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GASTROVIGILANCE OF GASTROINTESTINAL AND HEPATIC CONDITIONS

Table of Contents

Introduction

Gastrointestinal (GI) disorders are the source of substantial morbidity and mortality, and high healthcare costs.(1) They are common in general practice and account for about 10% consultation of general practitioners.(2) Diagnostic errors in GI disorders can seriously affect patients, health professionals, and the healthcare system, especially if they are malignant or rapidly evolving as they can cause great harm to patients if they remain undiagnosed.(3)

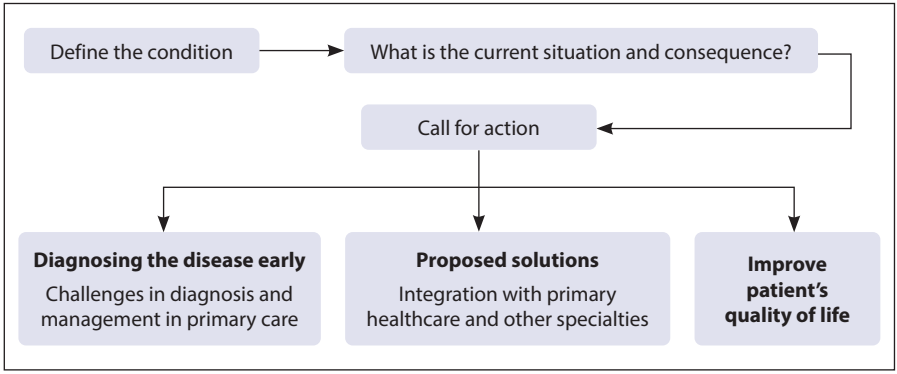
Several symptoms that overlap with GI and non-GI conditions create GI mimics and can ultimately lead to misdiagnosis. Gastrointestinal cancers are often misdiagnosed as digestive disorders or other stomach ailments, whereas gastroesophageal reflux disease may manifest as atypical, respiratory, nasopharyngeal, or cardiac symptoms that could delay treatment.(4) Reaching the final diagnosis of celiac disease can take quite long, and can take >9 years to diagnose from the onset of symptoms.(5) Similarly, granulomatous autoimmune disorders due to similar presentation are often misdiagnosed as inflammatory bowel disease.(6)

Primary care physicians can play a central role in identifying and managing patients at risk.(1) Failure of taking appropriate patient history, family history, travel history, or drug history, are some of the common errors in managing GI diseases. Sometimes treatments are prescribed to the patients without completely assessing them and a final diagnosis is derived, which leads to treatment errors, or delay in referring patients to better treatment centers or performing surgery; these can lead to wasting patient's crucial years.(5, 7) Hence, early diagnosis and effective management of GI disorders is needed.

Several approaches such as disease awareness programs, trainings for identification, recognition of risk factors, alarm signs and symptoms, decision checklist, management approach algorithms, and referral pathways could be an effective support system.(8) This entire scenario has been termed as "gastrovigilance".

The objective of gastrovigilance is to raise awareness on diagnostic challenges associated with GI and hepatic conditions, counter diagnostic and treatment challenges, analyze as well as present critical barriers and gaps that hinder access to the best practices, and help develop a shared-care model. Here, a summary of literature supporting the concept of gastrovigilance for GI and hepatic conditions is presented. The process of the gastrovigilance is shown in Figure 1.

Figure 1: Process of Gastrovigilance



Literature search was performed using PubMed/MEDLINE and Google Scholar search engines. Literature published in English and supporting the concept of gastrovigilance for GI and hepatic conditions was included. From a wide range of GI conditions, the list included in this booklet was narrowed down by a group of senior gastroenterologists from India. Draft of the summary of literature supporting the concept of gastrovigilance for GI and hepatic conditions was shared with these experts after a virtual/expert group deliberation. In this booklet, common challenges or errors in managing these conditions in Indian clinical practice have been included along with evidence-based practical approaches.

Gastroesophageal Reflux Disease

Challenges in Diagnosis and Treatment

Clinically, gastroesophageal reflux disease (GERD) manifests with symptoms of heartburn and regurgitation in addition to atypical manifestations such as chest pain, dental erosions, chronic cough, laryngitis, or asthma.(4, 9, 10) Diagnosis of GERD remains imprecise due to the lack of a gold-standard test, and the diagnosis is solely based on the presenting symptoms or in combination with other factors such as responsiveness to anti-secretory therapy, esophagogastroduodenoscopy, and ambulatory reflux monitoring.(11) In India, use of the term "indigestion" usually tends to delay the identification of any GI disorder such as GERD, functional dyspepsia, irritable bowel syndrome, or malabsorption in patients.(12) Differential diagnosis may be required for coronary artery disease, peptic ulcer disease, non-ulcer disease, esophagitis, achalasia, gastroparesis, gastric neoplasm, and rumination syndrome.(11) Kessing *et al.* showed that clinical presentation and diagnostic work-up of patients with achalasia can overlap with GERD, and can be mistaken occasionally for GERD; however, this can be avoided by performing esophageal manometry in all patients undergoing surgical fundoplication.(13)

