of vasoactive compounds, but the most common presenting features include flushing, diarrhea and intermittent abdominal pain [2]. Non-functioning tumors, accounting for about of 60-70% of GEP NETs, may be undetected for years, most of them being *incidentally* diagnosed.

Grading and Staging

The classification of neuroendocrine neoplasms (NENs) arising in the GEP system was firstly published by the World Health Organization (WHO) in 2000 and it was later updated in 2004, 2010 and 2017 [3]. The current classfication is based on a combination of mitotic count and Ki-67 proliferation index, categorizing NETs as grade 1 to grade 3 in the latest update. In addition, the nomenclature for MANEC was changed to mixed endocrine non-endocrine neoplasm (MiNEN) in order to adress the issue that not all MiNENs are high-grade malignant carcinomas [3] (Table **1**).

Table 1. The 2017 WHO classification for pancreatic neuroendocrine neoplasms.

2017 WHO classification	Mitoses/10 HPF	Ki-67 index %
Well-differentiated NENs		
NET grade 1	< 2	< 3
NET grade 2	2-20	3-20
NET grade 3	> 20	> 20
Poorly-differentiated NENs		
NEC grade 3 − Small cell type − Large cell type	> 20	> 20
MiNEN		

Regarding the pathological staging of NETs, TNM staging systems are currently developed for the following tumor sites: pancreas, gastric, duodenum/ampulla/ proximal jejunum, lower jejunum and ileum, appendix, colon and rectum. The 8th edition of the American Joint Committee on Cancer (AJCC) staging system has updated the T staging for pancreatic NETs (Pan-NETs), specifically T3, to be consistent with the European Neuroendocrine Tumor Society (ENETS) system for well-differentiated NETs, as the previous edition might have been a source of confusion for the clinicians (Table **2**) [4].

Table 2. The differences between the AJCC and ENETS staging systems for pancreatic NETs.

T Stage	7th Eition AJCC	8th Edition AJCC	ENETS
T1	Confined to pancreas, < 2 cm	Limited to pancreas, < 2 cm	Confined to pancreas, < 2 cm
T2	Confined to pancreas, > 2 cm	Limited to pancreas, 2–4 cm	Confined to pancreas, 2–4 cm
T3	Peripancreatic spread, without major vascular invasion	Limited to pancreas, > 4 cm, or tumor invading the duodenum or common bile duct	Confined to pancreas, > 4 cm, or invades duodenum or bile duct
T4	Tumor involves coeliac axis or superior mesenteric artery	Invading adjacent organs or the wall of large vessels	Invading adjacent organs or major vessels

Diagnosis

In general, the diagnosis of NETs is often incidental and usually delayed for several years, but patients suspected of GEP NETs should undergo initially a clinical evaluation (medical and family history, physical examination). The clinical assessment should exclude any cancer syndromes and also guide the appropriate diagnostic and therapeutic procedures [5, 6].

The diagnostic algorithm comprises a combination of blood and urine markers and various imaging modalities, such as conventional imaging (ultrasound, CT, MRI) and endoscopy (gastroscopy and/or colonoscopy), including endoscopic ultrasound (EUS), as well as functional imaging, with a combination of somatostatin receptor scintigraphy (SRS) and cross-sectional imaging using single photon emission CT (SPECT) in addition to CT (SPECT-CT). A minimal initial workup consists of a multimodality approach: a site-specific endoscopic assessment with tumor biopsy and computer tomography (CT) or magnetic resonance imaging (MRI). Over the last decade, functional imaging techniques, especially ^{68}Ga-DOTA-Phe^{1}-Tyr^{3}-Octreotide (^{68}Ga-DOTATOC) PET-CT or ^{99m}Tc-EDDA/HYNIC-Tyr^{3}-Octreotide (Tektrotyd) SPECT-CT, have been found

CHAPTER 6

Intestinal Microbiota and its Implications in Pathology

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Abstract: The intestinal microbiota develops as a results of various genetic, nutritional and environmental factors, becoming very specific for each individual. It totalizes more than 100 trillions of bacteria with a piece of genetic information more than 100x greater than the human genome. The functions of the microbiota can be grouped into metabolic, protective and structural. The microbiota-derived metabolites signal to distant organs of the host, which enable the microbiota to connect to the brain, the immune and endocrine system, metabolism and other functions of the host. These microbiota-host communications are essential to maintain the vital functions and health of our organism. So, microbiota, in eubiosis and especially in dysbiosis, has multiple effects on the human organism. The therapeutic possibilities for this are the administration of nonabsorbable antibiotics, pre-, pro, syn- or symbiotics, as well as FMT, which is in principle a complex human probiotic.

The most important digestive effects of microbiota are in Clostridium difficile-determined pseudomembranous colitis, in IBS, IBD, diverticulitis, functional dyspepsia, and in different digestive cancers: gastric, colorectal, liver and pancreatic cancer. Alcoholic liver disease is also influenced by microbiota.

The extra-digestive effects of microbiota are very complex. In some metabolic diseases, like obesity, NAFLD, atherosclerosis, dyslipidemias and T2D, special types of dysbiosis have important pathophysiologic implications. Microbiota has also implications in Alzheimer's disease, osteoporosis, CKD, different psychiatric disorders and some extra-digestive cancers.

In conclusion, it may be stated that the intestinal microbiota has multiple effects, even in diseases that apparently have no relation with the intestinal flora.

Keywords: Autoimmune diseases, Cancer, Digestive diseases, Intestinal microbiota, Metabolic diseases, Microbiome.

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INTRODUCTION

The intestinal microbial flora, called ***microbiota***, is formed beginning with the birth, the fetal intestine being sterile [1]. Depending on the natural or caesarian birth, namely the first contact with the vaginal flora or with the flora of the mother's tegument, the microbiota will develop differently [2]. The further development of the microbiota is related to genetic factors, nutrition (an important moment will be the diversification), as well as other environmental factors. Thus, the microbiota becomes very specific for each individual, called even "the second finger-print". But, the microbiota undergoes extensive changes across the lifespan, and age-related processes may influence the microbiota and its related metabolic alterations [3].

The microbial density rises from jejunum to colon, along with the microbial diversity (approximate 5000 species), totalizing approximately 100 trillion bacteria, which means 10 x more than the total number of cells in the human organism. The genetic information of the microbiota, called the microbiome, is 100 x greater than the human genome. It is necessary to clarify these two notions: the ***microbiota*** is the total of intestinal microorganisms (bacteria, viruses, protozoa *etc*.), the ***microbiome*** includes, without the microbiota, the totality of the microbial genes, as well as the totality of the microbial ecosystems [1]. Despite these differences, even gastroenterologists used the two notions as synonyms. In normal conditions, the microbiota is in perfect symbiosis with the human organism, being even a vital partnership. The microbiota was even called "the last discovered organ of the human body". The microbiota was studied very intensively in the last years. In 2007 PubMed included approx. 500 citations about the microbiome, ten years after, there were more than 8,000 [4].

The functions of the microbiota can be grouped into metabolic, protective and structural. The metabolic functions consist of the fermentation of indigestible glucides with the production of energy, synthesis of amino acids, short chain fatty acids (SCFA) and vitamin B & K, interaction with bile acids metabolism and absorption of water and salts. These microbiota-derived metabolites signal to distant organs of the host, which enables the microbiota to connect to the brain, the immune and endocrine system, as well as to the metabolism and other functions of the host. These microbiota-host communications are essential to maintain the vital functions and health of our organism [5]. The protective functions consist of the prevention of pathological colonization (existing a direct competition between microorganisms, as well as a synthesis of antimicrobial peptides), regulation of inflammatory cytokines and development and activation of the immune system (B cells, regulator and helper T cells). The structural function consists of the modulation of the mucus layer [6].

Normally an equilibrium exists between the different components of microbiota, called eubiosis. This equilibrium could be disturbed frequently, by the appearance of different kinds of dysbiosis. The causes of dysbioses could be viral, bacterial or fungal infections of the intestine, sudden environmental or dietetic modifications, immunodeficiency, drugs, especially antibiotics, or different diseases. Microbiota, in eubiosis and especially in dysbiosis, has multiple effects on the human organism. These effects could be digestive (acute and chronic intestinal infections, inflammatory bowel disease, irritable bowel syndrome, digestive cancers) or extra-digestive (metabolic diseases, allergies, autoimmune, neurological and psychiatric diseases *et al*.). In all these cases it is important to reestablish the eubiosis. There are a number of therapeutic possibilities such as: nonabsorbable antibiotics (Rifaximin, Neomycin), probiotics (Bifidobacterium, Lactobacillus, Lactococcus, Bacillus, Bacteroides, Enterococcus, Escherichia, Faecalibacterium, Propionibacterium, Saccharomyces), prebiotics (nondigerable glucides like inulin, lactulose, fructo- and oligosaccharides), synbiotics (combinations of pro- and prebiotics), symbiotics (combination of probiotics) and fecal microbiota transplantation (FMT), consisting in general of a colonoscopic infusion of a fecal suspension from a healthy donator, which is in principle a complex human probiotic [7, 8]. Maternal FMT in caesarian-born infants after birth has also been proved [9]. A very important role in reestablishing eubiosis has also been the diet [10, 11].

Digestive Effects of Microbiota

One of the most important acute intestinal infections in the last years all over the world is **pseudomembranous colitis**, caused by Clostridium difficile, mostly of an iatrogenic cause, unfortunately. This disease becomes a real public health problem. For instance in the EU in only one year, the costs are over 3 billion of euros and, unfortunately, the frequency is rising all over the world [12].

Through the microbiome - bowel - brain axis, called before bowel – brain axis, complex interactions take place between microbiome, central nervous system, neuro-endocrine system, neuro-immune system, autonomous nervous system and enteric nervous system. Thus are possible interventions of the microbiome in the reactions to stress, anxiety, memory, behavior or intestinal function [13]. Also the **irritable bowel syndrome** (IBS) could be influenced by the microbiota even through this axis [14]. IBS is a functional disorder, influenced by genetic predisposition, psycho-social factors and is characterized by motor disturbances and hypersensitivity. Studies on feces samples show that the microbiome is different in healthy and IBS patients (Lactobacillus, Veillonella, Clostridia, Ruminococcus, Proteobacteria, Firmicutes and others).

CHAPTER 7

Videocapsule Endoscopy

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Abstract: Videocapsule endoscopy is a non-invasive and important innovation in diagnostic endoscopy. This technology was first launched in 2000 and it has been widely used by gastroenterologists worldwide. This method requires the patient to swallow a miniature high-resolution camera which will pass through the digestive tract, while transmitting images to the recorder in order to be evaluated. It has its main advantages which are the non-invasiveness, and the possibility to yield a diagnosis in severely ill patients who cannot support invasive endoscopy procedures, but it also has disadvantages which include the impossibility to perform a biopsy or other therapeutic procedures. Over the years, this method has been revolutionized by not only approaching the small bowel, but also the esophagus and the colon. This chapter will also discuss the application of the esophagus capsule as well as the colon capsule. There are multiple indications for which patients can be referred to videocapsule endoscopy. The most frequent cause of referral to capsule endoscopy is the obscure GI bleeding, but it may be used in detecting small intestine polyps or tumors, searching for the cause of iron deficiency anemia or reviewing the extension of Crohn's disease. The main risk of this method is represented by retention which is also minimal.

Keywords: Anemia, Crohn's disease, Non-invasive, Obscure bleeding, Small intestine, Technology, Tumors, Videocapsule endoscopy.

INTRODUCTION

Video capsule endoscopy (VCE) represents a non-invasive method utilized to visualize the digestive tract, by sending images from a one-time use capsule which has been swallowed, to a receiver device attached to the patient's body. At the beginning, it was not a frequently used method as a first line approach, but usually employed after gastroscopy or colonoscopy if the diagnosis remains uncertain. Over time, this method has been improved to provide images with better pixels, prolonged battery life and also capability to visualize other segments the digestive tube (esophagus, stomach, colon) [1].

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HISTORY AND DEVELOPMENT

The first small bowel video capsule (M2A capsule) was produced by Given Imaging, Yokneam, Israel and was approved by FDA in August 2000. It was afterward remarketed as PillCam SB, which provides a 140-degree field of view. After years of application, VCE technology was improved hence newer versions of video capsules were launched. PillCam SB2 with better resolution images, and 156-degree field of view was released in 2007. In the same year, the FDA approved the Endocapsule launched by Olympus Medical Systems. Since then different manufacturers have launched their own version of video capsule endoscopy (OMOM pill-Jinshan Science and Technology, CapsoCam SV1-CapsoVision, MiroCam- IntroMedic,) [2]. The latest PillCam SB3 offers similar quality as the previous PillCam SB2 but offers a higher framerate, up to 6 frames per second. As for other parts of the digestive tract, different types of capsules were released. PillCam ESO (released in 2004) and the dual camera PillCam COLON (released in 2006) were released for viewing the esophagus and respectively, the colon.

TECHNICAL SPECIFICATIONS

The wireless video capsule system consists of three important elements: the camera-containing capsule, the image receiver which is attached to the patient's body, a personal PC workstation, with a proprietary program for image reviewing and interpretation. All capsules have the same elements: an external disposable casing, a power source, LED array sources, optical lens, CMOS image sensor or high-resolution charge-coupled device (CCD) image capture system, radiofrequency transmitter and antenna. The manufacturers have developed software that can reduce the time required to analyze the images, as well as minimizing the possibility of missing some lesions [3]. All the programs in the market are able to detect red pixels to help the examiner detect bleeding lesions. Although it reduces the reading time, it is not recommended without a complete capsule evaluation, due to the high miss rate (12%) [4]. Other additional features include quick reference image atlas, the stage of capsule passing through the GI tract, virtual chromoendoscopy, three-dimensional reconstruction software as well as the use of artificial intelligence for better diagnostic yield [5, 6].

INDICATIONS FOR SMALL BOWEL VCE

Obscure Gastrointestinal Bleeding

Obscure Gastrointestinal bleeding (OGIB) is a gastrointestinal bleeding, whose cause was not identified after bidirectional endoscopy (gastroscopy and colonoscopy). OGIB is the most common indication for VCE, and is responsible

for 5% of all GI bleeding, the small intestine being the most frequent site of bleeding [7]. Localization of the bleeding site is usually difficult. Patients with OGIB frequently need hospitalization, blood transfusions and at the same time other diagnostic investigations. Due to its safety and easiness, VCE is considered to be the first line examination for the small intestine.

Numerous diseases are accountable for OGIB. Angiodysplasia is the most common of OGIB in the elderly (30-40%), whereas tumors are the most frequent cause in patients around 30-50 years of age [8]. The excessive use of NSAIDs may cause ulcers, erosions also leading to OGIB. Other differential diagnoses are listed in Fig. (**1**) [9]. Studies have shown that VCE has a higher diagnostic yield rate in OGIB than small bowel radiography or push enteroscopy. VCE was reported to have a specificity and sensitivity of 95% and 88.9% respectively. The most significant accuracy rate was observed in those patients with obscure and active bleeding (44.2% and 92.3%, respectively), while those with recent overt bleeding has the lowest yield rate (12.9%). As to detecting the bleeding source, a recent study showed that VCE managed to detect the source in a higher percentage compared to mesenteric angiography and CT angiography (72% *vs* 56% and 24% respectively) [10].

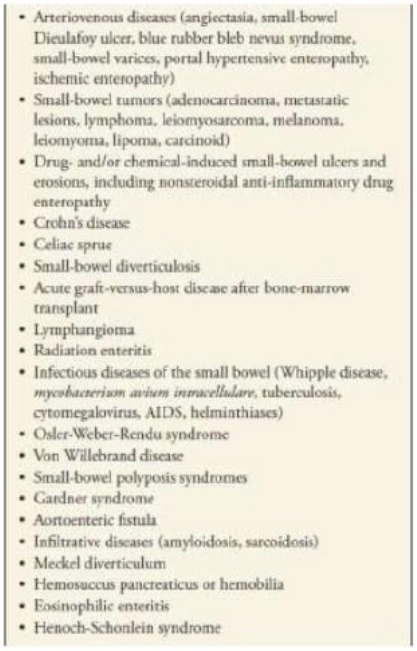

Fig. (1). Differential diagnoses in OGIB [9].

CHAPTER 8

Precision Medicine in Inflammatory Bowel Disease: Current Challenges

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Abstract: Inflammatory bowel diseases are chronic relapsing diseases with an increasing incidence worldwide, with variable and unpredictable evolution, as well as predisposition to complications throughout the disease. Despite the efforts of the academic world of research, their etiology remains incompletely elucidated, but intense research over the last decade showed that they are based on intricate complex pathophysiological mechanisms that occur in the genome, epigenome, microbiome, or immunome. Precision medicine is a new concept and its application in inflammatory bowel disease consists of adapting medical treatment to each patient who is viewed from an individual perspective, encompassing a multitude of evidence-based approaches in the literature, thus facilitating accurate medical decisions.

Significant progress has been made by studying genomic data such as genome, transcriptome, proteome, metabolome, and microbiome. With a wide range of treatments available, the demand for precision medicine in inflammatory bowel disease is of paramount importance. The goal of precision medicine is to provide individualized care so that the patient's voyage from diagnosis to treatment is based on the individual biological characteristics. Precision medicine, in order to adapt one specific therapy to a specific patient at one specific time based on the patient's biological characteristics, is an important aspiration in the medical world. Although much progress has been made in this area, some challenges remain unclear. In the future, precision medicine has the capacity to provide personalized care to patients with inflammatory bowel disease.

Keywords: Epigenome, Genetics, Genome, Immunity, Inflammatory bowel disease, Microbiome, Precision medicine, Proteomics.

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INTRODUCTION

The Role of Precision Medicine in Inflammatory Bowel Disease

Inflammatory bowel diseases (IBD), Crohn's disease and ulcerative colitis, are chronic diseases with an increasing incidence worldwide [1], with variable and unpredictable evolution, as well as predisposition to complications throughout the disease. Despite the efforts of the academic world of research, their etiology remains incompletely elucidated, but intense research over the last decade showed that they are based on intricate complex pathophysiological mechanisms that occur in the genome, epigenome, immunome [2]. Understanding the etiopathogenesis of these diseases gives the advantage of being able to apply many therapeutic molecules, but this strategy may not be cost-effective; also, patients may often fail to respond to treatment or will never respond to some therapies. Therefore, there is a growing need to apply a personalized, targeted treatment based on the molecular characteristics of each patient, and thus to change the paradigm of approaching inflammatory bowel disease from the "reactive" approach driven by the complications of the disease to the "proactive" approach to prevent complications [3]. Precision medicine is a new concept and its application in IBD consists of adapting medical treatment to each patient who is viewed from a unique, individual perspective, encompassing a multitude of evidence-based approaches in the literature, thus facilitating accurate medical decisions.

Precision medicine has as objective a patient-centred medicine and adaptation of treatment according to personal genetic, epigenetic, biological characteristics and clinical features of each patient [2]. Although it is similar to the concept of personalized medicine, precision medicine also includes a complex approach based on the objective data to facilitate clinical decisions and to better identify the molecular processes of the disease, related to the molecular characteristics of each patient. In 2015, the national initiative "Precision Medicine" [4], was initiated, which aims to bring together multi-omic data from over 1 million subjects to deepen the comprehension of the pathogenesis of inflammatory bowel disease and the application of treatments. The classical strategy "step-up" risks to treat ineffective patients who could develop complications; also, the strategy "top-up" risks to overtreat patients who could have remained stable and uncomplicated over time with only standard, cheaper therapies and no major side effects. Therefore, several parameters have been identified as risk factors associated with the severity of the disease: the location and the phenotype of the disease, the age, serological markers, and the need for early introduction of corticosteroid therapy or lifestyle. However, none is enough to guide early therapy.

Precision medicine, in order to adapt one specific therapy to a specific patient at one specific time based on the patient's biological characteristics [5], is an important aspiration in the medical world. Although much progress has been made in this area (which will be summarized below), some challenges remain unclear. In the future, precision medicine has the capacity to provide personalized care to patients with inflammatory bowel disease.

Etiopathogenesis of Inflammatory Bowel Disease: Current Challenges

Genetics

Patients with IBD have a genetic predisposition, and the risk of acquiring the disease is higher in subjects who have families with IBD. Genome-wide association studies (GWAS) have enabled the detection of many risk genes. Genetic polymorphisms also play a role in the control of the intestinal barrier. Even significant progress has been made in this area, only 25% of the heredity of IBD can be proven today [6]. In the last decades, scientific advances in genomics and the availability of genetic data from large studies have considerably contributed to a greater understanding of the relationship between certain genes implicated in the pathogenesis of IBD. GWAS has found more than 300 genetic forms that affect several host functions, such as: local homeostasis, intestinal barrier, microbiota structure, autophagy, production and secretion of antimicrobial substances, or regulation of acquired immunity [7]. Although Crohn's disease and ulcerative colitis are known to be two distinct diseases (at least clinically), 30% of genetic changes are common, suggesting the existence of common genetic pathways responsible primarily for the immune response, cytokine release, and lymphocyte response. These findings emphasize the importance of genetic predisposition in the pathogenesis of IBD. However, there are gaps in the full understanding of the pathogenesis as there are patients who do not have a genetic susceptibility and can still have the disease, suggesting that an isolated study of genomics is not enough to complete the “puzzle” of the pathogenesis of IBD.

Microbiome

Research into the microbiome of healthy and sick patients based on the genetic sequencing of 165 RNA genes using state-of-the-art technology made possible the analysis of the composition and functions of the microbiome, and also facilitated the understanding of the effects of various external factors [8]. Among the many roles it plays in the human body, the microbiota also has an essential role in preserving the integrity of the intestinal barrier, synthesis of molecules, digestion, and the development of immune cells. The environment of the gastrointestinal tract based on microbial diversity maintains a state of symbiosis. Intestinal dysbiosis is characterized as a reduction in microbial diversity that leads to a

CHAPTER 9

Fibrosis in Crohn's Disease - From Evolution to Treatment

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Abstract: One of the major complications of Crohn's disease is the development of fibrosis, this causes the intestine to lose its mobility. The most frequent intestinal "damage" occurrences are considered fibrosis, fistula, abscess, resected bowel. The Lemann index has been developed to describe the entire gut damage score in CD. It is summarizes the clinical, imaging, endoscopic, and surgical findings from all the segments of the digestive tract into one global score and provides a superior quantification of the severity of bowel, destruction. Chronic inflammation, hypertrophy of MP (muscularis propria) and smooth muscle hyperplasia of SM (submucosa) were the most valid histopathological features characterizing the intestinal stricture. Imaging methods such as MRI, CT or IUS can detect penetrating disease and intra-abdominal abscesses in different accuracy grades. Although the current imaging techniques were not able to determine the degree of fibrosis, MRI was preferred in the US for pelvic fistulae, abscesses or deep-seated fistulae. By decreasing MRTF and p38 MAPK activation and increasing autophagy in fibroblasts, local ROCK inhibition prevents and reverses intestinal fibrosis. Fibrosis is certainly reversible in animal models. The duration of treatment and toxicity are challenging for the time being.