Over the years, the mainstay in GERD management has been lifestyle modifications and the use of proton pump inhibitors.(14) Despite the availability of effective treatment, considerable proportion of patients with GERD experience inadequate disease management.(15,16) Refractory GERD is becoming increasingly common; hence, there is a need for developing a tailored approach for its management.(17) Alarming symptoms such as weight loss, dysphagia, or anemia help identify patients who need to be investigated to exclude malignancy, although 15–50% of the of dyspeptic patients with gastric cancer do not have these symptoms. Therefore, endoscopic evaluation is recommended for patients, especially the elderly (>55 years of age).(12) Studies have demonstrated that poor agreement between patients and physicians in assessing severity of GERD symptoms leads the physicians to underestimate symptom severity.(18, 19)

Evidence-based Practical Approach

Taking a detailed patient history to understand the predominant cause is an important part of managing GERD.(20) In older patients or patients with alarm symptoms such as *Helicobacter pylori* infections, weight loss, dysphagia, and anemia, a prompt referral for endoscopy and further investigations should be made.(1) The primary care physician should ensure treatment compliance and adherence *via* patient-physician communications.(21, 22)

Dyspepsia and *Helicobacter pylori* Infection

Challenges in Diagnosis and Treatment

Globally, 7–45% of the patients remain uninvestigated for dyspepsia and 11–29.9% for functional dyspepsia.(23) This may be possible as >25% of individuals have overlapping symptoms between dyspepsia and gastric esophagus reflux syndrome,(24) and >70% of the patients with dyspeptic symptoms have no underlying cause detected at endoscopy.(25) Esophagitis is more prevalent in the Western populations than Asians (25% *vs.* 3%), whereas the opposite is true for peptic ulcer disease (6% *vs.* 11%), respectively and this difference could reflect variations in the prevalence of *H. pylori* infection.(1,25) Moreover, epidemiology of dyspepsia and underlying diseases changes frequently with time.(26) Only 1–3% of infected individuals develop malignant complications, and *H. pylori* accounts for 15% of the total cancer burden globally and up to 89% of all gastric cancers are attributed to it.(27)

Dyspeptic symptoms are not a good predictor of the underlying endoscopic findings; however, guidelines recommend that patients with alarming symptoms should be referred for upper gastrointestinal endoscopy as these may be suggestive of malignancy.(1) Moreover, global studies reported a lack of knowledge regarding established diagnostic and treatment recommendations for *H. pylori* infection among primary care physicians.(28-30) The absence of guidelines specific to the Indian sub-continent makes it difficult to further manage the situation.(31) There is a considerable controversy and confusion regarding whom and when to treat for *H. pylori* infection in a country where 49.94–83.30% of the population could be harboring the infection.(32) Further, as treatment is associated with significant side effects and cost, it is debatable whether all those infected need to be offered treatment, especially as perceived health priorities could be different in resource constraint and asymptomatic individuals.(33) Some favor the "test and treat" for *H. pylori* in symptomatic patients diagnosed with peptic ulcer disease who are infected; the treatment decision for those at high risk for gastric malignancy could be understandable,(12) but the issue gets more blurred on being confronted with all dyspeptic patients with *H. pylori* infection, and furthermore, for subjects with symptomatic dyspepsia who have not been tested for *H. pylori* infection.(34)

Common errors seen in Indian practice are over testing, overmedication, initiating drugs without understanding resistance rates of antibacterial agents, lack of patient education regarding eradication regimen to ensure adherence and compliance, and most importantly, the failure to perform tests to confirm eradication post treatment.

Downstream consequences of failed treatment include clinical complications related to persistent *H. pylori* infection, repeated exposure to antibiotics and high-dose acid suppression, generation of antibiotic resistance in *H. pylori* and other organisms, as well as associated direct and indirect costs to the healthcare system.(34)

Evidence-based Practical Approach

Dyspepsia is complex, with several possible etiological mechanisms, which makes it difficult to decide on a uniform algorithm of management.(35) Clinical approach to a patient with dyspepsia should identify trigger factors in the environment or food, symptom pattern over time, and alarm symptoms, attempt to identify psychological stressors, implement education support, and provide reassurance to the patient.(12)

Initial management of functional dyspepsia should include positive clinical diagnosis, minimizing investigations, and reducing unnecessary repeated testing. It is best managed through a multifaceted approach using dietary and lifestyle interventions, acid suppression therapy, psychotherapy psychotropic medications, and establishing a good physician-patient relationship.(36) It is reasonable to offer a patient without alarm symptoms an initial 4 weeks trial with anti-secretory drug, proton pump inhibitors being the current favorite. Some with partial response can be offered another 4 weeks of a double-dose proton pump inhibitor and or with an additional prokinetic drug. If this fails, they should be referred to a specialist for further evaluation. Moreover, they should also be referred to specialists if they have an onset of alarm symptoms, severe pain, and there is a failure in resolving symptoms or to substantially improve their condition.(12)

Patients with progressive/persistent symptoms or disease require evaluation and treatment; if *H. pylori* infection is present, a triple drug combination therapy using two antibacterial agents seems to have the widest scientific evidence. However, the choice of antimicrobials needs to be based on local sensitivity reports and patient tolerance, and adequate doses and duration should be ensured. Commercially available anti-*H. pylori* kits vary considerably in composition, cost, and dosing. Although they make it easier for patients to take the course of therapy, inadequate dosing and local resistance could compromise their effectivity.

Inflammatory Bowel Disease

Challenges in Diagnosis and Treatment

For primary care physicians (PCPs), both early diagnosis and proper treatment are a real challenge in their effort to ensure the best quality of life in patients with inflammatory bowel disease (IBD).(37) Symptoms of Crohn's disease (CD) and ulcerative colitis (UC) are very similar; CD affects the mouth, anus, and all layers of the intestine, whereas UC compromises only the rectum and colon.(38, 39) Ulcerative colitis is associated with blood in stool, severe pain, and diarrhea, while CD also poses a risk of bleeding in severe cases. More than 50% of the patients with CD suffer from folate and vitamin D deficiency, whereas >50% of the patients with UC suffer from iron deficiency.(38) Early diagnosis of IBD is an important factor related to favorable response to treatment.(40)

An accurate diagnosis of UC and CD is mainly based on endoscopic and histological examinations.(41) In UC, abdominal pain is usually mild and physical examination usually reveals tenderness in the left iliac fossa of the suprapubic area, whereas in CD, pain is usually located in right lower abdomen with/without an accompanied palpable mass – A finding that could be difficult to differentiate from an attack of acute appendicitis. Pain can also be diffuse in other cases and may be accompanied by bloating, abdominal distension, and nausea or vomiting. It is particularly important for PCPs to recognize anal disease and oral manifestations, on the basis of which one can make correct clinical diagnosis for CD.(1) Recognition of extra-intestinal manifestations of IBD such as arthralgia, uveitis, and erythema nodosum, the presence of which could increase the possibility of early diagnosis, could help avoid unnecessary referrals to other specialties.(42)

Evidence-based Practical Approach

Optimal management of IBD requires a multidisciplinary approach with many key players including PCPs, general practitioners, surgeons, radiologists, pathologists, psychologists, rheumatologists, and dietitians.(43, 44) The PCPs play an active role in monitoring patient's treatment compliance and if necessary, for making dose adjustments in close co-operation with the specialist.(45) Moreover, PCPs must recognize the adverse effects of aminosalicylates, corticosteroids, or immunosuppressive drugs used in IBD early:

- Usage of steroids is prevalent in patients with moderate or severe IBD; thus, particular attention must be given to prevent and treat osteoporosis (e.g., calcium and vitamin D supplementation), and infections in people who receive corticosteroids for a long period.(46)
- Also, patients receiving immunosuppressive agents (azathioprine and 6-mercaptopurine) and immunomodulators (infliximab and adalimumab) should be subjected to regular blood tests to identify infections early and treat them appropriately. Physicians must also adopt preventive strategies.(47)
- Preventing infection is a key management strategy, which includes recognizing risk factors, monitoring clinical symptoms, scrutinizing laboratory results (tuberculosis and Hepatitis B), vaccination (for influenza and pneumococcus), and patient education.(44, 47)

The patient-physician relationship is the cornerstone of care in managing IBD and there is a need to improve communication strategies for enhancing IBD outcomes:(48, 49)

- One important factor that contributes towards improved quality of life in patients with IBD is educating them about the disease.(48) Expert consensus of UC reported that patients should be more involved in managing their disease, which will lead to improved adherence and disease outcomes.(50)
- Emotional state of patients with IBD keeps changing; therefore, the treatment should focus not only on disease activity but also on psychosocial problems that the PCP needs to recognize early and address accordingly.(51) Primary care physicians should utilize health-related quality of life (HRQoL) parameter tools to enhance the understanding of the disease impact and effects of treatments on the disease.(52)

Irritable Bowel Syndrome

Challenges in Diagnosis and Treatment

Awareness of alarm symptoms of irritable bowel syndrome (IBS) is crucial to facilitate early diagnosis.(53) Diagnosing IBS can be challenging and uncertain for several reasons. These reasons include no consistent biological marker for IBS that leaves physicians relying on patient symptoms alone to make the diagnosis, symptoms of IBS that are often difficult to quantify objectively, and many organic conditions that masquerade as IBS. Frontline healthcare providers often order a wide variety of tests with low diagnostic yield, and this can have significant economic implications.(54)