Keywords: Crohn Disease, Fibrosis, IL36A, Inflammatory bowel disease, Lemann index, MRFT, Penetrating disease, p38 MAPK, ROCK inhibition, Smooth muscle hyperplasia, Stricture.

INTRODUCTION

In Crohn's Disease there is a chronic inflammation which can develop and cause tissue damage, represented by thickening and hardening in the bowel wall, this process is called fibrosis. This may cause the intestine to lose mobility, causing a stricture (narrowing) of the bowel, which can then lead to blockage.

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Different proteins, such as collagens, which are normally involved in the tissue healing process, end up in a state of overproduction, consequently leading to fibrosis.

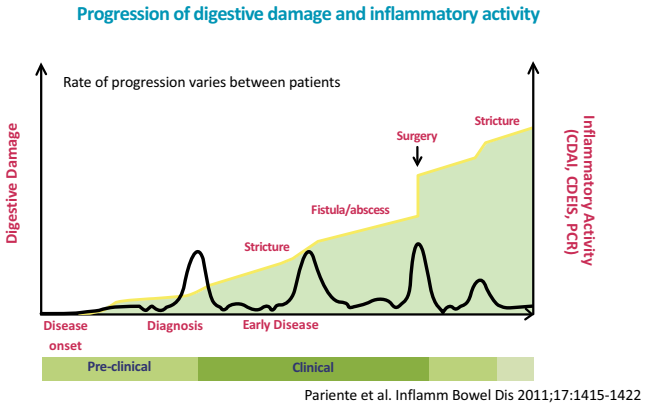

Fig. (1). Progression of digestive damage and inflammatory activity.

The Lemann index was recently created with the aim of determining the total gut damage score in CD. Medical, surgical, endoscopic, and imaging results from all parts of the digestive tract are combined into a single total score [1]. The Lémann score could be a clearer indicator of the magnitude of structural bowel injury and it should be used to monitor bowel damage development over time.

The slope of the digestive damage curve could be used to make decisions, regardless of the magnitude of the damage. As in the rheumatoid arthritis model, the slope of the curve may enable patients with rapid damage progression to be identified in order to propose accelerated therapy or, in other cases, to use less aggressive care. It will also be possible to assess the impact of medical treatments or interventions on disease progression. Such a score should allow better identification of patients with severe damage and those with rapid progression of damage [2]. During the follow-up period, the disease location and disease behavior has changed. Only biologic therapy was shown to be related to a shift in location. Changes in behavior or disease location in Crohn's disease patients have been seen to raise the risk of resection [3].

Regardless of early anti-TNF exposure, survival curve study of this matched cohort revealed comparable progression of stricturing behavior in patients. The transition in penetrating behavior was three times lower among those patients who received early anti-TNF, in contrast to patients who did not undergo early anti-TNF,, but this decrease did not achieve significance in the unadjusted study. The early anti-TNF response was described as achieving corticosteroid-free remission

6 months after diagnosis, and this outcome was noted in 124 (71%) of the 175 participants with available data. After 6 months, there was no discrepancy in the prevalence of B2 or B3 complications in anti-TNF responders and non-responders, despite the limited sample size of these subgroups [4].

Patients with strictures had genes regulating extracellular matrix aggregation induced at diagnosis, whereas those with penetrating disease had genes regulating the acute inflammatory response to microbes induced. In patients who experienced penetrating (B3) and stricturing (B2) complications, the balance between antimicrobial acute inflammatory and extracellular matrix aggregation pathways was investigated. In patients who experienced stricturing complications, the extracellular matrix of the structural constituent molecular function was mediated to a greater extent than those who remained complication-free (B1) and those who progressed to penetrating disease (B2) [4].

Internal penetrating disease and intra-abdominal abscesses can be identified with different degrees of accuracy using cross-sectional imaging such as MRI, CT or IUS [EL1]. For deep-seated fistulae, pelvic fistulae, or abscesses, MRI was preferred over ultrasound [EL4] [5]. The medical utility of MRI for diagnosing intraabdominal fistulas was calculated in five trials by van Gemert-Horsthuis, who looked at 51 lesions in a number of 210 patients. The plurality of lesions corresponded to enteroenteric fistulas, as in previous US and CT studies. As a comparison standard, four trials used a mixture of medical procedures, physical assessment (enterocutaneous fistulas), and surgery. In one analysis, there was no reference standard [6]. In a study from Panes, it was found that MRI had a sensitivity of 76 percent (95 percent CI 71–82 percent) and a precision of 96 percent (95 percent CI 92–98 percent) for the diagnosis of fistulas in a sample with appropriate comparison level [7]. The occurrence of intraabdominal abscesses was identified in four studies using MRI, with ten lesions found in 109 cases.

For the diagnosis of extraenteric lesions, one study did not use an acceptable reference level [8]; Lesions were confirmed in the majority of cases (8/10) in the remaining trials. The findings of the studies with an appropriate comparison level indicate that MRI has a sensitivity of 86 percent (95 percent CI 79–91 percent) and a precision of 93 percent (95 percent CI 88–97 percent) in detecting abscesses.

Small bowel strictures can be detected using cross-sectional imaging [EL2]. Since CT exposes patients to radiation, MRI and/or intestinal ultrasound [IUS] are the recommended approaches. In fact, none of the imaging methods will assess successfully the degree of fibrosis [EL3] [5]. A number of 239 patients,

CHAPTER 10

The Quality of Life of Patients with Inflammatory Bowel Disease: A Continuous Challenge

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Abstract: Inflammatory bowel diseases (IBDs) are chronic conditions of the gastro-intestinal tract with a remitting and relapsing course and an unpredictable evolution.

Patients affected by these diseases often have to deal with severe abdominal pain, diarrhea and loss of bowel control, fatigue, multiple surgeries and a wide range of extra-intestinal manifestations. Given these facts, the majority of them have a severely impaired health-related quality of life (HR QoL) and they are more prone to developing anxiety and depression.

Even though early clinical trials didn't show much interest in it, assessing the patients' QoL has become, over time, one of the main endpoints of the clinical trials, thus more and more articles involving the patients' QoL being published every year. Patients with active disease have a significantly lower HR QoL compared to those with inactive disease. Regarding the disease phenotype, especially when in remission, patients with Crohn's disease tend to have lower QoL than those with ulcerative colitis.

Anxiety and depression have a significant impact on the patients' HR QoL. Another concern regarding the patients with IBD is the high rates of fatigue. Fatigue is a common symptom in many other inflammatory conditions like rheumatoid arthritis or multiple sclerosis, and leads to a significant impairment of the QoL and lowers work productivity. In spite of this, it is frequently underdiagnosed or overseen by physicians, and many times remains unexplored and untreated.

Keywords: Anxiety, Depression, Fatigue, Inflammatory bowel disease, Quality of life.

INTRODUCTION

Inflammatory bowel diseases (IBDs) are chronic conditions of the gastrointestinal tract with a remitting and relapsing course. Crohn's disease (CD) and ulcerative

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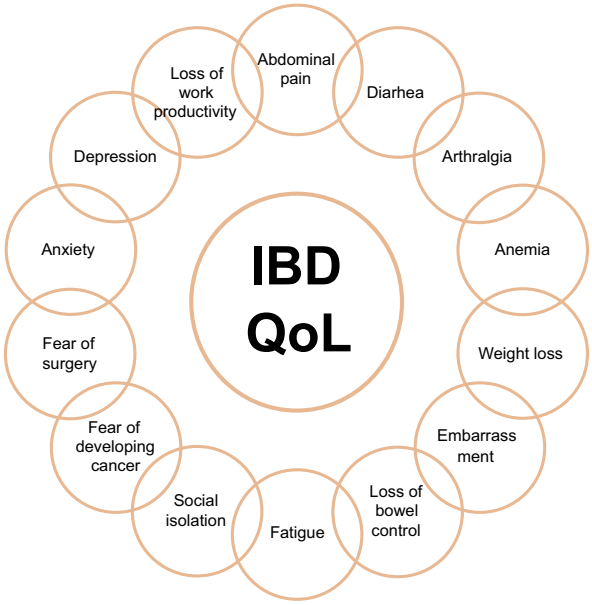
colitis (UC) represent the 2 subtypes of IBDs. Their etiology is not completely elucidated, but there is strong evidence on its multifactorial nature, involving environmental factor, genetic predisposition, intestinal microbiome and the altered immune response [1, 2]. The prevalence of IBDs is increasing, in Europe 322/100.000 inhabitants being diagnosed with CD and 505/100.000 inhabitants with UC [3].

Being a chronic disease with an unpredictable course, with sometimes embarrassing symptoms like chronic diarrhea, urgency, abdominal pain, arthralgia, undesired weight loss, anemia and the possibility of perianal involvement or the need for an ostomy, they have a significant impact on the patients' quality of life (QoL).



Patients with IBD are prone to develop anxiety and depression. The rates of anxiety are up to 19.1% in patients with IBD (*vs* 9.6% in healthy controls) and those of depression up to 21.2% (*vs* 13.4% in healthy controls) as showed by a clinical study [4]. Patients show significant concerns about the course of their disease, the possibility of developing cancer or the need for surgery [1].

Even though early clinical trials didn't show much interest in it, assessing the patients' QoL has become, over time, one of the main endpoints of the clinical trials, thus more and more articles involving the patients' QoL being published every year (currently, more than 400 new articles every year) [1].

Health-related Quality of Life (HR QoL)

The HR QoL can be explored using either generic measures that allow us to compare groups of patients with different pathologies or disease specific measures. Patients with IBD have a significantly poorer QoL compared to the healthy or general population, involving both mental and physical functions [1].

A French study conducted on 1185 patients with IBD shows that half of the patients have an impaired HR QoL (SIBDQ<45: 53.3%), suffer from extreme fatigability and exhaustion (FACIT-F<30: 47.4%) or have depressive symptoms (HADS-D>7: 49.4%). One third reported symptoms of anxiety (HADS-A>7: 30.3%), 22.4% had a moderate and 11.9% severe disability according to IBD-DI score [5].

According to a clinical study conducted by Casellas *et al*., it seems that symptomatic activity of the disease and socio-demographic variables (gender, level of education), along with the need for hospitalization and recurrence/year index are the most important predictive factors for an impaired HR QoL in patients with IBD [6].

However, when comparing patients with IBD and those suffering from other chronic conditions, such as irritable bowel syndrome (IBS), rheumatoid arthritis, chronic hepatitis or multiple sclerosis, the HR QoL seems to be similar, many studies presenting divergent results, especially those comparing the HR QoL of patients with IBD and IBS [1].

Regarding the activity of the disease, it has been shown that patients with active disease have a significantly lower HR QoL compared to those with inactive disease, in both mental and physical scores, but more pronounced for the mental function [7].

Overall, patients with CD tend to have a lower QoL compared to those with UC, but the differences were borderlines significant in the recent meta-analyses. When in remission, patients with CD have a significantly lower HR QoL compared to patients with UC. However, patients with the active disease tend to have a similar HR QoL, regardless of the IBD subtype [7].

The HR QoL of patients may improve over time. Many clinical studies report that patients with longer disease duration have a better HR QoL, which may be due to an adjustment to the chronic condition and an improvement of the self-management strategies [7].

CHAPTER 11

Advances in Colorectal Cancer Screening

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Abstract: Colorectal cancer (CRC) is the second most commonly diagnosed cancer in women and the third most commonly diagnosed cancer in men. There is a 5% lifetime risk of developing CRC in many regions and despite treatment, 45% of persons diagnosed with CRC die as a result of the disease. The development of molecular biology techniques and methods has allowed a thorough knowledge of the carcinogenicity process in the CCR. Currently, multiple guidelines are available that provide guidance to clinicians who refer patients to screening. Although colonoscopy is the preferred tool for detecting and diagnosing CCR, non-invasive stool-based tests are widely used. In this section we reviewed the most important studies that have been published regarding molecular biomarkers to identify new approaches, as well as metabolomics for identifying new biomarkers for colorectal cancer. Death occurring from colorectal cancer can be prevented by detecting cancer and precancerous lesions at an early stage. For achieving this goal, new screening tools are mandatory and research for better screening tests is needed.

Keywords: Colonoscopy, Colorectal cancer, Faecal test, Metabolomics, Screening.

INTRODUCTION

Digestive cancers are highly ranked all over the world in the matter of incidence and mortality. Colorectal cancer (CRC) is the second most commonly diagnosed cancer in women and the third most commonly diagnosed cancer in men [1, 2]. In 2018, the International Agency for Research on Cancer reported a worldwide incidence of 23.6/100,000 in men and an incidence of 16.3 in women and mortality of 8.9/100,000 in both men and women. In Europe, the highest incidence is found in Northern Europe (32.1/100,000), but the highest mortality in

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Central and Eastern Europe (15.2/100,000) [3]. Although there is an increase in colorectal cancer incidence, a decrease in mortality is observed especially in developed countries. The survival rate of patients is higher, the earlier the disease is detected. Screening programs are already implemented in western countries due to their high incidence rate, but the rising mortality rates in the Eastern part of Europe can imply a limited access to healthcare and suboptimal treatment for CRC [4].

There is a 5% lifetime risk of developing CRC in many regions and despite treatment, 45% of persons diagnosed with CRC die as a result of the disease. The adenoma to cancer sequence is known to be a process that develops over years, making it an ideal target for early detection through screening. Having the opportunity to detect the lesions in an early stage, advances in the molecular pathogenesis of CRC led to new insights and this may have an impact over the years in the strategy of detecting the precancerous and cancerous lesions of the colon [5].

COLORECTAL CANCER PATHOGENESIS

The development of molecular biology techniques and methods has allowed a thorough knowledge of the carcinogenicity process in the CCR. Understanding the pathogenetic mechanism has enabled new treatments to be introduced and accurate diagnosis and prognosis to be established (Fig. **1**) [6].

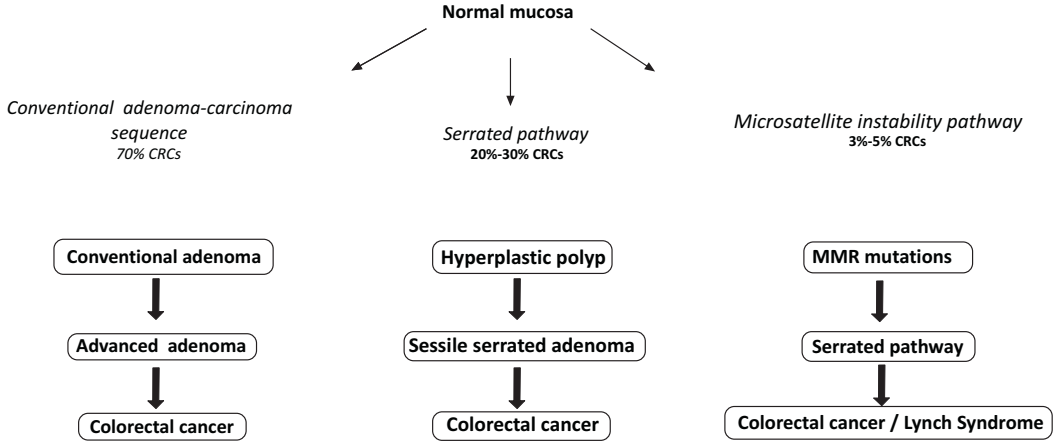

Fig. (1). Molecular pathways in CCR pathogensis. CCR: colorectal cancer. MMR: mismatch repair.

ADENOMA-CARCINOMA SEQUENCE

All the research published proves that CRC develops from precancerous lesions. Pathogenesis starts from an early dysplastic lesion to adenomatous polyps and invasive malignancy develops in the last stage. On the molecular setting, Vogelstein *et al*. published a genetic model for CRC, the adenoma to carcinoma sequence, stating that tumorigenesis usually begins with APC gene mutation and is followed by K-RAS and TP53 mutations.

SERRATED POLYP PATHWAY

This pathway is an alternative to CRC evolution from hyperplastic polyps or sessile serrated adenomas where BRAF mutations are the initial event. Dysbiosis in the intestinal microbiome has been implicated in the progression of the serrated polyp to adenocarcinoma, especially when excessive growth of Fusobacterium nucleatum is detected. The prognosis is difficult to be assessed, but a combination of different mutations such as high CIMP (CIMP-H), microsatellite stability (MSS) and BRAF mutation, can have the worst outcomes [7].

CHROMOSOMAL INSTABILITY PATHWAY/APC PATHWAY

Chromosomal instability occurs in 70% of patients with CCR. It is demonstrated by the loss of chromosomal material that causes the tumor suppressor genes to inactivate: APC gene at the level of the 5q chromosome arm, TP53 at the 17p arm. The CCR of phenotype LOH+ (loss of heterozygosity) is caused by genetic alterations such as aneuploidy, chromosomal instability, mutations of Kras (Kirsten Ras) and TP53. Colon cancers developing from CIN have worse outcomes than those with microsatellite instability [8].

MISMATCH REPAIR (MMR)

The instability of microsatellites is a genetic instability involved in colorectal carcinogenicity and is caused by the alteration of the genes involved in the mismatch repair genes. They are found in 80% of the cases of hereditary non-polypoid colon cancers (HNPCC) and in 15% of sporadic cancers. The HNPCC-characteristic MSI+ phenotype is the result of genetic instability. The genes involved are anti-mutation, stability (hMSH2, hMSH3, hMSH6, hMLH1, hPMS1, hPMS2) that repair defects that occur in DNA. The genome of these genes, called RER+ (positive replication error), precedes the mutations in the APC gene.

DNA errors are frequent in cells with mismatch repair. A deficient mismatch protein system leads to the expansion or contraction of these microsatellites, thus called microsatellite instability [9].

CHAPTER 12

New Guidelines on Post-polypectomy Colonoscopy Surveillance

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Abstract: Colorectal cancer (CRC) remains a frequent tumor, in spite of the screening programs developed in most of the countries. It is well known that CRC is developing from polyps and that the polypectomy prevents the CRC and ultimately the death of the patient. One important debate is about the post polypectomy surveillance of the patients, in regard to the timing of the second colonoscopy after the baseline one. Appropriate intervals spare the patient from an unwanted colonoscopy, however, in the case of advanced lesions ensures no recurrence of the lesion. Last year, important guidelines were elaborated and revised by different societies. This chapter is summarizing the recent European, American and British guidelines which are mostly similar, with small exceptions. The updated guidelines are reducing the number of colonoscopies in patients with small adenoma and serrated polyps without dysplasia. The villous proportion of a polyp is not considered a risk factor. In the piece-meal resection is indicated a shorter period to reevaluate the patient to reduce the risk of incomplete resection. The present guidelines are decreasing the unnecessary colonoscopies in patients that are considered with no risk, reducing the costs and ensuring a better psychical comfort for the patients.

Keywords: Colorectal cancer prevention, Guidelines, Polypectomy, Surveillance, Timing of the second colonoscopy.

INTRODUCTION

Colorectal cancer (CRC) is still one of the deadliest cancers, being in the second place as a cause of death worldwide, and ranks in the third place in incidence. These facts are in spite of the actual CRC screening programs. The disease begins as polyps, and some of these untreated polyps develop into cancer and ultimately causing death.

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In the screening programs the detection and removal of colorectal polyps is the most effective method of preventing CRC and related deaths. Polypectomy is considered a very efficient method and the post-polypectomy surveillance is important. The timing of the second colonoscopy after polypectomy has to be precise, so the patient should have no risk of recurrence. In patients with low-risk polyps is important to reduce the number of unnecessary investigations, for the best psychical comfort of the patients.

It is a real fact that each polypectomy may save lives, and to understand the importance of colonoscopy and screening for the patients involved and further on for their relatives.

There are very recent important studies in the literature that are evaluating the best surveillance interval after polypectomies to avoid the development of colon cancer. All the studies are taking into equation the polyp characteristics, as a number, histology, size, the quality of colonoscopy in view of the current guidelines and also the clinical condition of the patient. However, the guidelines about following-up the patients with polyps, after polypectomy, are continuously being updated, as new pieces of evidence are discovered.

In 2020 there were several new guidelines elaborated by different societies most important being the European, American and British recommendations.

The 2020 ESGE, the European Society of Gastrointestinal Endoscopy developed new guidelines [1] that, as the older ones from 2013 [2], are based on some definition as:

Table 1. Definition used on ESGE guidelines [1].

Term	Definition
High quality colonoscopy	Complete colonoscopy with a meticulous inspection of adequately cleaned colorectal mucosa. Neoplastic lesions have also been completely removed and retrieved for histological examination
Index colonoscopy	First high-quality colonoscopy on which surveillance strategy is based
Metachronous lesion	Any lesion that is detected at surveillance colonoscopies

In 2020 ESGE guidelines the terms high/low risk polyps or population have been replaced with new categories as patients that after polypectomy do not require surveillance and patients that after polypectomy do require surveillance.

1. The first category: without surveillance after Polypectomy includes

• the removal of small adenomas, less than 10mm, one or maximum 4 adenomas

even with dysplasia if it is low grade dysplasia, **the** villous components are not taken into account, **or**

• any small **serrated polyp less than 10mm, with no dysplasia detected,**

• these patients should be returned to screening **as they do not need surveillance**

• or they should undergo another colonoscopy in 10 years

Multiple studies revealed that the patients with non-advanced adenomas have a very low incidence of CRC and also death, compared to or even lower than the patients with a clean index colonoscopy [3, 4]. In a recent study, a high number of patients were followed 14 years. The low-risk adenoma group of 10978 patients did not present, in the follow-up period, a significant increase in the risk of CRC (HR 1.29; 95% CI 0.89–1.88) and also did not present a significant increase in death. (HR 0.65; 95% CI 0.19–2.18) [5].

In the group of patients not requiring follow-up have been included additionally the patients with villous components if the polyps are <10 mm and also those with serrated polyps <10mm.