The UK General Practice Research Database showed that about 10% of the patients with inflammatory bowel disease (IBD) are misdiagnosed and in 3% of the cases, this may persist for ≥5 years.(55) There is a lack of awareness and knowledge for managing IBS among primary care physicians (PCPs).(56, 57) Formal diagnostic tools including the Rome IV and Manning criteria are available; a minority of PCPs are aware of these tools (2–36%) and even lesser (0–21%) use them.(56) Patients in IBD remission complaining of IBS-like symptoms still pose a diagnostic and therapeutic dilemma. Nevertheless, attempts to classify these symptoms as "true IBS" or subclinical IBD are insufficient as they do not account for all available observations.(58) Hence, more investigations in the area of overlapping of IBS and IBD are needed as they may lead to a consensus on this issue, and provide a suitable and most effective therapy for these individuals.(59) Moreover, patient characteristics and attitudes differ substantially according to the severity of their diarrhea-predominant IBS symptoms, indicating a need for developing a symptom severity index.(60) This warrants further attention by the Rome IV Committees as part of their multiaxial work-up of patients with functional disorders.(61) A distinct need for improved pharmacological and supportive management of patients with IBS having diarrhea is also required in order to reduce symptom burden, particularly in those with more severe disease.(60)

Treatment of IBS relies on a positive diagnosis, reassurance, lifestyle advice, and pharmacological and psychological therapies.(62, 63) However, many patients suffer ongoing symptoms and remain unsatisfied with their treatment. Bulking agents and antispasmodics are the most commonly prescribed medications.(64) Contrastingly, the role of lactose or gluten dietary restriction in IBS treatment remains a subject of ongoing research without any high-quality evidence.(65) Primary care physicians are increasingly confronted with questions regarding suitability (or otherwise) of probiotics, but their familiarity with probiotics is limited. At the same time, the public is exposed to widespread claims for probiotics, with various products to choose from.(1)

A systematic review by Hungin *et al.* indicates that specific probiotics are beneficial in certain lower gastrointestinal problems, although many did not report their benefits, which could be possibly due to inclusion of new, less efficacious preparations.(66) Specific probiotics can relieve lower gastrointestinal symptoms in IBS and prevent diarrhea associated with antibiotics and *Helicobacter pylori* eradication therapy.(66)

Evidence-based Practical Approach

The clinical literature suggests a high prevalence of IBS-type symptoms in patients with IBD. An individualized and case-based approach to IBS management is crucial.(67, 68) It has been accepted that medications are largely ineffective in symptom management, and physicians are expected to design a long-term and non-pharmacological approach to help the patient adjust to their chronic illness. Moreover, general advice on healthy eating and lifestyle is recommended as the first-line approach in dietary management of IBS despite limited evidence for its beneficial role.(65, 69)

In summary, IBS is a chronic condition that requires long-term symptom management, which often frustrates both the patient and the physician.(70) A patient-centric approach with emphasis on effective communication is essential when helping patients manage IBS and in dealing with illnesses in general.(71)

Chronic Constipation

Challenges in Diagnosis and Treatment

The physician may commit common errors in drawing a diagnosis owing to a lack of assessment of complete clinical history, medication history, and comorbid conditions. The terms "constipation" or "bowel movement" are often misunderstood for "attempts at defecation" or "fragmented defecation" as they are not properly communicated by the patient to their physician. Thus, it is important to clarify the meaning of constipation, and physicians should investigate all attempts to defecate cases and give weightage to the feeling of incomplete evacuation before providing diagnosis. The feeling of incomplete evacuation was reported by 98.8% of the patients, and might feel like constipation to Indian subjects.(72) Chronic constipation can be difficult to diagnose, and can be divided into two groups, primary and secondary constipation based on its etiology:

- Primary constipation includes constipation predominant irritable bowel syndrome (IBS-C), functional constipation, slow transit constipation such as myopathy, neuropathy, and functional defecation disorders.(73)
- Secondary constipation may be a result of metabolic disorders (hypercalcemia, hyperthyroidism, and diabetes), medications (calcium channel blockers or opiates), primary colonic disorders (bowel obstructions, myopathies, anal stenosis, anal atresia, megacolon, cancer, and proctitis), psychiatric disorders (depression, eating disorders, and obsessive disorders), and neurological disorders (multiple sclerosis, spinal cord injury, autonomic neuropathy, and Parkinson's disease).(73-76)

Evidence-based Practical Approach

The first few steps of diagnosing constipation are: Gathering detailed medical history and physical examination with particular attention to anal examination. This primary evaluation should simplify identification of causes of constipation or confirmation of alarm symptoms, if present. The exact medical history should answer the questions about consistency, frequency, size of stools, sense of incomplete evacuation, abdominal bloating, straining, elongated or failed attempts to defecate, and the use of digital disimpaction.(77) Change in living conditions, medicaments, lifestyle changes, and duration and onset of symptoms are also relevant.(73)

Diagnosis of constipation is based on predefined symptoms and the Rome criteria; so the physicians should be guided accordingly,(73, 78) after which, they may use latest technologies for diagnosing constipation.(73) For differential diagnosis of functional constipation and IBS-constipation, presence of abdominal pain or discomfort relieved by defecation (typical of IBS) from the Rome IV criteria is needed.(73)

First-line therapy is a non-pharmacological approach. The main role of the physician is to educate the patient about the importance of diet, fiber intake, and physical activity.(73) Notably, there is a wide range of pharmacological agents such as laxatives, secretagogues, serotonergic agonists, and many other medications; however, every drug has its advantages and disadvantages, and they should be considered before prescribing them. Despite the wide range of therapeutic options, almost half of the affected patients report a lack of complete relief from their symptoms.(79) For cases refractory to medical treatment, referrals for further diagnostic evaluations may be warranted to assess alarm symptoms. If pharmacologic treatment fails, the definitive solution for constipation might be surgery.(73) To improve management of ambulatory patients with chronic constipation, a practical management algorithm using a multistep approach has suggested favoring early introduction of combined therapies and a long-term step-down strategy to the lowest satisfactory regimen.(79)

Celiac Disease

Challenges in Diagnosis and Treatment

Around 50–90% of the patients with celiac disease (CeD) remain undiagnosed.(80) Untreated CeD carries the risk of increased mortality from associated lymphoproliferative and gastrointestinal cancers.(80, 81) This may be due to misidentification of underlying etiology at the primary care physician level. Bacterial overgrowth or cereal intolerance can lead to similar abdominal symptoms. Diagnosing CeD is often missed in the elderly because the symptoms non-intestinal and are often attributed to their comorbidities.(81)

Evidence-based Practical Approach

Primary care physicians must cultivate a high index of suspicion for CeD and bear it in mind as a differential diagnosis in many clinical situations:

- Patients with signs or symptoms indicating CeD (chronic/intermittent diarrhea, persistent/unexplained gastrointestinal symptoms [nausea and vomiting], prolonged fatigue, recurrent abdominal pain, cramping/distension, sudden/unexpected weight loss, and unexplained iron-deficiency anemia) should be subjected to serological test for immunoglobulin A anti-tissue transglutaminase antibody.(1)
- Along with a systemic or locally detectable allergic response to wheat allergens, a variety of non-immunological mechanisms also need to be considered in the differential diagnosis of patients with wheat or cereal intolerance.(82)

Generally, laboratory investigations (serology and HLA diagnosis), transabdominal ultrasound, endoscopy, and histology are principally used in addition to thorough patient history.(82) Adhering to guidelines may reduce the burden of CeD misdiagnosis.(83) The symptoms, mortality, and risk for malignancy of CeD can be reduced by adhering to a gluten-free diet.(84)

Gastrointestinal Cancers

COLORECTAL CANCER

Challenges in Diagnosis and Treatment

Early detection (Dukes' A and B) represents the only chance for increasing the 5-year survival rates.(85) However, as majority of colorectal cancers (CRCs) appear as a result of pre-existing colorectal polyps, early endoscopic detection and their removal diminishes the incidence of neoplasm in countries where prevention programs for CRC are applied.(86)

Common symptoms of CRC include altered bowel habits, rectal bleeding, constipation, diarrhea, and unexpected weight loss, with rectal bleeding being the most important symptom.(87) Screening of CRC is broadly based on fecal tests (fecal occult blood testing, fecal immunohistochemical testing, and sDNA) and imaging tests (sigmoidoscopy, colonoscopy, double-contrast barium enema, and computed tomography colonography). The fecal occult blood testing remains a valuable screening test for CRC and colonoscopy remains the gold standard for investigating and managing bowel pathology. However, high-quality colonoscopy requires both technical expertise and thorough inspection of the colonic mucosa.(88) Computed tomography colonography is widely accepted in western countries, and its use is rare in India due to limited technical expertise.(87) Guidelines recommend that all men and women should be screened for CRC beginning at the age of 50 years (or earlier if they are at an increased risk because of a family history of CRC), and it has been generally accepted that successful screening starts with primary care.(89)

Primary care physicians (PCPs) could play an essential role in persuading people to participate in screening programs and supporting patients suffering from CRC.(90) In Asia, CRC testing compliance is quite low, probably owing to less knowledge of CRC symptoms and risk factors. An interesting study found that perceived health, psychological and access barriers to CRC testing in Asian countries is high. It is of interest that physician's recommendation might increase testing.(86) However, physicians mainly recommend testing only in individuals with positive family history for CRC. Thus, the role of PCPs differs according to the screening scheme in a particular country/region. Experienced PCPs use brief CRC screening promotion scripts, including counseling techniques that improve CRC screening performance.(91)