Patients Requiring Surveillance following Polypectomy

The recommendation of the ESGE guidelines is:

- In patients with complete removal of a large adenoma **more than 10mm or with high grade dysplasia**,
- Or in case of more than 5 adenomas, **or**
- Any large **serrated polyp more than 10mm or in case it has dysplasia.**
- **Colonoscopy is recommended after 3 years**

Multiple studies revealed that only advanced adenomas have a high risk for the development of CRC [3, 6, 7]. For example data from the Polish study demonstrated that only the adenomas ≥ 20mm had a higher risk of colon cancer incidence and death (age-adjusted HR 7.45, 95%CI 3.62 – 15.33; P < 0.001) compared to individuals with no adenomas [8].

Serrated polyp (SP) ≥ 10mm, traditional serrated adenoma (TSA), and serrated polyp with dysplasia require surveillance at 3 years [9]. A recent retrospective study evaluating 122 899 patients with 10 years of follow-up showed an increase in metachronous CRC (3.35, 95%CI 1.37 – 8.15) compared to negative

CHAPTER 13

Artificial Intelligence in Gastrointestinal Endoscopy

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Abstract: Artificial intelligence (AI) in endoscopy refers to the capacity of computer algorithms using "machine learning" to aid in the detection and characterization of lesions in the digestive tract. The field of AI in endoscopy is expanding at a very rapid pace and, while the potential for development is enormous, the only validated applications currently available in everyday practice are computer-assisted detection and characterization of colonic polyps. The main advantage of machine learning is the capability of analyzing vast quantities of data to detect patterns that are not readily available to the endoscopist, thus theoretically increasing the accuracy of detection and diagnosis of the predefined lesion. However, the current technology is still heavily reliant on adequate image databases which have to be appraised by expert endoscopists before the algorithms can be trained on these datasets. Furthermore, each individual algorithm is trained to answer very specific questions, usually in a binary fashion (*i.e.* – is the polyp neoplastic or hyperplastic?).

Endoscopists need to be aware of the developments in the field, because in the near future such applications as detection and characterization of early esophageal and gastric cancer might also be included in their diagnostic armamentarium. Finally, several ethical and practical questions regarding the implementation of AI-based diagnosis and treatment in everyday practice need to be addressed by the academic and medical community before the large-scale adoption of AI in endoscopy becomes a reality.

Keywords: Algorithms, Artificial intelligence, Cancer, Colonoscopy, Computer-assisted detection, Computer-assisted diagnosis, Deep learning, Endoscopy.

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INTRODUCTION

Artificial Intelligence: Basic Notions for the Endoscopist

Artificial intelligence (AI) is a very broad term which refers to the capacity of machines to mimic cognitive tasks such as "learning" or "problem-solving" [1]. The colloquial use for the term covers a wide range of functions performed by machines from autonomously operating cars to engaging in strategic games or understanding human speech. With respect to endoscopy, the main application of AI currently under development is *machine learning,* which refers to the iterative use of complex mathematical models and algorithms to capture structure in data [2]. This is currently achieved by using a form of machine learning called *deep learning*, which involves a neural network with several layers of algorithms, triggered in a cascade fashion, and exploiting the hierarchical relations in the data being analyzed.

While the mathematical and conceptual details behind machine learning are beyond the scope of this discussion, the basic construct of AI models used in endoscopy can be broken down in 3 main processes: training, validation and testing of the model [3]. Broadly speaking, the first phase requires feeding a large amount of labelled data (*i.e.* still images of videos of various lesions – polyps, tumors, *etc.*) into the algorithm, which can break down the data according to the salient features it recognizes as useful discriminators (size, shape, color, mucosal pattern *etc.*). This is followed by a second step in the process, wherein a new, unlabeled set of data is used to assess the performance of the AI algorithm and perform a sort of "fine-tuning" which ensures that the model is not over-fitted to the training data set, meaning that it can be applied successfully to previously unseen data. Finally, the algorithm is assessed by using a third, independent set of data to check its performance in real life.

In many ways, deep learning medical applications have been likened to a "black box" – data goes in the machine and, through an inscrutable, opaque process, a decision, or "label" is returned by the algorithm [4]. The decision process, because of its complexity, cannot be fully explained to the clinician and, indeed, to some extent, it remains impenetrable to the programmer or algorithm constructor. However, it is important that the clinician understand the main limitations of current AI applications, in order to ensure adequate use in real life practice.

Firstly, current models are developed using "supervised training" – which means that training data has previously been analyzed and labeled by a human operator, which in this case is an expert endoscopist. As a result, it is important that the dataset be as large as possible, and as representative as possible of real life

conditions, otherwise systemic errors or biases will be inherently built into the algorithm. Early experience with AI development showed that still images used for training were usually high quality images, carefully selected and labeled by expert endoscopists, which would not be usually found in real life conditions, leading to the selection bias and, ultimately, to overfitting, which means that the algorithm performed very well on the training dataset, but poorly in the real life [5]. Current algorithms are developed with an aim to minimize the risk of selection bias and rely on videos rather than still images, preferably from different operators, using different examination protocols, to ensure a wide variety of captured data and, ultimately, a robust AI algorithm [6].

Another significant factor that needs to be considered is the fact that AI algorithms are designed to perform very straightforward tasks (*i.e.* detecting polyps in the video feed from the colonoscope or classifying a lesion as neoplastic or non-neoplastic). The end product of the algorithm is, in fact, a probability calculated by the AI model, based on which the program returns a "label" that is usually binary in nature (*i.e.* labeling a polyp as neoplastic or hyperplastic). What this means is that AI applications currently available in endoscopy can only be used for very specific tasks and can only perform within very clear confines. A simple example of these limitations was showcased in a recent study which showed a non-negligible rate of false positive lesions classified by the AI as colonic polyps which turned out to be feces, submucosal tumors, cysts or normal mucosal folds [7].

CURRENT APPLICATIONS OF ARTIFICIAL INTELLIGENCE

AI Applications in the Lower Gastrointestinal Tract

Screening colonoscopy represents an ever-increasing burden on medical systems worldwide. However, current data suggests that up to 27% of post-colonoscopy colorectal cancers (interval cancers) are related to the missed lesions at the index colonoscopy, highlighting the need for better detection of neoplastic lesions during colonoscopy [8]. Almost two decades have now passed since the first reports of computer-aided detection of polyps using a computer program that analyzed white light images obtained at colonoscopy [9], which were then followed by the attempt to use computer-assisted diagnosis for characterization of narrow-band imaging (NBI) of colonic polyps [10]. However, more than a decade passed before computing power and the development of image-recognition software based on deep learning algorithms could allow real-time implementation of AI software, demonstrating high diagnostic accuracy for polyp detection [11] - computer-aided detection (CADe) and for computer-aided diagnosis (CADx), which usually referred to discriminating neoplastic from non-neoplastic lesions.

CHAPTER 14

Gallbladder Tumors

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Abstract: Conventional ultrasound (US) is the most important and fundamental imaging method for gallbladder diseases.

Biliary disorders are still very common nowadays, especially the ones affecting the gallbladder. Either benign (in most cases), or malignant, their diagnosis still relies on the abdominal ultrasound. Gallstones and their complications represent a major public health issue in Europe and other developed countries, and affect > 20% of the population.

According to GLOBOCAN 2020 data, gallbladder cancer is the 23rd most incident, but the 20th most deadly cancer worldwide, which could be explained by the late discovery of gallbladder cancer. Worldwide, gallbladder cancers represented 0.6% of the total cancer cases in 2020, with a mortality of 0.85% among all cancers.

US becomes more appropriate than computed tomography (CT) and magnetic resonance imaging (MRI) for the detection of gallbladder diseases, having the advantages of safety (without radiation), real-time imaging, considerable cost effectiveness and high spatial resolution.

Regardless of the previously mentioned advantages, the accuracy and sensitivity of US are not satisfactory, particularly when gallstones or other gallbladder lesions occupy the entire gallbladder lumen. Contrast-enhanced ultrasound (CEUS) is considered to increase the diagnostic precision of US.

Keywords: CEUS, Elastography, Gallbladder, Tumors, Ultrasound.

INTRODUCTION

Conventional ultrasound (US) is the most important and fundamental imaging method for gallbladder diseases. The biliary disorders are still very common now-

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adays, especially the ones affecting the gallbladder. Either benign (in most cases), or malignant, their diagnosis still relies on the abdominal ultrasound. Gallstones and its complications represent a major public health issues in Europe and other developed countries, and affect > 20% of the population. According to GLOBOCAN 2020 data, gallbladder cancer is the 23rd most incident, but the 20th most deadly cancer worldwide, which could be explained by the late discovery of the gallbladder cancer. Worldwide, the gallbladder cancers represented 0.6% of the total cancer cases in 2020, with a mortality of 0.85% among all cancers. The incidence and mortality of gallbladder carcinoma were the highest in Asia, followed by Europe and Latin America and Caribbean Region [1]. For Romania, the incidence is lower than the world average, and slightly higher in males than in females. Gallbladder cancer is the 30th most incident cancer, representing 0.23% of the total cancer cases in 2020. At the same time is the 25th most deadly cancer, accounting for 0.35% of the total number of cancer deaths [2].

US becomes more appropriate than computed tomography (CT) and magnetic resonance imaging (MRI) for the detection of gallbladder diseases, having the advantages of safety (without radiation), real-time imaging,considerable cost effectiveness and high spatial resolution [3]. Regardless of the previously mentioned advantages, the accuracy and sensitivity of US are not satisfactory, particularly when gallstones or other gallbladder lesions occupy the entire gallbladder lumen [4, 5]. Contrast-enhanced ultrasound (CEUS) is considered to increase the diagnostic precision of US. A meta-analysis of sixteen studies that was completed in 2016 has found that the specificity and sensitivity of CEUS in defining gallbladder carcinoma with diameterless than 1 cm was 92 and 91%, respectively, having an AUROC of 97% (IC 95% 0.94–0.98). Nonetheless, the authors suggested that additional studies need to be performed in order to clarify the utility of CEUS, because the methodological quality was only moderate [6]. Regarding bigger tumors, Zhuang *et al.* observed that branched intralesional vessels, hypo-enhancement in the late phase, and the irregular shapewere characteristics indicating malignancy in gallbladder disease. By combining any two of these three characteristics, the diagnostic sensitivity was 90%, specificity was 92.4%, and AUROC 0.91 [7].

THE CLASSIFICATION OF GALLBLADDER TUMORS

Intraluminal Polypoid Mimickers

Tumefactive Sludge/Pseudotumoral Gallbladder Sediment

Conventional 2D-US and Doppler US present difficulties in differentiating the immobile gallbladder sediment from gallbladder carcinoma (Fig. **1** - **3**).

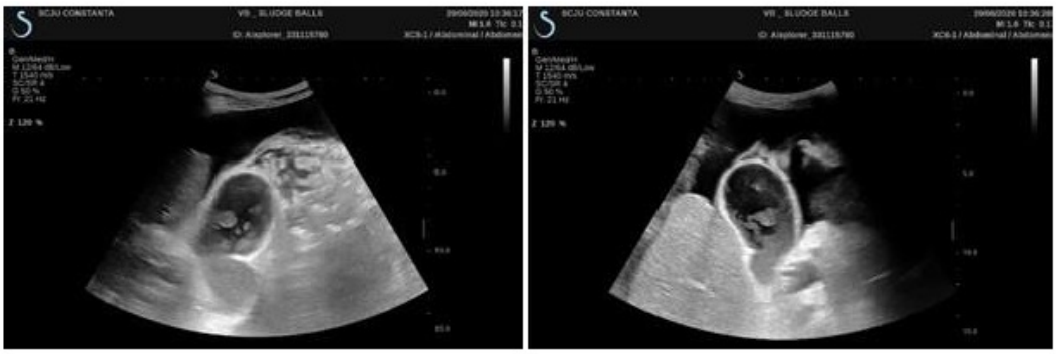

Fig. (1). Gallbladder sediment occupying > 50% of gallbladder lumen in conventional 2D-US.

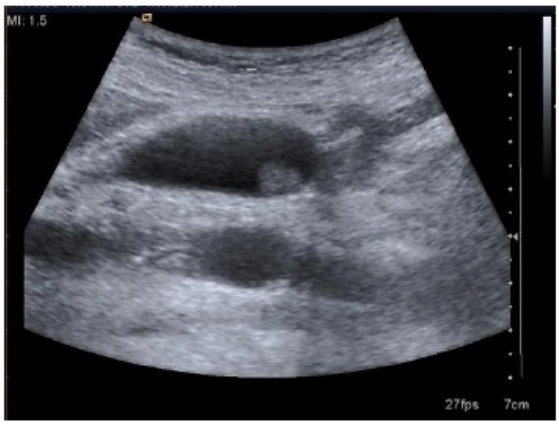

Fig. (2). Conventional 2D-US of gallbladder showing Tumefactive sludge presenting with polypoid aspect.

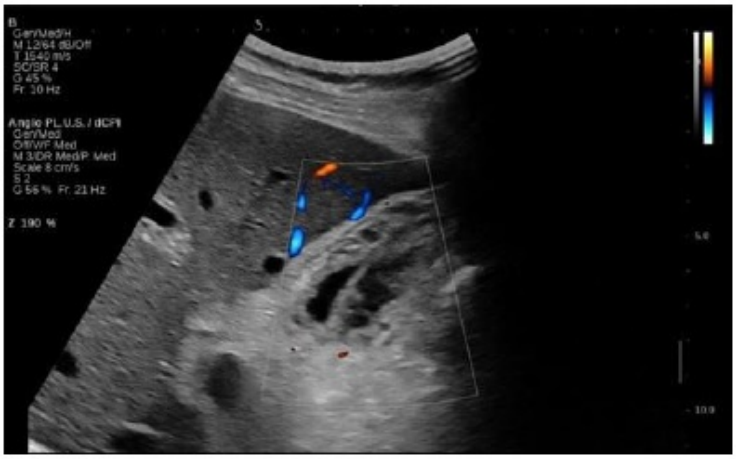

Fig. (3). Doppler US shows no vascularization present in the intraluminal hyperechoic structure in gallbladder.

CHAPTER 15

Management of Severe Acute Pancreatitis

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Abstract: One of the most important gastroenterological emergencies is acute pancreatitis. It is classified into mild, moderately severe, and severe pancreatitis depending on occurring complications. Establishing etiology and assessing disease severity is the first step of the management.

Severe pancreatitis is encountered in 25% of patients and carries the highest mortality. The therapy in these cases is structured on 4 interventions: fluid resuscitation, nutritional support, pain management, specific measures addressed to etiology or complications.

Fluid resuscitation for prevention of necrotizing pancreatitis is the foundation of early management. Quality of life in these patients relies on prompt pain management. Early enteral nutrition might reduce mortality, multiple organ failure and infection rate when compared to late enteral nutrition and parenteral nutrition.

Pseudocysts and infected necrosis can complicate severe pancreatitis. These symptomatic patients will need appropriate interventional maneuvers depending on imaging and disease extension. Antibiotics should only be given when infection is highly suspected, particularly when necrotizing pancreatitis is involved. Percutaneous drainage is recommended when the collected necrosis has less than 1 month from constitution. In walled-off pancreatic necrosis, endoscopic drainage and subsequent necrosectomy is preferred to percutaneous drainage.

Surgery has to be taken into account after failure of endoscopical/percutaneous procedures, intra-abdominal compartment syndrome, or acute on-going bleeding.

Keywords: Management, Pancreatic necrosis, Severe acute pancreatitis.

INTRODUCTION

Acute pancreatitis can frequently involve adjacent organs or other systems, representing one of the common gastroenterological diagnostic emergencies. The majority of cases can be self-limiting due to the mild edema, but severe pancreatic

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inflammation triggering necrosis, organ failure and death are also possible. The distinguishing feature of severe acute pancreatitis is the occurrence of persistent organ failure (48 h or longer) [1].

Epidemiology

Worldwide incidence of acute pancreatitis is 5 to 30 per 100 000 population, with an increasingly higher incidence since the late 2000s in UK and USA. Other factors like male gender, age and low economic status were also tied to an elevated incidence of acute pancreatitis [2].

Mortality rate ranges from 1%–7% and can rise to 15- 20% in patients with pancreatic necrosis. Persistent organ failure is generally associated with the highest mortality reaching 60% in some series [3].

Etiology

The main etiologies of acute pancreatitis are gallstones and alcohol, with the latter being the most common cause reported. Alcoholic intoxication is more frequent in men, while biliary lithiasis is more frequent in the female gender. Establishing the etiology is an important step because it will influence disease management. Other causes of acute pancreatitis are rare (listed below in Table **1**). The pancreatitis can be classified as idiopathic if we exclude all other causes. However, the most probable potential causes of "idiopathic pancreatitis" are believed to be microlithiasis and Oddi dysfunction [4]. In terms of risk factors, obesity has been proven to be frequently associated with severe acute pancreatitis [5].

Table 1. Causes of acute pancreatitis [4].

Toxic	**- Alcohol** **- Smoking**
Obstructive	- Gallstones - Pancreatic cancer - Pancreatic cystic tumor - Sphincter Oddi dysfunction
Iatrogenic	- ERCP - Drugs [thiazides, azathioprine]
Metabolic	- Hypertriglyceridemia, hypercalcemia, hyperuricemia
Autoimmune	- IgG4 pancreatitis
Genetic	- Mutations in PRSS1, SPINK1, CFTR genes
Infection	- HIV, Coxsackie, Mycoplasma, Legionella, Leptospira, Toxoplasma, *etc.*
Unknown	- Idiopathic

(Table 1) cont.....

Toxic	**- Alcohol** **- Smoking**
Endocrine	- Hyperparathyroidism
Other	- Abdominal trauma, hypovolemic shock, hypo/hyperthermia

Diagnosis

The hallmark of acute pancreatitis is abdominal pain which has an acute onset, is persistently severe, with typical epigastric localization, often radiating to the back. All other manifestations are usually related to complications [6].

The diagnosis of acute pancreatitis must be considered in all instances where acute abdominal pain is present. History and examination can be indicative of acute pancreatitis, however, for a definite diagnosis two out of the following three criteria should be met:

- Characteristic abdominal pain
- Elevated serum amylase or lipase (>3 x normal upper limit)
- Imaging [Computed tomography (CT), magnetic resonance imaging (MRI) or ultrasound] consistent with acute pancreatitis

Despite frequent clinical practice, routine CT is not recommended for diagnostic purposes if there are typical presenting symptoms. Laboratory testing includes complete blood count, plasmatic lipase, C-reactive protein, electrolytes and glycemia, hepatic enzymes. In addition, an abdominal ultrasound can identify gallstones, gallbladder complications and bile duct dilation, all indicative of a calculous etiology. Initial abdominal CT-scan should be preferred in cases of diagnostic uncertainty, signs of perforation or suspected abdominal bleeding [6, 7].

Severity Grading

In mild acute pancreatitis, patients have no complications (local or systemic). When transitory organ dysfunction [lungs, kidneys or cardiovascular system] is present, patients have moderately severe pancreatitis. In the presence of persistent organ failure (beyond 48 hours) the pancreatitis is classified as severe, imposing surveillance in an intensive care unit when accessible [6].

Local complications are frequently present in moderately severe and severe pancreatitis. Up to 25% of cases develop severe pancreatitis, which carries the worst prognosis in terms of mortality [8]. Infected necrosis in pancreatitis has a worse prognosis compared to sterile necrosis, with an average in-hospital

CHAPTER 16

Endoscopic Treatment in Chronic Pancreatitis

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Abstract: Chronic pancreatitis is a debilitating disease. A common symptom is a pancreatic pain, sometimes with an impact on the patient's life quality. The goal of the endoscopic approach of chronic pancreatitis with pain resisting standard drugs is the drainage of Wirsung duct and reducing the severity of pancreatic pain. Furthermore, biliary obstruction and pseudocysts are locoregional complications that may endoscopically be resolved. The long term safety and efficacy of the endoscopic approach is under investigation.

Keywords: Chronic pancreatitis, Endoscopic treatment, Pancreatic pseudocysts, Pancreatic stones, Pancreatic strictures.

INTRODUCTION

During the last decade, endoscopic treatment in patients with chronic pancreatitis has become an important therapeutic tool, due to the development of non-invasive imaging techniques [1]. Guidelines recommend endoscopic management in patients in whom the standard medical treatment fails [1].

The chronic pain is developed due to obstruction of pancreatic duct by stones and strictures with secondary ischemia [2], therefore the endoscopic duct drainage seems to be a rational approach [3, 4] and it may be successfully repeated if the episode of pain is relapsing. In patients unfit for surgery or those who are refusing surgery, endoscopic drainage can be chosen as a first-line treatment. Moreover, the endoscopic approach can be practice before surgery as a rescue therapy [4]. As few studies mentioned the quality of life can be improved [3]. The surgery remains the optional approach in the absence of success of endoscopic therapy [5].

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The endoscopic therapy of pain in chronic pancreatitis is performed by several procedures, to improve drainage of the Wirsung duct. These include pancreatic sphincterotomy, removal of pancreatic stones, stenting of pancreatic and biliary ducts, and the drainage of pseudocysts with standard endoscopy or with endoscopic ultrasound (EUS) [6 - 8]. Endoscopic procedures may be combined with extracorporeal shock wave lithotripsy (ESWL) for removal of pancreatic stones. In some cases the ESWL alone could be sufficient [6 - 8]. EUS provides important information regarding pancreatic stones and stenosis (Fig. **1**).

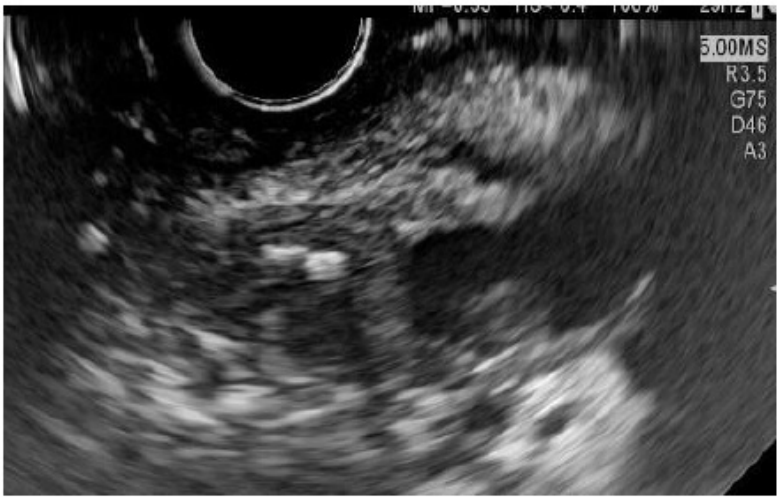

Fig. (1). EUS. Chronic pancreatitis. Pancreatic stones and dilated MPD (main pancreatic duct).

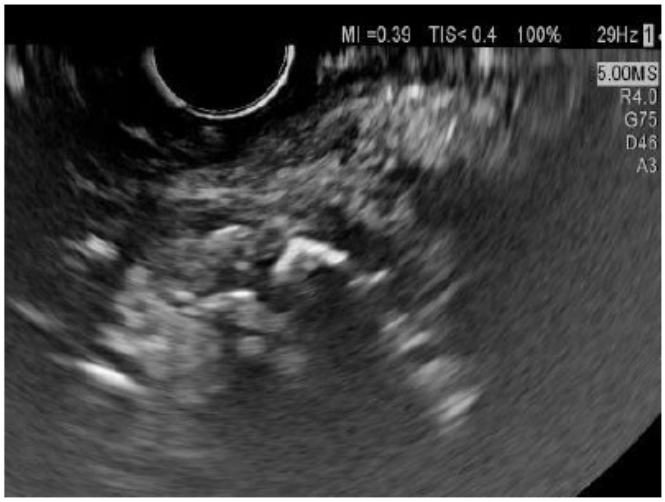

Fig. (2). EUS. Chronic pancreatitis. Intraductal pancreatic stones and head MPD stricture.

Several studies have highlighted the short-term and/or long-term efficiency of endoscopic treatment *versus* surgery in chronic pancreatitis [6]. Regarding the long-term efficiency in patients with pancreatic stones, strictures and dilated pancreatic duct surgery showed better results [6].

Pancreatic Strictures

In chronic pancreatitis, the pancreatic strictures are the consequences of chronic inflammation, fibrosis and pancreatic stones [7]. There may occur single/multiple and dominant/nondominant strictures of the main pancreatic duct (MPD) [8]. Technically successful treatment of dominant MPD strictures is obtained by stent insertion across the stricture. Clinical success is defined as the absence of pain at 1 year after the removal of pancreatic stent removal [8]. The pancreatic brushing and the endoscopic ultrasound with fine needle aspiration (EUS-FNA) rule out a pancreatic malignancy in cases with increased risk [9, 10] (Fig. **3**).

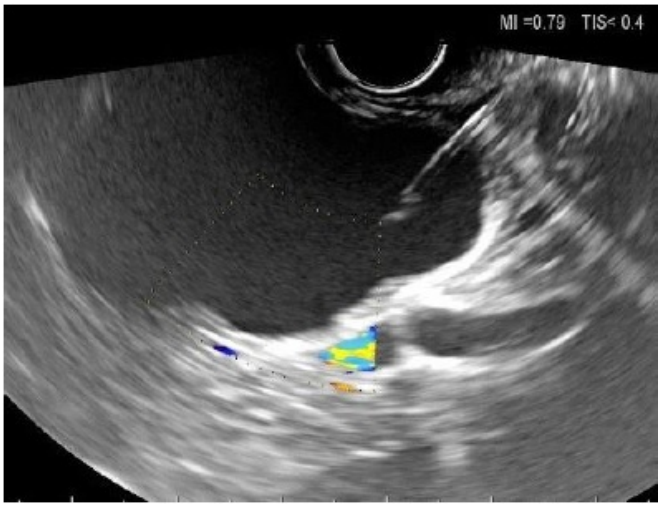

Fig. (3). EUS-FNA. Cyst of the tail of the pancreas.

Dilatation and stenting are endoscopic techniques for benign pancreatic strictures management [7]. Prior to MPD stenting, pancreatic sphincterotomy (Fig. **4**) is preferred in all studies [8, 11 - 13].

The difficult cannulation of MPD, jaundice with cholangitis, cholestasis or dilated CBP are the situations when the biliary and pancreatic sphincterotomy are performed [7, 8]. The pancreatic stenting is recommended in symptomatic cases with only one cephalic stricture of the MPD [7, 8]. In up to 90% of cases the pain is relieved immediately and in up to 50% of cases the pain start decreasing during the follow-up [11 - 13]. For dilatation, wire guided balloons and bougies are

CHAPTER 17

EUS Drainage of Peripancreatic Fluid Collections

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Abstract: Endoscopic ultrasound (EUS) has revolutionized the management of peripancreatic fluid collections (PFCs). In the last decades, new treatment strategies have been widely approached and recommended, by shifting from surgical interventions to minimally invasive modalities such as EUS-guided drainage. PFCs complicate the evolution of acute or chronic pancreatitis, traumas or surgical interventions. It is generally accepted, among scientific community, that PFCs may be managed conservatory in the first 4-6 weeks and that delayed intervention is currently preferred over early intervention in order to decrease morbidity and mortality. PFCs may be drained using different endoscopic approaches: transpapillary/transductal, transmural or in selected cases by a combination between both. Nowadays, transmural drainage by stents insertions under EUS-guidance represents the mainstay technique used in the management of pseudocysts or WONs. There are two types of stents: plastic stents and metal stents. Double-pigtail plastic stents are generally used to drain pseudocysts with mostly fluid content. Innovative stents, namely lumen-apposing covered self-expanding metal stents (LAMS) have been developed to simplify the procedure from a technical point of view. In addition, LAMS are preferred in drainage of WONs because of their large diameter which allows direct endoscopic necrosectomy by passing the endoscope through the stent lumen. In conclusion, EUS-drainage by placement of stents is currently the best option for the management of PFCs in terms of safety and efficacy.

Keywords: Drainage, Endoscopic ultrasound, Metal stents, Plastic stents, Pseudocyst, Walled-off necroses.

INTRODUCTION

Traditionally, surgical treatment was considered the procedure of choice for peripancreatic fluid collections (PFCs), unfortunately carrying the risks of recurrence (5-20%), morbidity (10-30%) and mortality (1-5%) [1].

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Recently, the management of PFCs faced a paradigm shift towards minimally invasive techniques which encompasses percutaneous and endoscopic drainage. Endoscopic methods have several advantages over percutaneous drainage: safer access to collections, lack of an external catheter, lower risks of complications (pancreatic-cutaneous fistula in particular), higher success rates, lower recurrence rates [2, 3].

Over the last two decades, EUS (endoscopic ultrasound)-guided drainage of PFCs has gained popularity in terms of safety and efficacy, being generally preferred over surgical and percutaneous drainage, as the standard procedure in many centres [4 - 6]. Data concerning technical and clinical success show high rates for EUS-guided transmural drainage (>90%) [7].

DEFINITION AND CLASSIFICATION OF PFCS

Peripancreatic fluid collections (PFCs) represent accumulation of fluid inflammatory contents and/or necrotic tissues, complicating the course of pancreatitis (acute or chronic), traumatic injuries or surgical interventions [8]. Based on duration of disease and their content, PFCs are subdivided, according to the revised Atlanta Classification stated in 2012, into four categories: ***acute peripancreatic fluid collections, acute necrotic collections, pseudocysts and walled-off necroses*** (Table **1**) [9].

Table 1. Revised Atlanta classification pancreatic/peripancreatic fluid collections [9].

Duration from the Onset of Acute Pancreatitis	Type of Collection	Features	Evolution
≤ 4 weeks	acute peripancreatic fluid collection	Homogeneous, no well-defined walls, no solid material, single/multiple	resolve spontaneously/ progress to pseudocyst
	acute necrotic collections	Heterogeneous, no well-defined walls, necrotic material, single/multiple	resolve spontaneously/ progress to pseudocyst
> 4 weeks	pseudocyst	Encapsulated, homogeneous, fluid content	resolve spontaneously asymptomatic→ symptomatic sterile → infected
	walled-off necroses	Encapsulated, heterogeneous, solid content	resolve spontaneously asymptomatic→ symptomatic sterile → infected

Acute peripancreatic fluid collections appear in the early phase of interstitial oedematous pancreatitis, have no well-defined walls, being confined to the

retroperitoneum and adjacent organs. Most of them resolve spontaneously, while 5% to 15% of cases evolve into pancreatic pseudocyst, after 4 weeks [10]. Pseudocysts are encapsulated, having no solid material inside and result from leakage due to the disruption of the main pancreatic duct or its branches [9].

Necrotizing pancreatitis accounts for 10% of all cases of acute pancreatitis. 20-40% of them may be complicated by *acute necrotic collections* [11, 12]. These distinguish from acute fluid collections because of their inhomogeneous necrotic content involving pancreatic parenchyma and/or peripancreatic tissues. They are seen within the first 4 weeks from the onset of necrotizing pancreatitis and may be single or multiple and multiloculated [8]. In their course, most of them progressively resolve, while in 1-9% persist as walled-off necroses (WONs). WONs is the term used to define encapsulated necrotic collections, after 4 weeks from the acute episode; 50% of them remain asymptomatic, while the other half become symptomatic [12].

Both pseudocysts and WONs are sterile in the beginning and might get infected by bacterial translocation or following iatrogenic maneuvers. If a necrotic collection is infected, the mortality rate is up to 30% [13]. Pseudocysts are more commonly seen in chronic pancreatitis associated with obstruction of the pancreatic duct due to strictures and stone formation, while WONs develop more frequently after acute pancreatitis. Regarding the etiology, the most frequent causes are alcohol consumption, biliary tract stones, iatrogenic procedures (endoscopic/surgical) [14].

INDICATIONS FOR DRAINAGE OF PFCS

Data concerning management of PFCs are vast and controversial among studies. However, it is generally considered that acute collections do not require specific therapy.

Pancreatic pseudocysts should be managed conservatory between 4 to 6 weeks, as studies have shown that almost one third of them regress spontaneously [15]. The main indications for interventional procedures of pseudocyst drainage are the presence of symptoms, progressive increase in size and persistence [1]. While collections smaller than 3 cm are not amenable to drainage, those larger than 5 or 6 cm are predisposed to complications, especially when the size does not decrease in six weeks. The larger is the size, the higher are the risks of complications and mortality. Rupture into nearby viscera (stomach, duodenum, colon) and peritoneum may cause melena, hematemesis, hematochezia, pancreatic ascitis, peritonitis or even hemorrhagic shock [16, 17]. Therefore, early drainage is mandatory for large pseudocysts, especially over 10 cm [1]. Symptomatic pseudocysts are also responsible for abdominal distension, nausea, vomiting, pain,

CHAPTER 18

Update in the Management of Pancreatic Cysts

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Abstract: Pancreatic cystic lesions (PCL) comprise a wide spectrum of pathological entities, from benign lesions such as retention cysts and pseudocysts to potentially malignant ones such as mucinous cystic neoplasms and intraductal papillary mucinous neoplasms. Due to the widespread use of cross-sectional imaging for various indications, PCLs are being increasingly identified in clinical practice and they can pose diagnostic challenges sometimes. Among the broad differential diagnosis of a PCL, the stake is to accurately detect lesions with a malignant potential. Along with the medical history of the patient and the imaging features of the PCL, endoscopic ultrasound (EUS) plays an important role in the management of these lesions, by providing detailed morphologic assessment including vascular pattern and detection of solid component, cyst fluid analysis and tissue diagnosis. We herein summarize the currently available evidence with regard to diagnostic updates in PCLs, focusing on recent advances in tissue acquisition and diagnosis – the micro-biopsy forceps, confocal laser endomicroscopy and cyst fluid markers. Although in an early phase, artificial intelligence applications in PCLs are briefly discussed. In summary, there has been significant progress in PCL diagnosis over the last few years and there is growing evidence that accuracy will be further improved by routine use of molecular markers in cyst fluid.

Keywords: Confocal laser endomicroscopy, Cyst fluid, Endoscopic ultrasound, Mucinous, Micro-biopsy forceps, Neoplastic, Pancreatic cyst.

INTRODUCTION

With the growing use of cross-sectional imaging for various indications, often pancreas-unrelated, pancreatic cystic lesions (PCLs) are being increasingly encountered in routine practice. The prevalence is 8% in asymptomatic individuals and increases with age [1]. This has led some authors to consider pancreatic cysts a "disease of technology". Although the vast majority of them are benign, detection of a PCL can generate significant anxiety for patients and pose diagnostic challenges for clinicians. In front of a patient with a PCL, the stake is

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to differentiate if the cyst is neoplastic or non-neoplastic and to assess its risk of progression to malignancy. This translates into a decision to either follow-up the cyst, when it has a low-risk of malignant transformation, or to sent it for surgery, when the risk is high. Misdiagnosing a cystic lesion can thus bear a risk of either missing an early cancer and the opportunity for curative resection or sending a patient for unnecessary, high morbidity and mortality surgery. Over the time there have been several guidelines published on PCLs, with some recommendations of low-quality evidence. Some of these guidelines are favoring a surgical approach, while others are more balanced towards a conservative, follow-up approach [2 - 7] (Fig. **1**). Several issues have been revealed when analyzing management decisions based on these guidelines [8, 9].

Fig. (1). – Evolution of guidelines on PCLs over the time.

Although currently available diagnostic techniques allow accurate characterization of PCLs and even subtyping of cysts, sometimes a definite diagnosis can be difficult. While diagnosis has improved considerably from the mere characterization of PCLs on imaging to cyst fluid analysis, *in-vivo* histology and sampling of cyst wall, management of PCLs is still far from being satisfactory. However, even if some PCLs may harbor cancer, we should keep in mind that the vast majority of lesions will not progress to malignancy. Surveillance on the other hand can be costly for health care systems and generates uncertainty for patients.

In this chapter, we aim to discuss the technological advances and the most recent evidence regarding the improvements in diagnosis and management of PCLs.

Approach to the Patient with PCL

In front of a patient with a PCL, the clinician should make use of all features and tools that could provide an insight for the diagnosis of the lesion. Age and gender are important to note, as some lesions are found mostly in young females (solid pseudopapillary neoplasm – SPN), others in females in their 30-40s (mucinous cystic neoplasm – MCN) and others in their 60-70s (serous cystic neoplasm – SCN). A thorough medical history is also warranted, particularly checking for episodes of acute pancreatitis and risk factors for pancreatic tumors. With regard to the characterization of the cysts, computed tomography (CT) is known to accurately demonstrate calcifications, while magnetic resonance imaging (MRI) better depicts the cystic structure of a hypodense lesion on CT scan and also

provides details about the communication with the main pancreatic duct. Besides morphological assessment, endoscopic ultrasound (EUS) is undoubtedly essential by providing cyst fluid and tissue sampling by fine needle aspiration (FNA) – (Figs. **2** - **5**).

Fig. (2). – Role of endoscopic ultrasound in the characterization of PCLs.

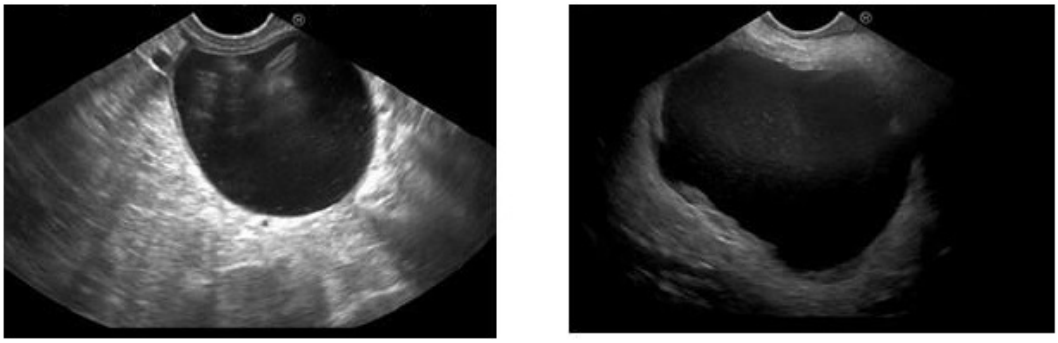

Fig. (3). – EUS images showing peripancreatic fluid collections in the setting of acute pancreatitis.

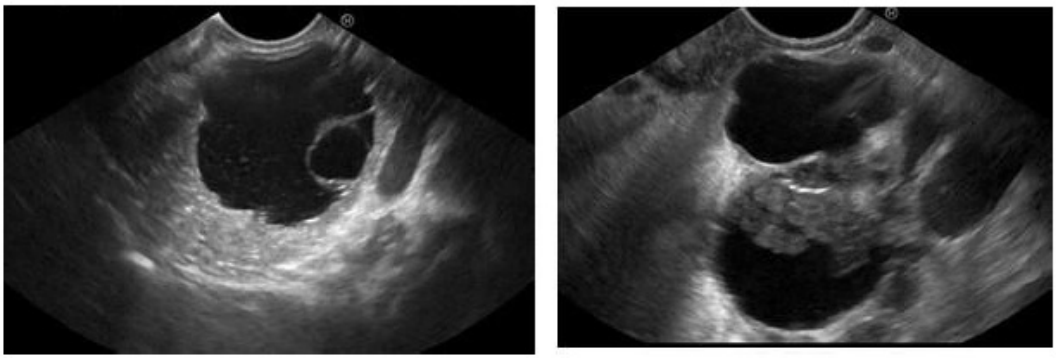

Fig. (4). – EUS images of mucinous cystic neoplasms – A: PCL with "cyst in cyst" appearance, B. Multiloculated PCL with solid component.

CHAPTER 19

Emerging Techniques for Assessment of Chronic Liver Diseases: The "Omics" Cascade

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Abstract: Chronic liver diseases are carrying an important social and economic burden, as they are having a high prevalence and are accompanied by many comorbidities. Furthermore, their progression ends frequently in a cirrhotic stage with its complications, the most fearful of these being the hepatocellular carcinoma. Therefore, diagnosing the disease at an early stage, then classifying the severity of the disease properly is mandatory. In addition, identifying the forms of liver diseases that are prone to progression towards severe fibrosis and cirrhosis is also very important. The invasive methods of diagnosis are almost completely replaced by noninvasive techniques, some of them failing to prove a high diagnostic accuracy, others being very expensive or not applicable or reliable. Consequently, the researchers are diving lately into a new domain of noninvasive diagnosis, namely OMICS cascade, which is very complex and through its multiple faces, addresses the different pathogenetic pathways of liver disease, increasing the probability of diagnosis, staging and prognosis to a higher level. The aim of this review is to present the data we have gathered until now from the field of genomics, proteomics, transcriptomics and metabolomics in the assessment of liver diseases.

Keywords: Genomics, Liver diseases, Metabolomics, Proteomics, Transcriptomics.

INTRODUCTION

The noninvasive approach of liver diseases is gaining weight in the last few years especially regarding the staging of the disease when we speak about fibrosis or when it comes to the severity of the disease. On the other hand, a noninvasive assessment is also important for the accurate diagnosis of nonalcoholic fatty liver disease, as the progression towards nonalcoholic steatohepatitis is still completely in the hand of liver biopsy. As the noninvasive approach, lacking the risks of liver

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biopsy, is equally awaitedby the hepatologists and patients also, we aimed to make a literature review with the latest data regarding the newest molecular assessment of liver disease, meaning the "omics cascade". It includes genomics, proteomics, transcriptomics and metabolomics (together with lipidomics and glycomics), with the highest tribute being given to metabolomics which is the most extensively studied lately.

GENOMICS

Over the past two decades, extraordinary advances have been made in the field of genetics, generating a vast amount of information regarding different maladies, including liver diseases. Genomics centers on identifying genetic variants linked to the disease, treatment response, or prognosis. This has been possible through the rapid development of new genomic techniques, including tests for single nucleotide variants (SNV), whole-genome sequencing or exome sequencing, which provide the possibility for the identification of a large number of genes that create an individual's predisposition to multifaceted, erratic or mutual traits [1].

The first major breakthrough in the field of hepatology was in 1993, through the cloning of the ATP7B gene, involved in Wilson's disease [2]. This paved the way for the next step, which was differentiating between monogenic diseases, where a single mutation in one gene is responsible for the disease, and polygenic diseases, which are the result of the collective breakdown of a number of traits and are associated with an abundant number of gene variants [3]. The first genome-wide association study (GWAS) in hepato-biliary diseases, identified the cholesterol transporter ABCG5/G8 as the main predisposition factor for the appearance of gallstones [4]. Since then, numerous studies have involved different genes in the development of hepatic diseases, leading to progress in the field of precision medicine.

When talking about etiologies of chronic liver disease, the main contributors seem to be chronic hepatitis B, chronic hepatitis C, alcohol-related liver disease and non-alcoholic fatty liver disease (NAFLD). Hepatitis B and C have a decreasing incidence due to advancements in treatment, but NAFLD is on an ascending path, mainly owing to the global epidemic of obesity. NAFLD's incidence has risen at an alarming rate, and non-alcoholic steatohepatitis (NASH) is now considered to be the second most common indication for liver transplantation in the USA [5]. NAFLD also leads to extrahepatic morbidity, through its association with cardiovascular disease, cancer and diabetes. Given its trajectory, there is a clear need also to understand this disease's genetic foundation, hence, contributing to the development of a specific treatment.

Data derived from different studies points to an existing heritable component to NAFLD [6]. Currently, there are at least five variants of genes that have been strongly correlated with the predisposition to and progress of NAFLD, explicitly: amino acid substitution p.I148M of the lipid droplet-associated triglyceride lipase PNPLA3, transmembrane 6 superfamily member 2 (TM6SF2), glucokinase regulator (GCKR), membrane bound O-acyltransferase domain-containing 7 (MBOAT7) and hydroxysteroid 17β- dehydrogenase (HSD17B13) [7].

GWAS studies have confirmed different variants of PNPLA3 and TM6SF2 as risk loci for alcoholic cirrhosis as well; these variants may also potentially play a role in hepatic steatosis in both hepatitis B and C [8]. In addition, variants of PNPLA3 and TM6SF2 have also been correlated to cardiovascular risk [9]. All this data highlights the importance of gene polymorphism, which is able to increase the intricacy of the clinical phenotype of the disease.

GWAS studies were also able to identify variants in the IL28b gene encoding interferon (IFN)-k3 which are related to the response to IFN therapy in patients with chronic hepatitis C virus infection [10], involving the significance of gene variants in treatment response. IL28b allele was also discovered to be a risk factor for the development of hepatocellular carcinoma (HCC) in patients with HCV infection, regardless of the sustained virologic response [11].

Another genome study for drug-induced liver injury (DILI) caused by amoxicillin-clavulanate exposure, found two human leukocyte antigen (HLA) genotypes that are related to the development of DILI; in addition, other studies found stirring evidence that relates HLA genotype to DILI susceptibility [12]. On one hand, drug toxicity related to the liver is one of the most common reasons for withdrawal of a drug and, on the other hand, there are many drugs being frequently used that can cause DILI, therefore, there is a logic in studying the potential mechanism that could diminish the development of DILI in predisposed patients or even the manufacture of hepatotoxic drugs.