Evidence-based Practical Approach

A systematic review suggested investigation of rectal bleeding or anemia in primary care patients, irrespective of other symptoms. The risks from other single symptoms are lower, although multiple symptoms also warrant investigation.(92) Improvement in CRC screening rates largely depends on the efforts of PCPs to implement effective systems and procedures for screening delivery.(86) Most patients with CRC seek medical advice from PCPs regarding the presence of relevant symptoms; thus, it is crucial to evaluate important symptoms that could lead to correctly diagnosing underlying CRC.(1) Moreover, positive engagement of PCPs with CRC screening is required to overcome barriers and reach acceptable levels of screening rates.(86) Adequately trained physicians should be able to provide safe screening using colonoscopy; they should also be trained to detect cancer and precancerous lesions.(88, 93-96)

GASTRIC CANCER

Challenges in Diagnosis and Treatment

Cure is only achieved with diagnosis at an early stage. However, the challenge in diagnosing at an early stage is the lack of specific symptoms.(97) *Helicobacter pylori* infection is a well-established carcinogen for gastric cancer (GC); thus, in developing countries, high *H. pylori* infections due to poor standards of hygiene are responsible for patients developing gastric cancer. Moreover, gastrointestinal (GI) investigations are not performed optimally by PCPs.(98, 99) As dyspepsia is very common in a significant patient cohort with early GC, it is challenging for PCPs to decide which patients should be referred early for further investigation.(100) While managing suspicious cases for upper GI malignancy, treating dyspeptic symptoms with acid suppression therapy prior to gastroscopy masks delays detection of gastric and esophageal adenocarcinoma on endoscopy.(101, 102)

Evidence-based Practical Approach

Given the fact that gastric malignancy is rare before the age of 40 years, and its incidence increases steadily thereafter, referral for endoscopy is recommended for all patients (aged ≥45 years) with new-onset dyspepsia.(103) Moreover, alarm symptoms such as weight loss, dysphagia, signs and symptoms of upper GI bleeding, anemia, and persistent vomiting are likely to be more frequently associated with upper GI malignancies and most guidelines recommend immediate endoscopy in all patients presenting with these symptoms.(104)

Thus, identifying patients with high-risk factors should be a part of their routine clinical practice.(105, 106)

According to the Asia-Pacific evidence-based consensus and a Brazilian consensus on GC prevention, a strategy of *H. pylori* screening and eradication in high-risk populations may reduce GC incidence.(105, 106) Moreover, differential diagnosis of iron-deficiency anemia should be performed. Guidelines also recommend that upper and lower GI investigations should be considered in all postmenopausal female and all male patients with iron-deficiency anemia.(107) There is endoscopic evidence showing that early malignancy within the gastric mucosa may be healed with acid suppression therapy; thus, prescription of proton pump inhibitors before endoscopy, particularly in patients older than 45 years, should be avoided prior assessments.(108)

ESOPHAGEAL CANCER

Challenges in Diagnosis and Treatment

Progressive dysphagia and weight loss are the most common presenting complaints of patients with esophageal cancer (EC). Evidence shows that diagnosis of EC is often delayed by a period of 1–11 months from the onset of symptoms.(109, 110) This may be due to lack of identification of risk factors and relying on limited symptoms such as dysphagia.(1) About 1 in 300 patients with Barrett's esophagus (BE) is estimated to develop EC each year.(111) There has been an association between adenocarcinoma and BE due to chronic inflammation from gastroesophageal reflux disease (GERD).(111, 112)

Evidence-based Practical Approach

Patients presenting with progressive dysphagia and weight loss should undergo urgent endoscopy, and the focus should be on assessing other alarm risks responsible for EC.(1) Detection of precancerous changes should be considered in smokers, alcoholics, and patients with other aerodigestive cancers including oral cancers as the risk factors are common for both.(113) Differential diagnosis for adenocarcinoma and BE should be done in patients with GERD-related chronic inflammation. Endoscopic screening for BE is suggested in patients with chronic GERD symptoms and multiple risk factors (at least three of the following factors: Age 50 years or older, white race, male sex, and obesity).(111, 112)

Hepatic Disorders

VIRAL HEPATITIS

There are five main strains of the hepatitis virus, referred to as types A, B, C, D, and E.(114) An estimated 354 million people worldwide live with hepatitis B or C, which may lead to chronic disease in hundreds of millions of people; together they are the most common cause of liver cirrhosis, liver cancer, and viral hepatitis-related deaths.(114) Differential diagnosis must be considered as many other viral infections can affect the liver, right from mild asymptomatic elevations of aminotransferases to fulminant hepatic failure.(115) Exposure to contaminated blood through injection drug-use is a primary risk factor for both hepatitis B virus (HBV) and hepatitis C virus, both of which are blood-borne pathogens.(116)