With regards to autoimmune and immune-mediate liver diseases, genome-wide association studies have connected HLA variants (SH3B2, CARD10) with autoimmune hepatitis type 1 (AIH type 1); these variants overlap with the ones found in primary biliary cholangitis (PBC), and sclerosing cholangitis (SC). The variants of SH3B2 are also associated with hypothyroidism, type 1 diabetes or celiac disease. Even though in the study regarding AIH neither of these associations reached the acknowledged level of significance mandatory to proclaim “genome-wide significance”, the implication is that part of the genetic susceptibility of this disease overlaps with other immune-mediated diseases [13]. The importance of the studies mentioned in regard to diagnosis or treatment is still

CHAPTER 20

Where are we Now with Ultrasound-based Liver Elastography?

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Abstract: While the spectrum of liver diseases has changed in last few years and non-alcoholic fatty liver disease (NAFLD) becoming the main field of activity in hepatology, the evaluation of patients with chronic liver disease has shifted mainly from invasive methods (liver biopsy) to non-invasive methods. Liver ultrasound-based elastography, as a non-invasive method for predicting liver fibrosis, has been extensively studied and developed in the last fifteen years, demonstrating its good value for the evaluation of chronic liver diseases of different etiologies. Current elastography guidelines advise on how and when to use these elastographic methods in clinical practice and highlight their advantages and also their limitations too. Moreover, the rapid innovation of ultrasound systems has allowed the development of new software tools that allow, in addition to quantifying fibrosis, the quantification of steatosis and the viscoelastic properties of tissues, such as inflammation, thus turning the ultrasound systems into multiparametric methods (multiparametric ultrasound-MPUS). Also, besides liver stiffness, spleen stiffness is a good predictor for liver cirrhosis complications, such as portal hypertension and there are current recommendations and clear criteria for when to use elastography for evaluating portal hypertension.

Keywords: 2D-SWE, Liver elastography, Liver steatosis, pSWE, Shear-wave elastography, Spleen stiffness, Steatosis quantification, Transient elastography.

INTRODUCTION

The etiology spectrum of chronic liver diseases is wide, and nowadays the number of patients with such diseases is increasing. Many years ago, chronic viral hepatitis B or C were the main fields of activity for hepatologists, today this spectrum is changing. Nowadays, the fatty infiltration of the liver represents the main field of daily activity in hepatology. Alcoholic liver disease (ALD) is also a

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problem worldwide, but the pathological condition with increasing prevalence is a non-alcoholic fatty liver disease (NAFLD). Why is NAFLD an emerging problem? Because the prevalence of overweight and obese population worldwide overpasses 2 billion, and one in eleven people in developed countries has type 2 diabetes mellitus (T2DM) patients [1] and the proportion of the dyslipidemic population has increased during the time. All these conditions are factors associated with the development of NAFLD. More recently, the term NAFLD was replaced with MAFLD (metabolic associated fatty liver disease) [2], this new terminology seems to be more appropriate in terms of etiopathogenic because the patients with fatty liver are mainly dysmetabolic.

Facing this very high number of subjects with liver diseases, with MAFLD and ALD, without losing sight of other liver diseases such as cholestatic or autoimmune, we must have simple solutions to evaluate these patients, especially for the decision of therapy, prognosis and follow-up. The main driver of the progression in chronic liver diseases seems to be liver fibrosis and this is why its assessment is important in clinical practice [3].

Evaluation of patients with chronic liver diseases can be performed invasively (by means of liver biopsy), or non-invasively, by using biologic or elastographic methods.

Liver biopsy (LB) was the traditional evaluation method of patients with liver diseases, percutaneous liver biopsy being used for more than 50 years. LB is usually performed echo-guided, allowing a precise evaluation of fibrosis, inflammation and steatosis [4]. LB is still considered the "gold standard" method of liver evaluation, but considering the very high number of liver associated pathological conditions, this method is not practicable in all patients. At the same time, LB has some limitations, mainly it is not well accepted by patients, it is rarely repetitive, can lead to complications (very rare mortality) and the liver specimen obtained is not always of the best quality. In a systematic review (that included more than 8,700 patients) on the quality of LB specimens [5], major and minor complications occurred in up to 6% of LB, 0.04 to 0.11% of them life-threatening. In this review, the LB specimens had an average length and number of portal tracts well below the recommended minimum sample size requirements in more than half of the cases (only 42% of LB with a large 17-gauge needle contained 10 or more portal tracts). Therefore, the size and quality of the liver specimen obtained by LB is a problem, when using this approach for evaluating liver diseases. In a meta-analysis performed between 2010-2020, that included 30 studies, reporting on complications following 67,552 percutaneous LB, the incidence of minor complications was 12.60% (mainly minor pain), major complications were reported in 2.44% (1/40 cases), with mortality of 0.01%

(1/10.000) cases, major bleeding in 0.48% (1/200) cases and hospitalization in 0.65% of cases [6].

An alternative for non-invasive evaluation of patients with liver disease, extensively developed during the last 15 years, is **liver elastography**. Starting from the physical properties of the tissue and an external excitation of the liver tissue, these elastographic methods can provide information regarding liver stiffness. They are quite simple and repetitive. Elastography can be divided into *ultrasound-based elastography* and *magnetic resonance elastography (MR-E)*. In this chapter, we will cover only the ultrasound-based methods, especially the development of these methods during the last years.

Many guidelines advise how and when to use these elastographic methods. The first guideline published was the EFSUMB guideline (European Federation of Societies for Ultrasound in Medicine and Biology) [7], which made the first classification of ultrasound-based elastographic methods. We can divide ultrasound-based elastographic methods into:

1. Shear Waves Elastography (SWE): a) Transient Elastography-TE (FibroScan); **b) Point Shear Wave Elastography - pSWE** [using Acoustic Radiation Force Impulse Quantification (ARFI): VTQ (Siemens), Elast PQ (Philips), Samsung, Hitachi, Mindray, Esaote, others] **c) Real-Time Shear Wave Elastography - 2D SWE** (Aixplorer, General Electric, Canon, Samsung, Philips, Siemens, others)

2. Strain Elastography (Hi RTE**)**

More recent guidelines [8, 9] describe exactly how and when to use these elastographic methods, the advantages and limitations of the methods.

Which are the ***advantages of SWE***? The probe produces the impulse that generates the shear waves inside the liver tissue, without any manual pressure. Thus, by pressing a button the result is immediately displayed, expressed either in kPa (such as in Transient Elastography -FibroScan) or in meters/second or both (available now on all ultrasound machines with elastography modules). The learning curve is not very long (at least 50 examinations) [10], however, for 2D SWE some ultrasound examination experience is necessary [10].

Considering all published papers, the EFSUMB and WFUMB (World Federation of Societies for Ultrasound in Medicine and Biology) liver elastography guidelines consider that strain elastography is not ready for clinical practice. Some Japanese studies showed quite good results for strain elastography [11], but these results can possibly be suited for a “slim” Asiatic population. Considering

CHAPTER 21

New Insights into NAFLD (Diagnosis, Risk Stratification, Treatment)

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Abstract: Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease, with a worldwide prevalence of 25%. Considering the ongoing obesity epidemic, the rise in diabetes, and other features of metabolic syndrome, the prevalence of NAFLD along with the proportion of those with advanced liver disease is expected to increase continuously.

NAFLD/NASH patients have a high comorbidity burden; those with advanced liver disease have significantly higher costs, especially for patients requiring hospitalization. Early identification and effective management is needed to minimize the disease progression and costs.

Experts reached a consensus that NAFLD does not reflect current knowledge, and metabolic (dysfunction) associated fatty liver disease "MAFLD" was suggested as a more appropriate overarching term.

Until now the biggest unmet need is a performant biomarker that can diagnose and stage NASH to replace the need for liver biopsy. Such a biomarker, will increase the ability to identify patients at risk, monitor disease progression, and response to the therapy.

Treatments need a multidisciplinary approach and include: drugs targeting intake and disposal energy, lipotoxic liver injury, inflammation and fibrogenesis that lead to cirrhosis.

Keywords: Biomarkers, Diabetes Mellitus, Disease Progression, Liver Biopsy, Liver Cirrhosis, Metabolic Associated Fatty Liver Disease, Metabolic Syndrome, Non-alcoholic Fatty Liver Disease, Non-alcoholic Steatohepatitis, Obesity.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), a part of a multisystemic disease, is considered the hepatic manifestation of metabolic syndrome. The disease has risen in prevalence, involving a quarter of the population, with a major impact on the clinical and economic burden on the society [1]. NAFLD encompasses two sub-types of conditions with different prognoses: fatty liver, which, in general, follows a benign non progressive clinical course, and steatohepatitis or NASH, a more serious form of NAFLD, which may progress to cirrhosis and end stage liver disease.

Although the term nonalcoholic fatty liver disease, an acronym, was introduced by Ludwig and colleagues in 1980, to describe fatty liver disease arising in the absence of significant alcohol intake, until now the nomenclature and criteria for a diagnosis have not been revisited [2]. The heterogeneous pathogenesis of this disease represents an important impediment to the discovery of effective drug treatments. That is why, recently, a group of experts suggested a change in terminology, to better reflect the heterogeneity of individual pathogenesis of the disease and proposed a more appropriate term, instead of NAFLD, Metabolic (dysfunction) Associated Fatty Liver Disease "MAFLD". This update of nomenclature will be a step ahead in an accurate identification of particular disease subtypes, to better characterize the disease and detecting new therapeutically targets with major implications on clinical practice and public health policy [3].

Natural History of NAFLD

Although a substantial proportion of the population (25%) has NAFLD, only a minority progress to advanced liver disease (patients with NASH) and it is a challenge for a physician to identify them within the large NAFLD population. Fig. (**1**) presents the natural history of NASH based on 40 different studies.

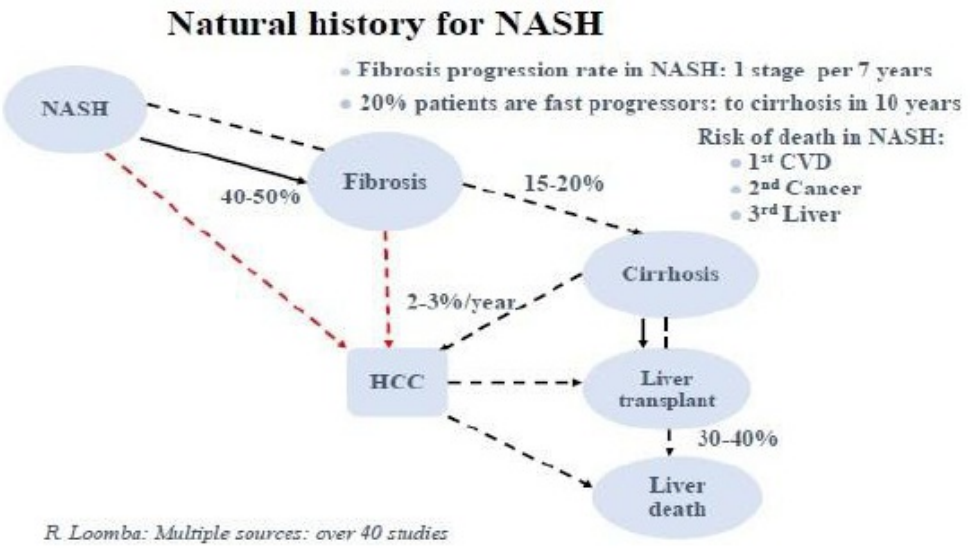

Fig. (1). Natural history of NASH.

From patients with NASH about 50% have fibrosis and 20% of them will develop cirrhosis in about 20-30 years. But 20% of patients are fast progressors and will develop cirrhosis in 10 years and a new challenge is to identify the patients with rapid progression to cirrhosis. There is an exponential manner of increased risk parallel to the increase in the fibrosis stages [4]. Once cirrhosis is developed the patients are at even higher risk for poor hepatic prognosis (hepatic decompensation, HCC, and liver-related mortality) [5]. In addition, those with NAFLD/NASH have a two times higher risk for death related to cardiovascular disease and non-liver cancers as compared to those without NAFLD [6, 7].

Liver-specific and overall mortality rates among NAFLD and NASH patients are 0.77 (range, 0.33–1.77) per 1000 and 11.77 (range, 7.10– 19.53) per 1000 person-years and 15.44 (range, 11.72– 20.34) per 1000 and 25.56 (range, 6.29–103.80) per 1000 person-years, respectively [8]. Factors identified to influence the NAFLD evolution with the established association are comorbidities (features of metabolic syndrome), genetic factors (PNPLA3, TM6SF, A1AT PIZ), microbiome products and nutritional factors (alcohol, cholesterol, fructose) [9].

The new data published from the largest prospective cohort of NASH patients revealed the dynamic nature of the disease evolution regarding the progression of NASH and the progression of fibrosis. The study showed that a large number of patients with NAFLD are likely to progress to NASH (46.9%) and fibrosis can be

CHAPTER 22

The Role of Cytokines and Inflammatory Mediators in Alcoholic Liver Disease

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Abstract: Cytokines are low molecular weight substances, mediating intra and inter-cellular communications. They are produced by several cell types, including the liver with a special focus on Kupffer cells. In the liver, pathological stimuli induce cytokines release and are responsible for cell lesions, destruction, necrosis, apoptosis and regeneration. In alcoholic liver disease (ALD) inflammatory cytokines such as interleukin-8 (IL-8) tumor necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6) as an acute phase-cytokine are involved in the liver injury. Another pro-inflammatory interleukin is interleukin-12 (IL-12), which seems to be related to chronic alcoholism. Transforming growth factor β (TGF-β) has the most important fibrogenic properties in the liver and it is also involved in regulating apoptosis along with tumor necrosis factor. Several types of cytokines are described to induce anti-inflammatory effects on the liver with chronic alcoholic exposure: Kupffer cells produce the hepatoprotective cytokine IL-6 and the anti-inflammatory cytokine interleukin- 10 (IL-10) during liver injury induced by alcohol. IL-6 acts in a protective manner *via* the activation of transcription 3 and induction of hepatoprotective genes in hepatocytes. IL-10 inhibits alcoholic liver damage in Kupffer cells/macrophages. Interleukin-22 (IL-22) is another important hepatoprotective cytokine against acute and chronic alcoholic liver injury. Adipocytokine adiponectin decreases hepatic insulin resistance and attenuates liver inflammation and fibrosis. Thus findings in the complex "puzzle" of ALD could launch the research for new therapeutic perspectives.

Keywords: Adiponectin, Alcoholic liver disease, Cytokines, Fibrosis, Inflammation, Interleukins.

INTRODUCTION

Alcoholic liver disease (ALD) is a syndrome consisting of a large spectrum of abnormalities, in which chronic ethanol intake induces progressive inflammatory liver injury.

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The liver injury evolves through different stages from simple fatty liver (steatosis) to fatty liver associated with inflammation (steatohepatitis), to destruction of the liver structure (fibrosis/cirrhosis) and higher risk of liver cancer (hepatocellular carcinoma) [1]. However, only 30-35% of chronic alcohol consumers develop clinically significant ALD, thus multiple co-factors may be involved.

The risk factors include, drinking habits, obesity, genetic, metabolic factors, cigarette smoking and sex [2]. A higher sensibility to alcohol-induced liver lesions is encountered in females. Obesity also facilitates alcohol induced liver damage, due to the activation of pro-inflammatory cells such as macrophages, thus determining the appearance of resistance to insulin and adiponectin [2 - 5]. Genetic factors including genetic polymorphism of patatin-like phospholipase domain-containing protein 3 (PNPLA3) have been recently described. Their expression induces the development of alcoholic cirrhosis in patients with ALD [2, 5 - 8].

Pathogenesis of this progressive destruction is evident multifactorial. ALD is the result of the innate and adaptative immune responses. The inflammatory pathways in ALD includeadaptive immune cell types, signaling receptors/pathways, together with anti- and pro-inflammatory responses.

Cytokines and their Role in ALD

In immune responses, cytokines are cell signaling molecules that help cell to cell communication and aids the movement of cells towards sites of inflammation, infection and trauma. They are polypeptide mediators of cellular communication that are produced and released by different cell types [9]. The production of cytokines is very low or even absent in most tissues, including the liver; nevertheless, in special situations, upon physiologic or pathologic stimuli, cytokine production is upregulated and these molecules induce the tissue response to the stimuli. Within the liver, cytokines as a response to pathological stimuli are involved in inflammation, cell necrosis and apoptosis. They are also responsible for fibrosis and regeneration following liver injury [10]. In the liver, several cytokines mediate hepatic inflammation, necrosis, and fibrosis but there are some hepato-protective and anti-inflammatory types, too.

In alcoholic hepatitis, there is a raising of tumor necrosis factor (TNF-α), a major trigger that leads to a succession of metabolic changes that harms the liver. Kupffer cells, activated *via* their toll-like receptors (TLR 4) by a high amount of lipopolysaccharides (LPS) – (intestinal derived gram-negative bacteria) [11], which secrete TNF-α and other pro-inflammatory cytokines determining free radical formation that are involved in the steatosis and fibrosis of the liver [12].

TNF- α

TNF- α is a pleiotropic cytokine that is produced by various types of cells in the organism. In the liver it is mainly produced by activated Kupffer cells and intervenes in the pathophysiology of various pathologies such as viral hepatitis, alcoholic liver disease, and nonalcoholic fatty liver disease (NAFLD) [13, 14]. TNF- α has a role in various physiological processes like cell proliferation, inflammation, and cell death (apoptosis).

More studies evidenced that ethanol intake may raise the liver's sensitivity to inflammatory cytokines, in two ways. Firstly, alcohol consumption leads to a stimulation of Kupffer cells to produce and then release TNF–α into the small vessels that allow blood flow in the liver. One indirect mechanism is represented by the augmentation of bacterial endotoxin concentration in the blood and its further explained mechanism [15]. The second mechanism is a higher response of hepatocytes to TNF–α in presence of alcohol [16]. This could lead to an increased production of small oxygen–containing molecules called reactive oxygen species (ROS) in the mitochondria. Unless they are rapidly eliminated or converted into harmless molecules by antioxidants, they can damage complex molecules in the cells (*e.g.*, proteins and DNA). ROS activates a protein called nuclear factor kappa B (NFκB), that influences the expression of numerous genes, including those encoding TNF–α, that promote apoptosis. Thus, hepatocytes could be activated a vicious cycle: TNF–α initiates ROS production, which activates NFκB, and NFκB and thus induces a larger production of additional TNF–α that promote apoptosis [16]. Within the liver, endotoxin levels are extremely low due to the intestinal barrier and Kupffer cell mediated detoxification role [17]. Ethanol consumption will increase endotoxin levels in the blood by damaging the permeability of the intestinal wall, as a consequence endotoxin cross that wall more easily. This "leaky gut", was demonstrated in animal studies [16]. By this mechanism gut-derived endotoxins invade the portal circulation activating Kupffer cells through the LPS/TLR-4 pathway.

IL-1/ IL-1β

IL-1β is a potent inductor of inflammation augmenting the expression of a large number of pro-inflammatory molecules. IL-1β is an endogenous pyrogen, apromoter of other proinflammatory mediators [18]. On hepatocytes induces steatosis by a direct effect. IL-1β also sensitizes hepatocytes to the killing effect of TNF-α, thereby causing a synergistic effect between pro-inflammatory cytokines regarding hepatocyte injury [19].

CHAPTER 23

Noninvasive Assessment of Steatosis and Fibrosis in Alcoholic Liver Disease

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Abstract: Alcohol-related liver disease (ALD) is the most frequent cause of severe chronic liver disease in Europe and worldwide. The diagnosis of ALD is usually suspected when there is the documentation of regular alcohol consumption of >20 g/day in females and >30 g/day in males and in the presence of clinical and/or biological abnormalities suggestive of liver injury. Non-invasive methods of evaluation in chronic liver diseases, including ALD, gain a lot of interest in the last years due to the large number of studies that have proven their usefulness and accuracy and due to the easy acceptability by patients, even that liver biopsy is still considered the gold standard method of evaluation. In ALD non-invasive techniques are available for the evaluation both of steatosis and fibrosis, including biological tests, ultrasound, attenuation imaging, elastography. Most noninvasive techniques allow a prediction of steatosis and advanced liver fibrosis with good accuracy, allowing also the dynamic follow up in these patients.

Keywords: Alcohol-related liver disease, Biological tests, Liver elastography, Liver fibrosis, Liver steatosis, Noninvasive assessment.

INTRODUCTION

Worldwide, harmful use of alcohol is associated with more than 3 milion deaths every year [1], with impact on over 200 diseases and types of injuries, the liver being one of the most important targets.

Alcohol-related liver disease (ALD) is the most frequent cause of severe chronic liver disease in Europe and worldwide [2]. The spectrum of alcohol-induced liver pathology is wide. ALD can progress from alcoholic fatty liver to alcoholic steatohepatitis, which is characterized by hepatic inflammation, to alcoholic liver

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cirrhosis, with the risk of developing hepatocellular carcinoma as a complication. In addition, severe alcoholic hepatitis (with or without cirrhosis) is an acute liver injury associated with high risk of liver failure and mortality.

The diagnosis of ALD is usually suspected when there is the documentation of regular alcohol consumption of >20 g/day in females and >30 g/day in males and in the presence of clinical and/or biological abnormalities suggestive of liver injury [2].

Liver biopsy can distinguish between different stages of ALD based on the histopathological features, with macro- and microvesicular steatosis in alcoholic steatosis, hepatocellular injury with ballooning, necrosis and lobular inflammation in alcoholic steatohepatitis and the presence of severe fibrosis in alcoholic liver cirrhosis [3]. Even if liver biopsy has also the advantage of establishing the positive diagnosis of ALD or offering an alternate diagnosis when this is not the case, it is still an invasive procedure, with risk of complications and not so easily accepted by patients.

Non-invasive methods of evaluation in chronic liver diseases gain a lot of interest in the last years due to the large number of studies that have proven their usefulness and accuracy and due to the easy acceptability by patients. In ALD non-invasive techniques are available for the evaluation both of steatosis and fibrosis, the major role players in the prognosis of these patients.

Steatosis Evaluation

Liver steatosis is a central pathological element in ALD, identified as an independent prognostic factor for these patients [4]. It is estimated that up to 90% of heavy drinkers can have steatosis [5]. The non-invasive methods for steatosis evaluation in ALD include biological tests, ultrasonography, Controlled Attenuation Parameter (CAP) and Magnetic Resonance Imaging (MRI).

Biological tests for the diagnosis of *presence of steatosis* were mainly developed for evaluation of patients with non-alcoholic fatty liver disease. These tests include formulas based on simple parameters, such as Fatty Liver Index (FLI) or Hepatic Steatosis Index (HSI), but also patented formulas, such as SteatoTest [6], the later with the disadvantage of the cost. The advantages of these tests would be the large availability, acceptability by the patients, while the major disadvantage is that they lack large prospective studies on accuracy and effectiveness. Their utility may be more in rule in and rule out the presence of steatosis, and identify those patients that most need further investigations.

Ultrasound on the other hand proved its utility for screening and assessment of fatty liver [7]. It is also a non-invasive technique, widely available, well accepted by the patients and rather inexpensive that showed to have sensitivity ranging between 60–94% and specificity ranging between 88–95% in detecting steatosis [8 - 10], with better performance for severe steatosis as compared to mild forms. While ultrasound is a useful imaging technique for liver evaluation, that has also the advantage to demonstrate alternate abdominal disorders, the evaluation of steatosis is qualitative and subjective, based on the liver brightness, the gradient between the liver and the kidney parenchima echogenicity and the posterior attenuation of the ultrasound beams [11], the degree of attenuation allowing a subjective grading in mild, moderate and severe steatosis. It is also an operator dependent technique and can not give information related to the presence of fibrosis, with the exception of advanced liver cirrhosis.

Controlled Attenuation Parameter (CAP) is a new non-invasive tool that uses the same features as ultrasound for the assessment of liver steatosis, but has the advantage of being quantitative and objective. It is incorporated in the Fibroscan (Echosens, Paris, France) equipment, thus allowing in the same session the evaluation of steatosis by CAP and the evaluation of fibrosis by Transient Elastography. The technique proved to have good accuracy for diagnosis moderate and severe steatosis in studies and meta-analysis mainly in NAFLD and mixed cohorts [12, 13]. The technique was studied also in ALD [14], as compared to ultrasound and liver biopsy and showed for mild, moderate and severe steatosis AUROCs of 0.77, 0.78 and 0.82, respectively, and proved to be superior to ultrasound in diagnosing steatosis in ALD.

MRI using ***PDFF*** (proton density fat fraction), can also be used with good accuracy for liver fat quantification. Several studies have compared the accuracy of PDFF to CAP, all in favor of the MRI method [15, 16]. These studies showed an accuracy of approx. 90% for PDFF and 73% for CAP. A meta-analysis that included a total of 6 studies (n = 635) showed very good summary AUROC values of PDFF for differentiating steatosis grades 0 *vs.* 1-3, 0-1 *vs.* 2-3, and 0-2 *vs.* 3 (0.98, 0.91, and 0.90, respectively) [17]. However, the main disadvantages of this technique are the availability and the costs, and no specific studies in ALD patients are available until now.

Fibrosis Evaluation

Fibrosis evaluation is the landmark for assessment prognosis in chronic diffuse liver diseases. Liver biopsy is still considered the gold standard for fibrosis assessment, but it is continuously challenged by non-invasive tests, which are easier to use in clinical practice and are currently considered viable alternatives.

CHAPTER 24

Can we Stop Nucleos(t)ide Analogs in HBV Chronic Hepatitis?

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Abstract: Chronic infection with Hepatitis B Virus (HBV) is a public health problem, since more than 240 million people are infected worldwide. Not all of them require antiviral treatment, but only those with chronic hepatitis, either HBeAg positive or HBeAg negative.

Complete cure of HBV infection is impossible due to the persistence of covalently closed circular DNA (cccDNA) integrated into the hosts' liver cells. An ideal end-point is the functional cure: HBsAg loss with or without HBs seroconversion, which is also rather hard to achieve, especially after nucleos(t)ide analogs (NA) treatment. Thus, the main endpoint of all current treatment strategies is long-term suppression of HBV DNA levels. All NA therapies have a potent inhibition effect on HBV replication. The problem is that after NA cessation the viral replication restarts.

The only firm indication to stop NA therapy is HBsAg loss, preferably with seroconversion to anti-HBsAb. In HBeAg positive non-cirrhotic patients, NA therapy can be stopped if HBeAg seroconversion and HBV DNA undetectability are achieved, but only after 12 months of consolidation therapy. In HBeAg negative chronic hepatitis, life-long NA long-term treatment is recommended. However, published data showed that viral relapse following NA cessation in these patients can trigger an immune response that would lead to a durable remission. In HBeAg-negative patients, treatment discontinuation can be considered after more than 3 years of on-treatment undetectable HBV DNA and only if close monitoring is possible. NA treatment should be continued indefinitely in cirrhotic patients.

Keywords: HBeAg seroconversion, HBsAg loss, Hepatitis B virus, Nucleos(t)ide analogs, Stop treatment, Virologic response.

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INTRODUCTION

Chronic infection with Hepatitis B Virus (HBV) is a public health problem considering that more than 240 million people around the world are currently infected with this virus [1]. However, the prevalence is not the same, varying from low (< 2%) in Western Europe for instance, to high endemic areas (>8%) such as in South Eastern Asia and Africa [2]. In the last few years, the prevalence in high endemic areas seems to decline due to vaccination and efficient treatment [3], while in well-developed countries, with historical low endemicity, a small increase was observed, mainly due to migration from high endemic areas [4].

Not all patients chronically infected with HBV (HBsAg persistent for more than 6 months) require antiviral treatment. According to the latest EASL Guidelines, chronic HBV infection can be divided into 5 phases according to the HBeAg status, HBV DNA level, cytolysis and presence of liver lesions, as shown in Table **1**. Those 5 phases are not necessarily successive and repetitive assessment of HBeAg, HBV DNA and ALT levels is needed in order to categorize patients and assess their need for treatment. The fifth phase, the "occult HBV infection" is characterized by the absence of HBsAg in the serum, with anti-HBcAb positive and anti-HBsAb positive or negative, most often with undetectable serum HBV DNA but with cccDNA detectable in the liver [1, 5].

Table 1. The new classification of Chronic HBV infection. Adapted from the EASL Guidelines on the management of hepatitis B infection [1].

Chronic HBV Infection	**HBeAg Positive**		**HBeAg Negative**		**-**
	Phase 1	**Phase 2**	**Phase 3**	**Phase 4**	**Phase 5**
	Chronic Infection	**Chronic Hepatitis**	**Chronic Infection**	**Chronic Hepatitis**	**Resolved HBV Infection**
HBsAg	High	High/Intermediate	Low	Intermediate	Negative
HBeAg	Positive	Positive	Negative	Negative	Negative
HBV DNA	$>10^7$ IU/ml	10^4 - 10^7 IU/ml	< 2000 IU/ml	> 2000 IU/ml	<10 IU/m
ALT	Normal	Elevated	Normal	Elevated	Normal
Liver disease	None/Minimal	Moderate/Severe	None	Moderate/Severe	None
Old terminology	Immune tolerant phase	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis	HBsAg negative /anti-HBc positive

Treatment Goals and Who Should be Treated

Complete cure of HBV infection is impossible to achieve due to the persistence of covalently closed circular DNA (cccDNA) integrated into the hosts' liver cells. The treatment goal in chronic HBV hepatitis is to improve survival and quality of life by preventing disease progression and the development of hepatocellular carcinoma (HCC) [1]. To reach this goal, the ideal end-point is the functional cure: HBsAg loss with or without HBs seroconversion (apparition of anti-HBsAb), which has proven to further reduce the risk of HCC in patients with viral suppression under NA therapy [6].

HBsAg loss is unfortunately rather hard to achieve, especially after NA therapy [1, 7, 8]. Thus, the main endpoint of all current treatment strategies in chronic HBV hepatitis is long-term suppression of HBV DNA levels. On-treatment virologic response is defined for nucleos(t)ide analogs (NA) treatment as undetectable HBV DNA in the serum by a sensitive assay. For PegInterferon (PegIFN) treatment, the virologic response is defined as HBV DNA <2000 IU/ml 6 months following PegIFN discontinuation, while sustained virologic response as HBV DNA <2000 IU/ml for at least 12 months following discontinuation [1].

In HBeAg-positive chronic hepatitis, it is considered that HBeAg loss with or without seroconversion to anti-HBeAb achieves immune control and thus is considered a treatment end-point [1, 7, 8]. Normal ALT levels (biochemical response) are generally obtained in patients with efficient long-time suppression of HBV replication.

As mentioned before, not all patients chronically infected with HBV need treatment. Only those with chronic hepatitis, either HBeAg-positive or HBeAg-negative should be treated (phase 2 and 4 from the new EASL classification) [1]. Cirrhotic patients should be treated by NA regardless of the HBV DNA level if detectable.

Treatment Options

Regarding treatment options, two strategies are available:

Interferon Based Therapy

Treatment with Interferon alpha (IFN-α) became available in 1992, followed in 2005 by Pegylated Interferon (PegIFN). It is a difficult treatment, with parenteral administration, with numerous side effects and contraindications, and should be considered as a first line therapy only in patients with mild or moderate liver disease as well as in selected cases with compensated cirrhosis [1, 7, 8]. It is a

CHAPTER 25

Hepatitis C Virus and Chronic Kidney Disease – What is New?

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Abstract: It is a close, bidirectional relationship between hepatic C virus (HCV) infection and chronic kidney disease (CKD). On one hand, HVC patients have an increased risk of CKD, the most frequent form being cryoglobulin-immune-mediated glomerulonephritis. On the other hand, CKD patients, especially those in dialysis units, have an increased risk of HCV infection, with an increased cardiovascular and all-cause mortality. Direct acting antiviral agents (DAA) has revolutionized the treatment of HCV, including patients with CKD, dialysis, and kidney transplantation (KT). Patients with CKD stage 1-3b can be treated with any DAA approved regimen. In patients with CKD stages 4-5, including hemodialysis patients, there are three regimens approved: glecaprevir/pibrentasvir, elbasvir/grazoprevir and paritaprevir/ritonavir/ ombitasvir/dasabuvir. However, more recently, there are many pieces of evidence that, in spite of initial recommendations, Sofosvubir-based regimens can be safe and effective in patients with end-stage CKD. Many DAA regimens demonstrated very good results (sustained viral response – 98-100%) and very well tolerability in KT recipients, the main concern being drug-drug interaction between DAA and immunosuppressive therapy. One of the major challenges of the last years is the possibility to transplant an HCV- positive kidney in an HCV-negative recipient, with DAA treatment following transplantation, with the increase of the organ supply and the avoidance of long term dialysis complications. With preventive measures in dialysis units and DAA treatment in all categories of patients, the elimination of HCV infection in CKD patients can be a realistic goal.

Keywords: Chronic kidney disease, Direct acting antiviral agents, Hemodialysis, Hepatitis C virus, Kidney transplantation, Sustained viral response.

INTRODUCTION

Hepatitis C virus (HCV) infection is a major problem of public health. More than 71 million people (global prevalence 1%) are infected with HCV worldwide, with

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an increased risk of morbidity and mortality [1]. Liver cirrhosis and hepatocellular carcinoma are the main liver-related complications, but, at the same time, there are a lot of extra-hepatic manifestations linked to HCV infection: type 2 diabetes mellitus, lichen planus, porphyria cutanea tarda, non-Hodgkin's lymphoma, cardiovascular and renal diseases [2].

Chronic kidney disease (CKD) has an estimated worldwide prevalence between 8% and 16% [3]. It is classified by Kidney Disease: Improving Global Outcomes (KDIGO), based on cause, albuminuria (A1-3) and glomerular filtration rate (GFR): G1-G5. (Table **1**) [4].

Table 1. Current KDIGO classification of CKD based on GFR (mL/min/1.73 m^2) [4].

G1	**Normal or high**	**≥ 90**
G2	Mildly decreased	60-89
G3a	Mildly to moderately decreased	45-59
G3b	Moderately to severely decreased	30-44
G4	Severely decreased	15-29
G5	Kidney failure	< 15

Patients with end-stage kidney disease (ESKD) have a GFR < 15 mL/min/1.73 m^2, requiring hemodialysis or peritoneal dialysis.

It is well-known that between HCV infection and CKD it is a bidirectional, close relationship: it has an increased prevalence of HCV in CKD patients and, at the same time, increased proteinuria and CKD in HCV-infected patients. More than that in CKD – HCV positive patients, there is an increased risk for cardiovascular and all-cause mortality [5]. In the last years, direct acting antiviral agents (DAAs) have revolutionized the treatment of HCV, including those with CKD, dialysis, and kidney transplantation (KT).

Renal Impairment in HCV Patients

HCV infection is associated with microalbuminuria and the development of CKD. The main risk factors for renal involvement are: age < 50 years, male sex, diabetes, hypertension, hyperlipidemia, and liver cirrhosis [6]. The most frequent form of renal involvement is membranoproliferative glomerulonephritis, although tubulointerstitial injury also appears. There are two major mechanisms for HCV – related glomerulopathy: cryoglobulin immune-mediated tissue damage and the direct cytotoxic effect of the virus. The major glomerular diseases associated with HCV infection are: mixed cryoglobulinemia syndrome, membranous nephropathy, and polyarteritis nodosa. Mixed cryoglobulinemia is a small vessel vasculitis leading to immune complex deposition in many organs: skin, joints,

nerves, liver, and kidneys [6]. Renal involvement is reported in 20-35% of HCV-cryoglobulinemia patients with variable clinical presentations: proteinuria, hematuria, nephritic or nephrotic syndrome, acute or chronic renal failure [7]. Achievement of sustained viral response (SVR) is associated with remission of hematuria, proteinuria, decrease of cryoglobulin levels, and improvement of GFR [8]. As cryoglobulins persist even after successfully HCV eradication in patients with nephritic syndrome and progressive kidney failure, immune-suppressive therapy with rituximab with/without plasma exchange is recommended. Rituximab should be considered as first-line therapy before DAA in patients with rapidly progressive kidney failure, acute cryoglobulinemic flare, or nephrotic syndrome [9].

Implications of HCV Infection in CKD Patients

Prevalence of HCV in CKD

The prevalence of HCV infection in persons with CKD, particularly in dialysis units, is higher compared with the general population, with a supplementary risk of nosocomial transmission during hemodialysis. According to the Dialysis Outcomes and Practice Patterns Study, the medium HCV prevalence in dialysis patients is 13.5%, ranging from 2.6% to 22.9% [10]. In Romania, in 2015, the prevalence of HCV infection in the hemodialysis population was 27.3% [11]. KDIGO recommends HCV infection screening (using an immunoassay – anti - HCV antibodies, followed by HCV-RNA if the immunoassay is positive) at the time of initial evaluation of CKD, before initiation of dialysis and at the time of evaluation for KT. In dialysis centers, screening for HCV infection will be done every 6 months (more often if a new HCV infection is reported!) [4].

Several routes of transmission can explain the higher HCV prevalence in CKD patients: frequent healthcare procedures, blood transfusion, and shared use of dialysis equipment. According to KDIGO, the main preventive "hygienic precautions" for HCV transmission are: proper hand hygiene and glove changes, proper injectable medication preparation and administration practices, proper cleaning, disinfection of surfaces at the dialysis station, and adequate separation of clean supplies from contaminated materials [4]. It is considered that the isolation of chronic hemodialysis, HCV positive patients, and dedicated machines has no benefit for preventing infection transmission in the absence of good infection control practices [12]. In the last years, HCV prevalence has declined due to routine screening, follow-up and implementation of infection control practices in dialysis patients; however, the prevalence of HCV infection still remains higher in dialysis patients compared with the general population [13].

CHAPTER 26

Advances in Imaging Diagnosis of Hepatocellular Carcinoma - the Place of Contrast Enhanced Ultrasound (CEUS)

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Abstract: Hepatocellular carcinoma (HCC) is a primary malignant liver tumor that complicates advanced chronic liver disease, especially liver cirrhosis. Surveillance of this category of patients is mandatory for early detection of HCC and improved prognosis. Screening should be carried out by the abdominal US every 6 months with or without alpha-fetoprotein.

The diagnosis of HCC is confirmed by imaging methods that highlight the typical behavior of HCC: hyper-enhancement in the arterial phase and washout in the late phase. Imaging methods used for HCC diagnosis are Multi-detector computer tomography (MDCT), multi-phase nuclear magnetic resonance imaging (MRI), or contrast-enhanced ultrasound (CEUS).

LI-RADS algorithm is now one of the most used widely systems for the imaging diagnosis of HCC. It is a standardized system for technique, interpretation, reporting, and data collection for imaging (CT, MRI, and CEUS). The algorithm includes 8 categories with an increasing probability of HCC and malignancy with higher categories.

Studies that have attempted to validate this LI-RADS scheme for the diagnosis of HCC shown that LR-5 is highly predictive for HCC.

Keywords: Contrast-enhanced ultrasound, Diagnosis, Hepatocellular carcinoma, Liver cirrhosis, Liver Imaging Reporting and Data System, Magnetic resonance imaging, Multi-detector computer tomography.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most frequent primary liver cancer, being the second most common cause of cancer death worldwide [1, 2]. The incidence of hepatocellular carcinoma (HCC) has been increasing in the last few years and is expected to increase until 2030 in some countries where the prevalence of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are raised [3].

Chronic liver diseases, especially liver cirrhosis, represent the major risk factor for hepatocellular carcinoma that accounts for 70% to 80% of the total liver cancer [4]. Most clinical practice guidelines recommend surveillance for early detection of HCC in this category of patients.

Hepatocarcinogenesis is a complex multistep process that includes the transition from regenerative nodules to hepatocellular carcinoma accompanied by changes in the blood supply of the nodules and malignant transformation consisting of gradually reducing the number of portal tracts while the number of unpaired arteries increases. In most cases, HCC is supplied mostly by the hepatic artery system, *via* abnormal unpaired arteries (a hypervascular tumor) [5].

This explains the characteristic enhancing pattern of HCC with hepatic arterial phase hyperenhancement and portal venous and/or delayed phases washout relative to the background liver on contrast enhanced imaging.

Imaging Diagnosis of Hepatocellular Carcinoma

Recent EASL guidelines recommend that the diagnosis of HCC in cirrhotic patients should be based on non-invasive criteria and/or pathology and in non-cirrhotic patients, diagnosis of HCC should be confirmed by pathology [6].

In clinical practice, all patients with liver cirrhosis and chronic hepatitis with advanced fibrosis included in the category of risk for HCC must be followed for early detection of HCC. Screening should be carried out by the abdominal US every 6 months with or without alpha-fetoprotein (AFP) [6]. The ultrasound sensitivity as a surveillance test ranges from 58 to 89%, with specificity greater than 90% [7]. Because the US's performance in early detection of HCC is highly dependent on the expertise of the operator and the quality of the equipment, the guidelines recommend that surveillance be performed by experienced personnel [6].

After US screening, liver nodules found must be characterized using imaging methods: multi-detector computed tomography (MD-CT) or multi-phase nuclear magnetic resonance imaging (MRI), or contrast enhanced ultrasound (CEUS) [6].

Multi-detector Computer Tomography (MD-CT) and Multi-phase Nuclear Magnetic Resonance Imaging (MRI) in the HCC Diagnosis

The noninvasive diagnosis of HCC using contrast enhanced imaging methods can be established only if the typical pattern is present. According to the European Association for the Study of Liver (EASL) guidelines, a single dynamic technique showing intense arterial uptake followed by a washout of contrast in the venous-delayed phases is valid to diagnose HCC [6]. Most guidelines recommend the diagnostic cut-off size of 1 cm.

These guidelines also recommend first-line imaging methods: multiphasic contrast-enhanced CT, multiphasic contrast-enhanced MRI, or gadoxetic-enhanced MRI. If the imaging method used is not typical, then another method will be used, including contrast enhanced ultrasound (CEUS) [6].

The MRI and CT sensitivity in HCC diagnosis was evaluated in a recent meta-analysis that included 19 studies [8]. This study showed a significant higher sensitivity for MRI with extracellular or with hepatospecific contrast over CT (82% *versus* 66%), but the specificity of MRI *versus* CT (91% *versus* 92%) was not different. For all imaging modalities, the results were better for HCC ≥2 cm, but not for HCC less than 2 cm in size. The study concludes that due to low to moderate quality of evidence and possible publication bias, the differences in pooled diagnostic performance are considered insufficient to definitively recommend MRI over CT.

In clinical practice, the choice between CT and MRI depends on patient safety preferences, local expertise, and possible contraindication, especially for MRI. Other MRI disadvantages are: higher cost, higher technical complexity, longer scan times, claustrophobia, increased tendency to the artifact. CT is more accessible, faster (has a short exposure time), but has the disadvantage of radiation exposure. For both diagnostic methods, renal insufficiency is the major limitation, because the kidneys eliminate most of the contrast agents used in CT and MRI.

LI-RADS Algorithm for CT and MRI

In order to provide standardization for HCC imaging diagnosis, LI-RADS algorithm was developed. The first version of LI-RADS was released in 2011,

CHAPTER 27

Treatment of Intermediate Stage Hepatocellular Carcinoma – from Guidelines and Beyond

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Abstract: Hepatocellular carcinoma (HCC) BCLC-B class is characterized by an extensive heterogeneity due to the wide range of liver function (Child Pugh A or B cirrhosis) and variable lesion number and size. With this regard, hepatologists must develop a better stratification of this HCC stage for patients to benefit from a better treatment allocation.

Trans-arterial chemo-embolization (TACE) procedure is the most widely used therapeutic option for intermediate stage HCC. One therapy is not beneficial unless clinicians might predict its outcome. Along these lines, several predictive factors for the TACE success have emerged such as mRECIST criteria, HAP and mHAP, Munich and CHIP score. The overall survival (OS) after the TACE procedure is around 16 months and in rigorous selected candidates, might increase the survival up to 3 years. Nevertheless, in some BCLC B patients, other therapies have proved their benefit compared to TACE. Resection and liver transplantation when technically possible is associated with an increased OS *versus* TACE. Moreover, astounding results have arisen from the combination of TACE with radiofrequency ablation. However, the literature fails to support the use of multi-kinase inhibitors in combination with TACE. Selective internal radiation therapy (SIRT) also known as radioembolization (TARE) induces fewer side effects and maintains a better tumoral control than TACE, but it is less available worldwide and is less cost-efficient.

In conclusion, navigating through all these treatment options, we believe that intermediate stage HCC has to be managed in a personalized way for each patient in order to have the best outcome.

Keywords: Hepatocellular carcinoma, Intermediate stage BCLC B, TACE.