Reduction in healthcare transmissions is partially seen due to the availability of single-use needles, syringes, and medication vials, safety-engineered technologies and strategies such as prefilled syringes with tamper-proof packaging, and improved labeling. However, enhanced infection control practice, education, oversight, and enforcement are critical strategies to further reduce transmission of viral hepatitis in healthcare settings.(116) Although only selected patients with immunosuppression are at risk or being considered at risk for disease progression and need monitoring or referral for secondary care, incorrect or inappropriate secondary care or referral is one of the common mistakes due to lack of awareness.(117) In patients who are hepatitis B e antigen negative, with low levels of HBV DNA, but significantly high levels of alanine transaminase (ALT) and aspartate aminotransferase, and having established liver disease, it is imperative that hepatitis D virus (HDV) co-infection is excluded as active HDV infection usually occurs in a setting where hepatitis B viremia is low.(118, 119)

Although treatment options for hepatitis D are limited, it is critical that HDV co-infection is excluded so that patients can be appropriately managed and risk stratified.(118, 119) Patients at risk of metabolic syndrome with raised ALT levels (patients with non-alcoholic fatty liver disease [NAFLD]/nonalcoholic steatohepatitis [NASH]) or abnormal liver parameters should have other possible excluded — In some cases, a liver biopsy is indicated to determine appropriate management. Thus, comorbidities such as coexistence of NASH should not be avoided as it could lead to increased risk of disease progression.(120, 121) Hepatitis B virus is the most common cause of hepatocellular carcinoma (HCC). Although antiviral therapy may reduce the risk of HCC development, it does not completely eliminate HCC.(122) The risk of developing HCC is higher in patients with certain host-related factors, which include: Cirrhosis, older age (>40 years), male sex, a family history of HCC, coexisting liver disease, chronic coinfections (e.g., with other

hepatitis viruses or human immunodeficiency virus), and a high level of HBV DNA.(123, 124) Therefore, patients require appropriate screening and surveillance in terms of the timing of initiation and its frequency.(124)

Before diagnosis, for cirrhotic patients with parenchymal cyst, it is required to make sure that the lesions fulfill all of the criteria for parenchymal cysts so that they are not misdiagnosed as a malignancy such as a necrotic HCC.(125) Moreover, the presence of cirrhosis complicates liver imaging because the distortion and replacement of normal liver parenchyma with fibrous and regenerative tissue occurs, which can change the typical appearances of many benign lesions, potentially leading to a false-positive diagnosis of malignancy.(126) In addition, the high incidence and prevalence of HCC among patients with cirrhosis puts radiologists on high alert for any suspicious findings, especially because not all HCCs have a typical imaging appearance.(126) Patients with cirrhosis require life-long treatment irrespective of their laboratory parameters to prevent disease progression and reduce the risk of HCC development.(127) Viral suppression can potentially halt the progression of chronic hepatitis B (CHB) and reduce the risk of developing advanced liver disease, cirrhosis, and HCC. The timing of the "decision to treat" remains a subject of debate in the management of CHB. Delaying treatment until the later stages of chronic infection is another mistake in the management of CHB. Treating patients too early in the course of chronic infection may be problematic due to the potential long-term side effects of therapy; thus, each patient must be considered on an individual basis.(127)

NON-VIRAL HEPATITIS

Non-viral hepatitis can be caused by exposure to some medications, drugs, alcohol, toxins, or autoimmune diseases. Other possible causes of non-viral hepatitis include contaminated water or food, dietary and herbal supplements, traditional or home remedies, wild-growing mushrooms and plants, and chemicals such as metals, solvents, paint thinners, or pesticides.(128)

Drug-induced liver injury (DILI) most often presents as an acute viral hepatitis-like syndrome, without symptoms that specifically point to the drug etiology, unless rash or other cutaneous manifestations reinforce the suspicion of drug toxicity. (128) Acetaminophen, generally perceived as a safe medication, is the most common cause of acute liver failure in the United States, with inadvertent hepatotoxicity in half of all cases. It was speculated that consumer ignorance is a significant reason why acetaminophen is a leading cause of acute liver failure.(129) The diagnosis of DILI is an uncertain process, requiring a high degree of awareness of the condition and the careful exclusion of alternative etiologies of liver disease.(130) The clinical spectrum of DILI can mimic almost every other liver disorder. Accompanying blood eosinophilia is uncommon in large series of patients with DILI, but is clearly suggestive of drug

allergy. Histopathological findings in DILI can resemble many other liver disorders, thereby limiting the value of liver biopsy in DILI diagnosis.(130, 131) However, biopsy can be useful to establish an alternative diagnosis when the underlying liver disease worsens (i.e., alcoholic hepatitis or autoimmune hepatitis). Adherence to Clinical Practice Guidelines, which provide evidence on risk factors, diagnosis, management, and risk minimization strategies for DILI, should be reinforced.(132)