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INTRODUCTION

BCLC B Subgroup and Beyond

The Barcelona Clinic Liver Cancer (BCLC) system grading was first presented more than 20 years ago, along its way has incorporated changes according to the clinical setting and treatment options and nowadays it still represents the cornerstone of hepatocellular carcinoma (HCC) classification [1, 2]. Since its original publication, it is acknowledged that BCLC-B class is defined by a subset of patients categorized as intermediate-stage HCC with multifocal disease confined to the preserved liver function, without vascular invasion and good performance status.

In theory, patients with BCLC-B stage are ineligible for curative treatment, but can benefit from trans-arterial chemo-embolization (TACE) as a standard of care [2]. According to the European Association for the Study of the Liver (EASL) the median survival for untreated patients at an intermediate-stage [BCLC-B – multinodular disease, good performance status (PS), without vascular invasion or extrahepatic spread] is around 16 months and in rigorous selected candidates, TACE can increase the survival up to 3 years [3].

On this subject, hepatologists and oncologists have agreed that BCLC-B class is characterized by an extensive heterogeneity due to the wide range of liver function (Child Pugh A or B cirrhosis) and variable lesion number and range. In order to limit the variability of TACE results worldwide, a sub-classification of intermediate stage HCC has been proposed by Bolondi (Table **1**) and later by Kudo (Table **2**) [4, 5]. Taking into account these subclassifications patients might benefit from a better treatment allocation as given below.

Table 1. Bolondi BCLC-B subclassification. TACE- transarterial chemo-embolization; LTx- liver transplantation; SIRT- selective internal radiation therapy.

BCLC-B Subclassification	***B1***	***B2***	***B3***	***B4***
Child-Pugh score	5-7	5-6	7	8-9
Beyond Milan within up-to-7 criteria	In	out	Out	out
ECOG PS	0	0	0	0-1
PVT	No	no	No	no
First treatment option	**TACE**	**TACE/ SIRT**		**BSC**
Alternative	LTx/ TACE+ ablation	Sorafenib	Trials TACE+Sorafenib	LTx

Table 2. Kinki score.

BCLC-B subclassification	***B1***	***B2***	***B3***	
Child-Pugh score	5-7	5-7	8,9	
Beyond Milan within up-to-7 criteria	in	out	Any	
Treatment	**curative**	**palliative**	**3a** **If up-to-7 leads to curative treatment**	**3b** **Out up-to-7 leads to BSC**

Clinicians have to bear in mind that a solitary nodule of HCC beyond 5 cm without vascular invasion and metastasis and without cancer-related symptoms might benefit from surgical resection if technically feasible and thus should be reclassified as BCLC-A [6]. Moreover, a poor outcome of treatment might be defined by an impaired performance status, refractory ascites, and events such as spontaneous bacterial peritonitis, hyponatremia or recurrent encephalopathy. In the absence of liver transplantation which is the only possible treatment, dismally the patient must be restaged as BCLC-D [7].

TACE Treatment Point of View

As a result of an exclusively arterial vascularization of HCC tumors and comprising the fact that the normal surrounding liver parenchyma is vascularized from branches of the portal vein, TACE and other image-guided transcatheter treatments were born in order to destruct arterial tumoral vessels and hence inducing tumor necrosis [8].

TACE procedure is based on intra-arterial infusion of a chemotherapy agent such as doxorubicin or cisplatin, frequently embedded in lipiodol as a vehicle to increase vulnerability to the drug. Furthermore, the tumoral blood vessels will be embolized with different agents such as gelatin sponge particles, metallic coils, polyvinyl alcohol, starch microspheres and autologous blood clots leading to an increased tumoricidal and ischemic effect [9, 10]. The five most common adverse effects reported are liver enzyme abnormalities (18.1%), fever (17.2%), hematological/bone marrow toxicity (13.5%), pain (11%), and vomiting (6%), which are related to the occurrence of postembolization syndrome. The overall mortality rate was reported less than 1% and is due to acute liver insufficiency [11].

Nevertheless, TACE therapy has its vicissitudes, the contraindications ruled out by Raoul *et al.* being listed in Fig. (**1**) [12].

CHAPTER 28

Direct-acting Oral Anticoagulants in Liver Cirrhosis: What is the Current Status?

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Abstract: In the last few years, the coagulation abnormalities associated with liver cirrhosis were better characterized, concluding that the patients with liver cirrhosis are predisposed to thrombotic or bleeding complications. Portal vein thrombosis is the most frequent thrombotic event, associated with liver cirrhosis. Atrial fibrillation is also a frequent comorbidity in patients with liver cirrhosis associated with higher risks of embolic complications, needing an anticoagulant prophylactic treatment. Direct-acting oral anticoagulants (DOACs), warfarin, unfractionated heparin or low weight molecular heparin are not always efficient in liver cirrhosis. According to recent studies, DOACs are relatively safe in Child-Pugh class A or B liver cirrhosis for the treatment of acute portal vein thrombosis or prevention of embolic events in patients associating atrial fibrillation. All DOACs are contraindicated in patients with Child-Pugh class C liver cirrhosis.

Keywords: Anticoagulation, Atrial fibrillation, Direct-acting oral anticoagulants, Liver cirrhosis, Portal vein thrombosis, Thrombosis.

INTRODUCTION

The role of anticoagulant (AC) treatment in patients with liver cirrhosis (LC) is still a debated subject. Patients with cirrhosis were considered to be naturally anticoagulated due to the decreased production of pro-coagulant proteins and platelets, combined with an increased international normalized ratio (INR). New data have shown that patients diagnosed with LC are at a concomitant risk of hemorrhagic and thrombotic events due to increased platelet aggregation, decreased fibrinolysis, and decreased synthesis of natural anticoagulants as protein C, protein S and antithrombin III (AT III) [1] (Fig. **1**).

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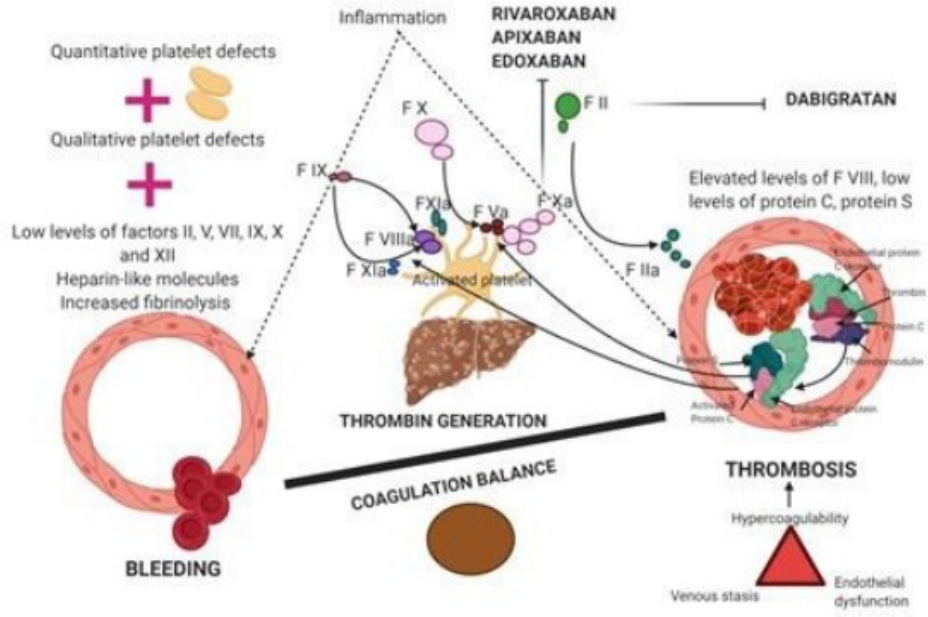

Fig. (1). Coagulation balance in patients with liver cirrhosis.

Multiple beneficial effects were attributed to AC in LC including decreasing decompensation rate or liver fibrosis [2]. A recent meta-analysis that evaluated survival rate and the antifibrotic effects of AC in animal models of liver cirrhosis concluded that the AC treatment could influence liver fibrosis, portal pressure and liver inflammation, with no impact on survival [3].

Direct Oral Anticoagulants in Liver Cirrhosis-real World Evidence

During the last decades, several indications of anticoagulation in patients with liver cirrhosis arise, starting with acute non-malignant portal vein thrombosis (PVT), preventing deep vein thrombosis (DVT) or thrombotic complications in non-valvular atrial fibrillation (AF) patients, to even prevent LC decompensation [4]. Many AC regimens were proposed and the studies were very inhomogeneous regarding this aspect [5]. There are four main direct-acting oral anticoagulants (DOACs) used frequently in our daily practice: rivaroxaban, apixaban or edoxaban (inhibitors of activated factor X) and dabigatran (inhibitor of thrombin). These anticoagulants are indicated in stroke prevention in non-valvular AF, venous thromboembolism (VTE) prophylaxis in patients after orthopaedic surgery, and the treatment of acute thromboembolic diseases [6]. The possibility of oral administration with no need of laboratory monitoring, and the mechanism of action not evolving the AT III make, in theory, the almost perfect anticoagulant

treatment for patients with LC, although we have to consider that both rivaroxaban and apixaban are in majority metabolized in the liver (67%) with half-lives between 5 hours and 12 hours [7]. Also, their concentration is depending on the plasma total protein level. Half of the total quantity of edoxaban is metabolized in the hepatocytes and has half-live of 10-15 hours [7]. Dabigatran is the DOACs with very low hepatic metabolism and his half-live [12-14 hours] is not influenced by the plasmatic proteins [7]. Also, dabigatran has a potent antidote – Idarucizumab (a monoclonal inhibitor antibody). Adexan *et al*fa is a recombinant modified human factor Xa protein and represents the antidote for the factor Xa inhibitors [8]. Idarucizumab has an intravenous administration, in a single dose with maximum effect [9]. Ciraparantag directly interacts with factor Xa inhibitors [10], but also with dabigatran, LMWH, and unfractionated heparin and at the moment there are ongoing studies evaluating its effect as an antidote for all the above anticoagulants. Also, gastric lavage soon after ingestion and hemodialysis in very severe cases could represent emergency therapeutic measures in dabigatran overdose.

Until now the ideal anticoagulant was not yet developed. In patients with cirrhosis, the efficacy of LMWH is decreased due to decreased levels of AT III, protein synthesized by the liver. The International Normalized Ratio (INR) is not correctly representing the real coagulation status in patients with LC and the INR could not be used to monitor the anticoagulant treatment (warfarin oracenocoumarol) [1]. DOACs would have theoretical advantages over antivitamin K antagonists (VKAs) or LMWH in cirrhosis and PVT [5].

DOACs have several advantages over VKA therapy, including oral administration, no need for frequent laboratory monitoring and low drug-drug interaction or food interactions. DOACs pharmacokinetics is represented in Table **1** [7, 11].

DOACs are indicated in non-cirrhotic patients for prevention or treatment of venous embolism, excepting patients with mechanical heart valves or those with antiphospholipid syndrome. Compared to VKA, DOACs do not need a dose adjustment and frequent laboratory testing and, most important, DOACs do not reduce protein C and S levels.

Table 1. DOACs hepatic metabolism and pharmacokinetics.

	Rivaroxaban	**Apixaban**	**Edoxaban**	**Dabigatran**
Mechanism of action	Factor Xa inhibition	Factor Xa inhibition	Factor Xa inhibition	Thrombin inhibition
Peak drug levels [C_{max}]				

CHAPTER 29

Latest Data on the Epidemiology, Pathological Classification, and Staging of the Combined Hepatocellular Carcinoma-Intrahepatic Cholangiocarcinoma

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Abstract: Combined hepatocellular carcinoma–intrahepatic cholangiocarcinoma (cHCC–CCA) is a primary liver cancer with features of both hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA). This combined tumor represents 1% of all primary liver cancers, but recent studies have shown its increasing incidence and incidence-based mortality. The risk factors (identifiable in about 30% of the cases) are similar to those of HCC and CCA: cholestatic liver diseases, hepatobiliary flukes, toxins, liver cirrhosis of any etiology, and metabolic diseases such as obesity and diabetes mellitus. The first pathological classifications of cHCC-CCA described three types of tumors: collision, transition and intermediate tumors. Intermediate tumors develop from a cell intermediate between the hepatocyte and biliary epithelial cell. The 4th WHO classification of digestive system tumors (2010) was the first one to report cHCC-CCA as a distinct entity, with two main subtypes: classical type and cHCC-CCA with stem-cell features. The collision type was no longer accepted. In the 5th WHO classification (2019), the tumors of the subtype with stem cell features were re-categorized as either HCC or iCCA. Due to the cHCC-CCA mixture of phenotype characteristics, the staging criteria have been also controversial. Presently, the cHCC-CCA tumors are staged by a similar algorithm as for iCCA: the TNM staging of HCC is used for clinical applications and prognosis, and the SEER staging is used for epidemiological studies. The growing interest in molecular research, genetic biomarkers identification, diagnosis and staging of these combined tumors will eventually lead to the development of effective therapeutical approaches.

Keywords: Combined tumor, Epidemiology, Hepatocellular carcinoma, Intrahepatic cholangiocarcinoma, Pathology, Tumor staging.

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INTRODUCTION

Combined (mixed) hepatocellular carcinoma–intrahepatic cholangiocarcinoma (cHCC–CCA) is a rare primary liver carcinoma, an independent entity sharing features of both hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA). The cHCC-CCA is an aggressive disease, with increasing incidence and a poor prognosis. Due to its rarity, the clinical, diagnostic, therapeutic, and prognostic characteristics of cHCC-CCA have not been entirely defined and are under constant research, as for all other types of cholangiocarcinomas (CCAs). The interest in this heterogeneous class of tumors, difficult to be diagnosed and with limited therapeutic options available, has been proved by the numerous publications in recent years, including the recent Expert European Consensus Statement (Cholangiocarcinoma 2020: the next horizon in mechanisms and management) [1]. Here we will review some of the topics related to cHCC-CCA.

Epidemiology

Epidemiology of Cholangiocarcinomas

Cholangiocarcinomas (CCAs) are a group of malignancies with pathologic features of biliary tract differentiation. They have a heterogeneous anatomical location and pathology. Intrahepatic CCA (iCCA) arises from small intrahepatic bile ducts (above the second-order bile ducts), while perihilar (pCCA) and distal (dCCA) tumors arise from extrahepatic and large intrahepatic ducts, being anatomically extrahepatic CCAs. The three entities have distinct epidemiology, pathogenesis and management requirements. Presently, there is a growing interest in establishing the prevalence, risk factors, diagnosis and staging of these tumors, and identifying better therapeutic options.

Extrahepatic CCAs represent the most common type of CCA accounting for more than 80% of cases. Their incidence has remained stable or slightly declined during the past decades. Conversely, the iCCA, the second most frequent primary hepatic malignancy, has an increasing prevalence. The data of the Surveillance, Epidemiology, and End Results (SEER) registry for the interval 1973 to 2012 demonstrated an increasing iCCA incidence, and a stable incidence of extrahepatic CCAs [2]. Intrahepatic CCA may frequently be misdiagnosed as the metastasis of a cancer of unknown primary (CUP), therefore the authors analyzed in parallel the CUPs incidence. They observed a dramatic decrease during this time interval and suggested that improved clinical distinction between the two entities might have contributed to the apparent increase in iCCA incidence. Using the data of the SEER registry, Petrick *et al*. [3] evaluated the incidence of iCCA and HCC for a period of 25 years (1992 – 2016). They found increasing rates for

iCCA, due to better investigation possibilities, and an overall increased incidence of CCAs.

The most recent data comes from a systematic review and meta-analysis of 53 epidemiological studies published both in Western and Asian countries between 2008 and 2019 [4]. The incidence of primary liver cancers increased during this interval with an annual percentage change (APC) of +2.6 for HCC and a higher APC (+4.3) for iCCA. The increase occurred mainly in Western countries, whereas trends decreased in the Asian region, although still remaining high.

Epidemiology of the Combined HCC-CCA

Intrahepatic CCA accounts for about 15% of all the primary hepatic malignancies [5]. The cells-of-origin of iCCAs are cholangiocytes, peribiliary glands and hepatic stem/progenitor cells. The hepatic progenitor cells have the potential to differentiate into either hepatocytes or cholangiocytes, depending on the damaged cell population, and represent the origin of cHCC-CCA. Intrahepatic CCA shows several histological variants (conventional, *i.e*. large-duct type and small-duct type, cholangiolocarcinoma and rare variants). The small-duct type and cholangiolocarcinoma occur more often in chronic viral liver disease and cirrhosis.

The cHCC-CCA is a very rare tumor, which shows features of both hepatocellular and biliary epithelial differentiation. The presence of cholangiocarcinoma elements in the tumor could be confirmed with cytokeratin 19 (CK19) and cytokeratin 7 (CK7) staining by immunohistochemistry. Generally, reports on these tumors were published decades ago mostly as small patients series or case reports. The first analysis of the prevalence of cHCC-CCAs in a series of patients with primary liver cancers was published by Allen and Lisa in 1949 [6], who found a prevalence of 14.2%. Later studies indicated a lower incidence. Taguchi *et al*. [7] mentioned a prevalence of 6.3% of the combined tumors among primary liver cancers.

In a SEER registry (1973-2003) comprising 22,583 patients with intrahepatic tumors, 282 patients had combined tumors (1%), 2,935 (13%) had iCCA and the remainder (85.7%) had HCC. In this study, the combined tumors had the poorest prognosis compared with the other tumors and the authors concluded that, when deciding therapy, “the combined tumors should be considered neither HCC nor CCA” [8]. A 1% prevalence of the combined tumors was also found by Berquist *et al*. [9], who retrospectively reviewed a population of 106,103 patients registered with primary liver cancers in another database, the US National Cancer Data Base (NCBD) (1998-2011). Most patients had HCC (90,499 - 85%), 14,463 (14%) had iCCA and 1,141 (1%) had combined tumors.

CHAPTER 30

Endoscopic Therapy in Cholangiocarcinoma

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Abstract: Cholangiocarcinoma is an aggressive tumor with a poor prognosis. In its early stages, the diagnosis is difficult and mostly incidental, for example during routine abdominal ultrasound we may see some indirect signs like biliary tree dilatation and rarely an intrabiliary three hypoechogenic lesion (extrahepatic cholangiocarcinoma) or focal hypoechogenic mass (intrahepatic cholangiocarcinoma).

The prognosis of the patients with metastatic and advanced unresectable extrahepatic cholangiocarcinoma is very poor. More than 50% of patients with jaundice are inoperable at the time of the first diagnosis.

The development of new minimally invasive techniques provides these patients a chance to symptoms relief, symptoms that sometimes impair the treatment (like jaundice), and a better quality of life.

Endoscopic treatment in patients with obstructive jaundice ensures bile duct drainage in preoperative or palliative settings. Relief of symptoms (pain, pruritus, jaundice) and improvement in quality of life are the aims of palliative therapy. Stent implantation by endoscopic retrograde cholangiopancreatography is generally preferred for long-term palliation. There is a vast variety of plastic and metal stents, covered or uncovered. The stent choice depends on the expected length of survival, quality of life, costs, and physician expertise.

Keywords: Biliary stents, Cholangiocarcinoma, Cholangioscopy, Endoscopic drainage, Endoscopic retrograde colangiopancreatography.

INTRODUCTION

Cholangiocarcinomas (CCAs) have a very high mortality rate worldwide [1]. Due to clinical asymptomatic behavior in the early stages in most of the cases, the lack of a standardized protocol for screening for early-stage disease and the limitations of using CA19-9 as a cancer marker, the diagnosis is delayed in most of the patients [1]. The ability to achieve a definite cytopathological or histopathological

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diagnosis in patients with suspected CCA remains at 26–80% [1 - 4]. CCAs are divided into 3 types: intrahepatic CCAs (iCCAs), distal CCAs (dCCAs) and perihilar CCAs (pCCCAs) or Klatskin tumors. The majority of CCAs are perihilar CCAs (60-75% of cases). Distal CCAs are present in 15%to 25% of cases and intrahepatic CCAs account for 5% to 15% of cases [3, 4]. Magnetic resonance imaging (MRI) plus magnetic resonance cholangiopancreatography (MRCP) is the preferred imaging modality as it can assess resectability and tumor extent with a high accuracy [3, 4]. Endoscopic ultrasound (EUS) and fine needle aspiration guided by EUS is a useful technique in diagnosis and staging of CCAs (Figs. **1** - **3**) and should be always taken into consideration for CCAs clinical management.

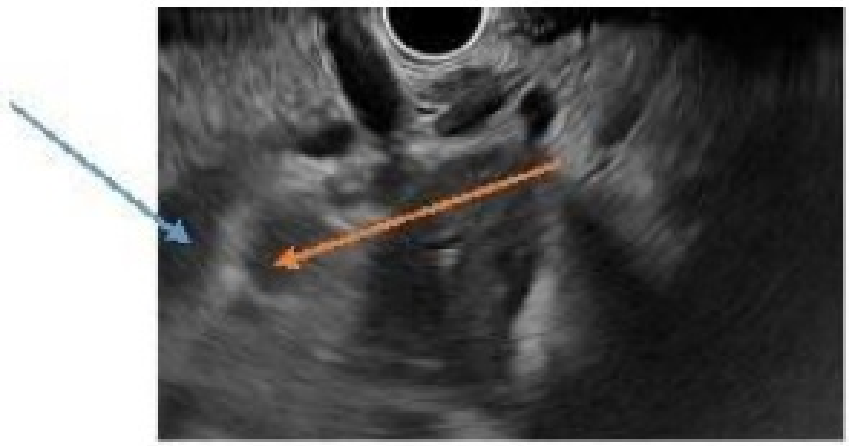

Fig. (1). Upper endoscopic ultrasound. Klatskin tumor. A hypoechoic tumoral mass (blue arrow) at the level of hepatic hilum can be seen. In the center of the tumor was placed a biliary stent (orange arrow).

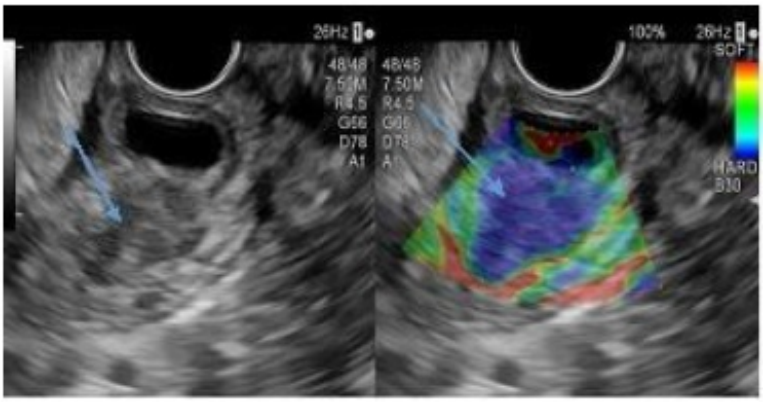

Fig. (2). Upper endoscopic ultrasound. Distal cholangiocarcinoma. On the left, a dilated distal common bile duct and a hypoechoic tumoral mass (blue arrow) can be seen. On the right is an image of the elastography examination with the tumoral mass colored in blue (hard tissue) (blue arrow).

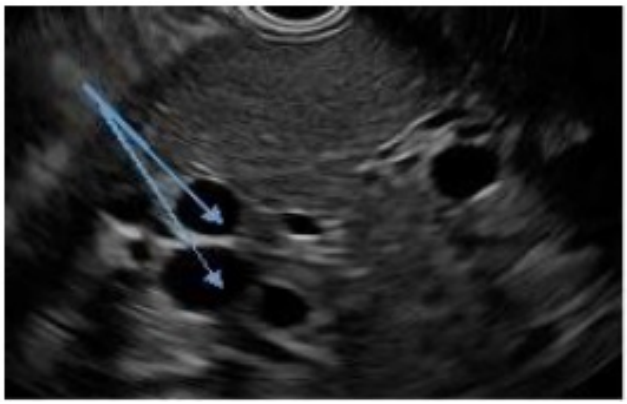

Fig. (3). Upper endoscopic ultrasound. The liver with dilated intrahepatic biliary ducts (blue arrows).

Also, in patients with obstructive jaundice, intraductal ultrasonography may be useful for the assessment of bile duct strictures and local tumor staging [5]. Peroralcholangioscopy (POC) allowing direct visualization of the biliary tract with targeted biopsy of suspicious lesions has shown to be a useful diagnostic procedure in the evaluation of biliary strictures (Figs. **4** and **5**).

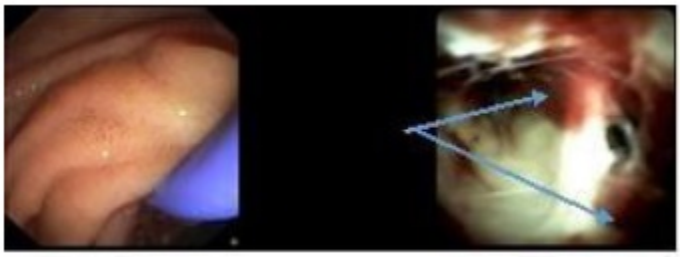

Fig. (4). On the left-endoscopic view, the Vater ampulla is accessed by cholangioscopy (in blue). On the right-cholangioscopic view with a tumoral mass at the level of the hilum (Klatskin tumor) (blue arrows).

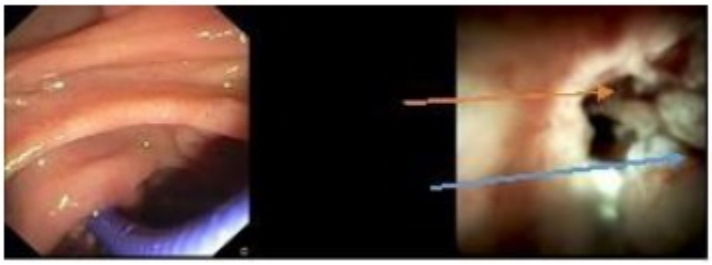

Fig. (5). On the left- endoscopic view, the Vater ampulla is accessed by cholangioscopy (in bleu). On the right-cholangioscopic view with a tumoral mass at the level of the hilium (Klatskin tumor)(blue arrow), the right biliary duct is invaded (orange arrow).

CHAPTER 31

Telemedicine in Hepatology, is it Time to Move Forward?

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Abstract: Telemedicine has been suggested as a potential alternative for specific medical situations and has even been embedded in some countries in their medical systems. Due to current time challenges, its involvement might be embraced more rapidly, since medical consultations have become difficult due to the COVID-19 pandemic. Patient's access to medical care might be hampered, thus, telemedicine might offer new opportunities for both the medical system as well as patients. Healthcare technology is under continuous evolution and the medical care is taking part not only with specific therapeutic medical devices, but also with remote medical information and monitoring. Patients suffering from chronic liver disease require personalized management plans according to their clinical and biological disease evolution, thus new alternatives should be considered for isolated locations. This may help us fight new global challenges that may surface in the years to come. In this chapter, we have discussed the current status of telemedicine and its implementation for the various liver diseases over the years.

Keywords: Electronic consultation, Hepatitis C, Liver disease, NAFLD, Store and forward, Telemedicine.

INTRODUCTION

Nowdays, when we feel utterly defenseless in front of the COVID-19 pandemic, the use of special medical care, although strongly associated with improved survival rate in patients with liver pathologies, is not always feasible or in accordance with each individual`s need in protection against the virus. Conventional approach regarding the healthcare services (one-to-one meeting between the patient and the medical personnel) is becoming rather difficult. The subject of telemedicine has not been exploited enough, creating knowledge gaps that were meant to be filled in this short amount of time given by lockdowns worldwide. Telemedicine is an innovative method that offers care remotely, using

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different types of electronic communication, with great advantages for all the parties involved, such as physicians, patients or even hospitals or governments.

Defined by the American Telemedicine Association (ATA), telemedicine is the exchange of medical information from one site to another *via* electronic communication to improve a patient`s clinical health status [1]. On the other hand, *TeleHealth* offers a more broadly general concept and includes other forms of devices to communicate and even remote patient monitoring. Because of the pandemic, telemedicine became an indispensable way to provide clinical care, used for the monitoring of patients, self-management plans, treating different conditions and even for educational purposes, limiting the exposure of patients and medical practitioners. This path of care delivery is needed to be embraced and integrated more efficiently in our routine, as new technologies develop, offering a wider range of medical procedures to be made and highlighting the inefficient resource utilization for diverse acts for which telemedicine promises alternatives.

According to a report from 2017, from 15 different leading causes of death in the United States, which were accountable for almost 80% of total deaths, chronic liver diseases and cirrhosis were on the eleventh place, climbing a place in the ranking report compared to 2016 [2]. Responsible for approximately 2 million deaths in one year worldwide [3], liver diseases ask for new strategies regarding medical care, quality of life and survival rate improvement.

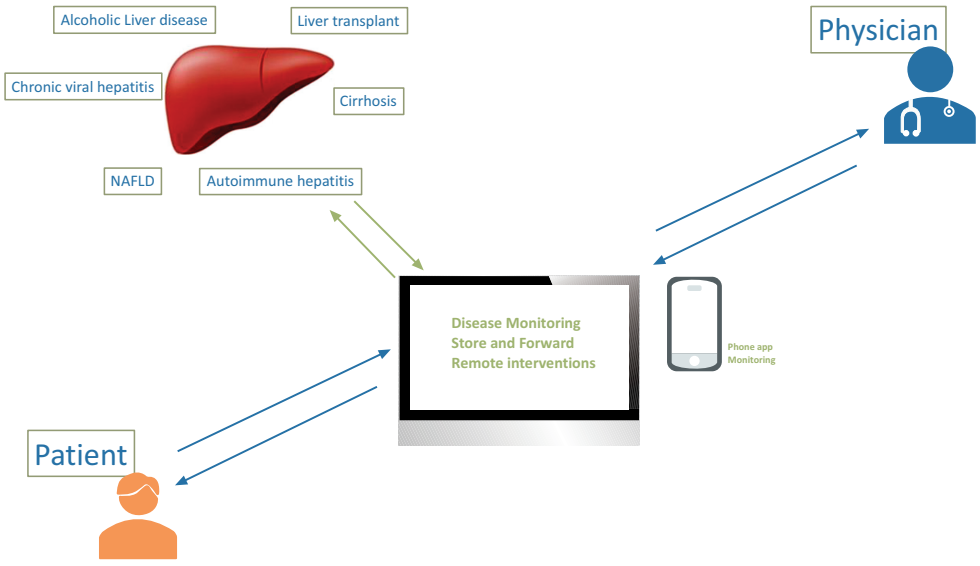

Fig. (1). Telemedicine concept in liver disease.

Electronic Consultation and Monitoring

Electronic consultation, although a term used for decades, has expanded, including a wide variety of means such as video, email, phone calls or even multimedia messages, used both by healthcare workers and by patients, facilitating the medical practice in inconvenient times for a proper traditional consultation. Telemedicine embraces an increase in its use in daily practice as technology improves and as access to a computer or a smartphone became almost universal. A study made by the Pew Research Center`s Internet and American Life Project found that in 2013 almost 91% of adults owned a mobile phone [4]. As patients become more connected to the digital sphere, it feels like a natural service to be addressed, looking for a more comfortable and easy access to a basic need.

HCV

With almost 71 million people suffering from chronic HCV infection, the prevalence remains high, with an estimated 1,75 million new individuals infected annually, highlighting the continuous rise of this disease [5]. Telemedicine has been used for many years for hepatitis C in rural and impracticable populations and one durable example is the ECHO program, Extension for Community Healthcare Outcomes, which targets specialized primary care providers to help develop skills through problem-based learning with video conferences to subspecialty health practitioners. This method is an effective tool to initiate treatment of HCV in incarcerated patients or those who are located in remote regions. The study also shows that there is no difference in SVR in patients who underwent telemedicine consultation or the traditional clinic visit. Adverse situations were estimated as lower in the ECHO program, compared to the on-site visit, 6.9% *versus* 13.7% [6], giving a new perspective regarding the management of hepatocellular carcinoma and cirrhosis. Collaboration with other medical specialties through telemedicine is another point of interest. Ensuring direct antiviral therapies may have adverse drug reactions, especially skin lesions, which may require a rapid dermatology consultation. Involving a teledermatology service would allow a unique collaborative model and may be the starting point for other potential therapies [7].

More studies emphasized that telehealth is as useful in managing HCV therapy as face-to-face consultation and sustained virologic response rates are not different (93% telehepatology *vs* 89% specialty care p=203) [8]. Thus, access to modern therapies may have similar outcomes and serve as valid options alternatives. Another study by Schulz *et al*. [9] suggests that by their telehealth use for HCV treatment, they saved a median of 634 km of patient travel which is definitely a

CHAPTER 32

Pathologies of the Peritoneum, Mesentery and Diaphragm

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Abstract: Pathologies of the peritoneum, mesentery and diaphragm are uncommon, making their diagnosis more challenging. We present the main issues in diagnosis and treatment.

Peritonitis represents acute inflammation of the peritoneum that can be caused by perforation, inflammation or gangrene of an intra- or retroperitoneal structure. The most frequently encountered peritoneal tumours are metastases originating in gastrointestinal, ovarian, lung, pancreatic and breast adenocarcinomas. Lymphomas can primarily or secondary affect the peritoneum.

There are two main categories of diseases affecting the mesentery: diseases that start from the mesentery (which can also affect neighbouring organs) and diseases that originate in neighbouring organs.

The most encountered hernias of the diaphragm are those occurring through the oesophageal hiatus, but there can also be congenital hernias (oesophageal, Morgagni and Bochdalek) or through post-traumatic defects. As in all other organs, primary diaphragmatic tumours can be classified as benign (cyst and lipomas) or malignant (rhabdomyosarcoma and fibrosarcoma), with other types of primary tumours than those aforementioned being very rarely seen.

Keywords: Ascites, Diaphragmatic hernias, Mesentery, Peritoneal tumours, Peritonitis, Pseudomyxoma peritonei, Tuberculosis.

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GASTROENTEROLOGICAL PATHOLOGIES OF THE PERITONEUM

Peritonitis

Secondary peritonitis (surgical peritonitis) represents acute inflammation of the peritoneum that can be caused by perforation, inflammation or gangrene of an intra- or retroperitoneal structure. Surgical therapy is often required, although more recently, several antibiotics have been shown to be beneficial in acute diverticulitis and appendicitis. Without treatment, the natural evolution is SIRS, a septic shock that can eventually be lethal [1].

The most common causes of secondary peritonitis are peptic ulcer, appendicitis, diverticulitis and gallbladder disease (although sterile bile leakage can be tolerated even in large volumes). Internal haemorrhage (ovarian cysts or tubal pregnancy rupture) can be a non-infectious aetiology; blood is highly irritative to the peritoneum, and the clinical presentation is similar [2].

The most common microorganisms (74%) responsible for secondary peritonitis are mixed aerobes and anaerobes, the most frequently encountered being *E. coli, enterococci, Clostridioides spp. and B. fragilis*. Fungal supra-infection is related to poorer outcomes, as is the presence of haemoglobin, barium, devitalised tissues or bile, all of which have the capacity to interfere with the immune response [1].

The cardinal signs of secondary peritonitis are intense abdominal pain and abdominal guarding. Pain can be absent or diminished in several situations, such as intoxication with ethanol, polyneuropathy, elderly patients and patients on glucocorticoids, NSAIDs or immune suppressants. Ascites can evolve without pain if the peritoneum is not involved in inflammation. Several signs can be noticed in the initial phase: fever (>37.5 C), abdominal immobility, tachycardia (that can be in response to pain, not to SIRS), the absence of hepatic dullness or rebound tenderness (Blumberg sign). Iliopsoas and obturator signs along with extensive rectal and pelvic examination can be helpful in identifying possible abscesses.

The hallmark of laboratory tests in this condition is leucocytosis with a left shift (immature WBCs/band cells), a lack of which might signify that the bone marrow is exhausted. Haemoconcentration, metabolic acidosis, prerenal azotaemia and Gram-negative septicaemia are also associated [3]. Ultrasound can help identify lesions such as large fluid collections, abscesses, bile duct enlargement and occasional pancreatitis. Abdominal and pelvic CT scans are the gold standard for diagnosis, as they can identify causes that will not necessitate surgical therapy (*e.g.*, diverticulitis).

Although laboratory and imaging studies can be helpful, the diagnosis can be confirmed only by laparoscopy or laparotomy when purulent fibrinous peritonitis is found. If the effluent has >500 WBCs/mm^3, positive Gram staining or higher than normal serum bilirubin or amylase, then the probability for secondary peritonitis is 90%.

The main therapeutic resources in secondary peritonitis are fluid resuscitation (recommended monitorisation in an ICU setting), broad-spectrum antibiotics and laparotomy or laparoscopy. Vasopressors should be avoided until the intravascular volume is replaced [4]. Empirical therapy with a broad-spectrum beta-lactam associated with aminoglycoside or 3rd/4th generation cephalosporines and metronidazole should be started, although in every case, a tailored therapy should be used if an antibiogram is available.

Surgical therapy should not be postponed and will need to be targeted to the cause, peritoneal toilet and prevention of recurrence [5]. The prognosis is variable, with poorer outcomes in elderly patients and those who develop MODS before the development of clinical manifestations of peritonitis. The mortality rate ranges from 10% in appendicitis and perforated duodenal ulcers to 50% in postoperative peritonitis, with an average of 14% [1].

Other Types of Peritonitis

Spontaneous bacterial peritonitis is a condition associated with ascites caused by cirrhosis or nephrotic syndrome. Its definition and treatment are currently highly protocolised [1].

Continuous ambulatory peritoneal dialysis is a frequent cause of bacterial peritonitis. It is estimated that this condition occurs 1,4 times/year in the peritoneal dialysis population. Most frequently, the isolated microorganism is *S. epidermidis* together with other commensal skin flora (secondary to poor patient education in regard to sterile dialysis techniques). Rarely, *M. tuberculosis* can be found (see below). Presentations include abdominal tenderness and pain, hypotension, diarrhoea, polydipsia, cloudy effluent with more than 100 neutrophils/mm^3 and the presence of microorganisms on Gram staining [4]. Antimicrobial therapy with vancomycin and 3rd generation cephalosporins should be started, but if there is a possibility to review an antibiogram, then it is recommended to follow that result. Heparin addition to the dialysis bag might lower the risk of postinfectious peritoneal adhesions.

Tuberculous peritonitis is considered a rare disease, but there is recrudescence, especially in immune-compromised patients, and it is increasingly an isolated disease, with only 20% of cases having pulmonary urogenital tuberculosis.

CHAPTER 33

Overview of Iron Products in Gastroenterological Anemia

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Abstract: The gastrointestinal tract is the site of iron absorption and also the most common localization of hemorrhage. The cause of iron deficiency anemia (IDA) is often chronic blood loss. One liter of blood contains approximately 500 mg of iron. Despite the representative increase in the absorption rate, the loss in this case cannot be compensated and the body's iron reserves decrease. Iron deficiency leads to disruption of hemoglobin synthesis: iron deficiency anemia.

The etiology of iron deficiency anemia can be widely categorized into: decreased iron uptake (malabsorption due to gastrointestinal disease or surgery, inadequate diet) and increased iron use/loss (blood donation, pregnancy, acute/chronic blood loss, rapid growth during childhood, menses). IDA can be the first sign of celiac disease, gastritis and occult GI malignancy.

The first choice treatment (after finding and disposal of the cause of the bleeding) consists of the oral administration of Fe II compounds. It can take several months to replenish iron reserves. Oral administration, however, has the major advantage that it is difficult, even impossible to overload the body with iron, because the absorption is regulated through an intact mucosa (enteral blockage). Only when adequate oral replacement is not possible, parenteral administration of iron compounds is indicated. There are potential side effects: administration of persistent pain at the injection site (i.m. administration) and facial flushing, hypotension, anaphylactic shock (i.v. administration).

Keywords: Anemia, Blood loss, Hemoglobin, Hemorrhage, Iron.

INTRODUCTION

Iron is an important component of myoglobin and hemoglobin and many enzymes involved in redox reactions and energy supply. It plays an essential role in both

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the storage and transport of oxygen and oxidative metabolism as well as in growth cells and proliferation. Most plasma iron is intended for bone marrow erythropoiesis. The absorption of dietary iron from the duodenum is an elaborate process, controlled by different proteins and it is determined by the need for iron in the body, the concentration of iron in the intestinal lumen and anatomical cell wall integrity.

Iron deficiency is a dominant cause of anemia, which affects over half a billion people around the world. The greatest iron deficiency is manifested in newborns and children and may be caused by abnormal absorption of iron from the gastrointestinal tract, by reduced bioavailability, which can be altered by increasing gastric pH, the presence of inhibitors or disturbance of intestinal structure (celiac disease, Crohn's disease). The gastrointestinal tract is the site for iron absorption and also the most common localization of hemorrhage. Other causes of bleeding are gastroduodenal ulcer, hiatal hernia, gastric parasite infestation and Helicobacter pylori infection.

Women, infants, children and adolescents need iron to develop muscle mass. A baby has 70-80 mg of iron per kg at birth, of which 2/3 is iron hemoglobin. Iron ingested in food is present in various forms. Trivalent Fe^{3+} is virtually unabsorbable in the small intestine, and bivalent Fe^{2+} is much better absorbed. Absorption is especially effective in the form of heme (present in hemoglobin and myoglobin). In the cells of the intestinal mucosa these iron complexes (hemoglobin, myoglobin) are very well absorbed and represent the physiological source of iron, before the appearance of iron-enriched foods.

IRON DEFICIENCY ANEMIA AND ASSOCIATED CONDITIONS IN GASTROENTEROLOGY

The cause of iron deficiency anemia (IDA) is often chronic blood loss. One liter of blood contains approximately 500 mg of iron. Despite the representative increase in the absorption rate, the loss in this case cannot be compensated and the body's iron reserves decrease. Iron deficiency leads to the disruption of hemoglobin synthesis: iron deficiency anemia.

The etiology of iron deficiency anemia can be widely categorized into: decreased iron uptake (malabsorption due to gastrointestinal disease or surgery, inadequate diet) and increased iron use/loss (blood donation, pregnancy, acute/chronic blood loss, rapid growth during childhood, menses). IDA can be the first sign of celiac disease, gastritis and occult GI malignancy.

GI bleeding is a usual cause of IDA, whether the bleeding is chronic or acute. Patients may present signs like blood in their stools or just maroon-colored stools,

but symptoms like the above mentioned are often unrecognized. GI bleeding can occur at any location within the GI tract and can be associated with a variety of lesions. IDA is prone to occur in patients taking chronically nonsteroidal anti-inflammatory drugs or aspirin. By endoscopic evaluation of the GI tract, the site can be visualized for those with angiodysplasia or other structural contusions.

Esophagitis and Hiatal Hernia

One of the established causes of iron deficiency anemia is gastric bleeding in hiatal hernia or Cameron lesions. There has been reported an incidence from 8% to 42%, with a moderate of 20%, of IDA for types of hernia [1]. Suggested causes of hernia that are related to iron deficiency anemia are erosions, gastro-esophageal acid reflux and mechanical trauma plus esophagitis [1]. Even if during the endoscopy, there are no lesions visible, a large hiatal hernia can still be a possible cause of iron deficiency anemia with unidentified etiology. Treating and preventing recurrences of IDA can properly be made with proton pump inhibitor (PPI), even in larger hiatal hernia [1].

Nonvariceal Upper GI Bleeding

A retrospective study recently made acknowledged that more than 85% of the patients accepted by the hospital with nonvariceal acute upper gastrointestinal bleeding (disorder associated with a rate of mortality of 3% to 15%), were anemic at the time of release [2]. There are rare studies analyzing the risks associated with anemia and the clinical impact after nonvariceal acute upper gastrointestinal bleeding, but one of them reported that patients that had Hb values $\geq$ 10 g/dL got two-fold lower risks of mortality and re-bleeding than patients that had Hb values $\leq$ 10 g/dL [3]. A placebo-controlled trial, established the clear benefit given by oral and intravenous iron supplementation on patients with iron deficiency anemia after nonvariceal acute upper gastrointestinal bleeding. Regarding iron stores, they were restored with intravenous iron supplementation more effectively than by oral iron administration. However, only 16% of the patients that were anemic at the time of discharge from the hospital with nonvariceal acute upper gastrointestinal bleeding received a suggestion of oral iron supplementation, but intravenous iron administration was not considered.

NSAID-associated Blood Loss

The GI injury can include bleeding that can often result in hospitalization. The upper and lower GI injuries can be associated with nonsteroidal anti-inflammatory drugs (NSAIDs) administrations. From low aspirin doses as well as NSAIDs to $\geq$ 1800 mg/d aspirin doses, they increase mean fecal blood loss from 0,5 mL/d ($\geq$ 2.5 mg iron loss/d) to $\geq$ 5 mL/d (*i.e.*, $\geq$ 2.5 mg iron loss/d). Long term use of

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