NON-ALCOHOLIC STEATOHEPATITIS

Noninvasive detection of NASH and accurate determination of fibrosis stage remain key diagnostic challenges.(133) Patients at high risk for NASH with subsequent fibrosis and liver cancer should receive advanced testing to confirm the diagnosis, evaluate the level of hepatocyte damage, and stage the fibrosis. Liver biopsy is the traditional and most widely accepted method of diagnosing NASH and staging fibrosis; however, its limitations and potential complications together with increasing availability and accuracy of noninvasive methods have made liver biopsy less common.(134)

It is important to rule out other causes of hepatic steatosis, particularly alcohol and metabolic syndrome.(133) Moreover, imaging modalities have poor sensitivity, detect fat only when 20–33% of the liver parenchyma is involved, and cannot accurately quantify the amount of hepatic fat present.(133) Serum aminotransferases, which are often used in clinical practice as a surrogate for inflammation, have poor predictive value for NASH. Serum alanine aminotransferase greater than two times the upper limit of normal (>70 U/L) has only 50% sensitivity and 61% specificity for NASH. In addition, patients with NAFLD can have normal alanine aminotransferase levels, particularly as the disease progresses. Therefore, although elevated aminotransferases should raise suspicion for NASH, normal levels should not be used to exclude NASH.(133) Correctly diagnosing and staging NAFLD and distinguishing the subset of patients with NASH is not only critical for disease monitoring and prognostication, but also holds potential implications for therapies. Several pharmaceutical agents have been evaluated for the treatment of NASH; however, no single therapy has been approved so far.(135)

Gallstones

The critical feature of gallstones is that they are not all symptomatic and may be a common incidental finding on ultrasonography.(136) There is a dilemma regarding deciding the correct treatment approach for asymptomatic gallstones/incidental gallstones. Proper decision making for gallstone disease necessitates that clinicians and patients recognize silent (asymptomatic) or symptomatic (with uncomplicated biliary pain) disease categories for choosing most appropriate treatment.(137) Cholecystectomy should be advised only if symptoms or disease can be definitely attributed to it.(138)

Challenges and Evidence-based Practical Approach

Proton pump inhibitors (PPIs) are not only irreplaceable drugs in the management of acid-related diseases, but they also have a risk for developing adverse effects.(139) Although overall benefits of therapy and improvement in quality of life significantly outweigh potential harms in most patients, those without clear clinical indication may have chances of exposure to the risks of PPI prescription.(139) However, underuse of PPIs is also a matter of concern. Despite all guidelines supporting the use of PPIs for gastroprotection in at-risk patients treated with nonsteroidal anti-inflammatory drugs, low prescription rates of PPI have been reported.(140-143) Moreover, primary care physicians should also consider addressing issues related to dosing and treatment adherence that may be involved when an incomplete response to PPI therapy is apparent.(1)

Use of long-term high dose of steroids or immunosuppressants and aminosalicylates requires regular monitoring for side effects and liver functions.(144) Long-term use of nonsteroidal anti-inflammatory drugs for pain relief in chronic disease conditions could be responsible for gastroesophageal reflux disease.(145) Ursodeoxycholic acid (UDCA) treatment is common in patient with gallstone disease. However, right upper quadrant abdominal pain and skin reactions in patients with primary biliary cirrhosis can be due to UDCA side effect. Reports also exist of skin reactions in those with primary biliary cirrhosis. The most common dermatological manifestation was an exacerbation of pruritus, although UDCA has demonstrated effectiveness in relieving pruritus in patients with primary biliary cirrhosis. Ursodeoxycholic acid usage deserves discussion amongst physician groups regarding its true benefits and its adverse effects.(146)

Summary

Gastrointestinal and hepatic disorders are highly prevalent, and associated with significant mortality and morbidity.(1) Although many evidence-based consensuses for individual conditions are available, effective management of GI and hepatic disorders relies on effective diagnosis and monitoring of the conditions. Differential diagnosis plays a major role in reducing the diagnostic errors and helps reduce long-term malignancy risk in patients with GI and hepatic disorders.(12, 82, 91, 116, 120)

Primary care physicians have primary role compared to gastroenterologists for diagnosis and treatment of the patient with early symptoms.(1) However, evidence suggests that the lack of awareness and knowledge of diagnosis among PCPs and limited facilitation of diagnostic resources at clinician settings leads to inefficient treatment of patients.(30-32) Moreover, there are gaps in communication between patients and the PCPs, which reduces the chances of better patient education and lack of PCP's in-depth understanding of symptoms that results in inefficient treatment or error in diagnosis.(23,24)

Inappropriate prescription patterns among the PCPs has been observed, and awareness can be improved by filling the knowledge gaps among the PCPs by conducting surveillances, educational and training programs, conferences, and workshops.(1) Primary care physicians should also utilize HRQoL parameter tools to enhance the understanding of the disease impact and effects of treatments on the disease.(52)

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