

Published: August 31, 2023

**Citation:** Choudhuri G, Abraham P, et al., 2023. Gastrovigilance: A Close Watch on Gastrointestinal and Hepatic Disorders- An Indian Perspective, Medical Research Archives, [online] 11(8).  
<https://doi.org/10.18103/mra.v11i8.4191>

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DOI  
<https://doi.org/10.18103/mra.v11i8.4191>

ISSN: 2375-1924

## RESEARCH ARTICLE

### Gastrovigilance: A Close Watch on Gastrointestinal and Hepatic Disorders- An Indian Perspective

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#### ABSTRACT

Gastrointestinal and hepatic disorders account for about 25% of consultations among general practitioners in India. Errors in clinical judgement and hesitancy in recommending necessary tests owing to lack of health insurance could result in delayed diagnosis and increased patient morbidity and mortality. Clinicians should thus be well equipped with effective strategies for skilful diagnosis and in a position to weigh the benefit-risk-ratio of recommending pertinent and disregarding less useful diagnostic tests. 'Gastrovigilance' includes disease-specific training for recognising risk factors, algorithms and referral pathways. This narrative review focuses on the common challenges or errors in managing these conditions in Indian clinical practice and their proposed solutions. Literature searches were performed using PubMed/MEDLINE and Google Scholar following the shortlisted gastrointestinal conditions. Based on the published literature and expertise of the senior gastroenterologists, improving disease-specific knowledge can enhance rates of correct diagnosis. Improved screening and patient education can reduce the risk of presentation at advanced stages and consequently improve prognosis. Another significant contributory factor is the patient-physician interaction which affects every stage of the disease management and methods to improve it, therefore vital in improving gastrointestinal and hepatic disease conditions. The most important means of improving gastrovigilance is optimising knowledge access in primary care. This shall improve diagnostic accuracy and reduce the burden of misdiagnosis. In the current narrative review, we have tried to elucidate the concept of gastrovigilance for gastrointestinal and hepatic conditions and substantiate it with published evidence.

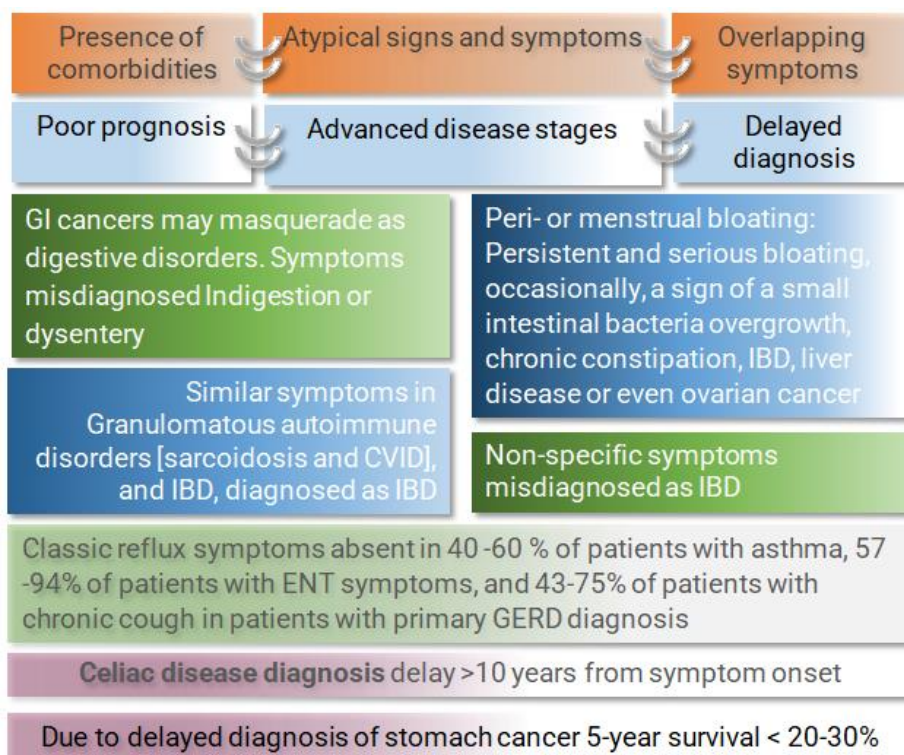
**Keywords:** Inflammatory bowel disease, Gastroesophageal Reflux Disease, Irritable bowel syndrome, Constipation, Gastrointestinal cancer

## Introduction

Gastrointestinal (GI) and hepatic disorders are major sources of morbidity and mortality and are associated with substantial healthcare expenditure.<sup>1,2,3</sup> GI diseases have demonstrated an age-standardised death rate (ASDR) of 28.4 deaths per 100,000 population in Western countries and 17-19.45 per 100,000 population in India.<sup>4</sup> These disorders are widespread in general practice and account for about 10% of general practitioner (GPs) consultations in Western countries (UK) and ~25% in India.<sup>5,6</sup> Thus, for a fairly large section of the population in India, the GP is the first contact point, and their role is therefore crucial in correct diagnosis. In clinical practice, the spectrum of consequences related to diagnostic errors (misdiagnosis, a missed diagnosis, or a delayed diagnosis at any stage in the diagnostic process) could be averted with the appropriate identification of patients at risk.<sup>7</sup> Serious health consequences particularly occur if the patient has a malignancy or an aggressive form of a disease.<sup>8</sup> Evidence demonstrates that there has been a progressive rise in diagnostic errors, these being reported generally in 5% of out-patients, 10% of in-hospital fatalities, and 7–17% of in-hospital adverse events.<sup>9</sup> Some illustrations of diagnostic challenges in GI disorders reported in the literature are depicted in **Figure 1**. These diagnostic errors could generally be attributed to limited access to

diagnostic testing resources, lower doctor-patient ratios, limited availability of specialists and insufficient record-keeping systems. Apart from these technical challenges, another important decisive factor leading to deviation from guideline practice is the absence of health insurance coverage for a large subset of the population in countries like India.<sup>10</sup> It leads to hesitation among physicians and patients, hindering the conduct of required tests to restrict out-of-pocket expenditure. **Figure 2** Specific challenges in managing GI diseases also include the failure to obtain sufficient information on patients' medical-, travel- and medication history. Treatment based on such incomplete data is likely to delay referral to specialist centres, develop complications, poor prognosis, and higher rates of negative outcomes.<sup>11,12</sup>

To overcome these challenges in real-life clinical settings and reduce the GI disease burden, clinicians well equipped with effective strategies for skilful diagnosis are critical. Among the various approaches, 'Gastrovigilance', which includes disease-specific training for recognition of risk factors, algorithms and referral pathways, could prove highly beneficial. In this narrative review, we present a summary of literature supporting the concept of gastrovigilance for GI and hepatic conditions.



**Figure 1. Illustrative Clinical Evidence Depicting Factors Associated with Diagnostic Errors and its Consequences (Disease-Related)<sup>13,14,15,16,17</sup>**

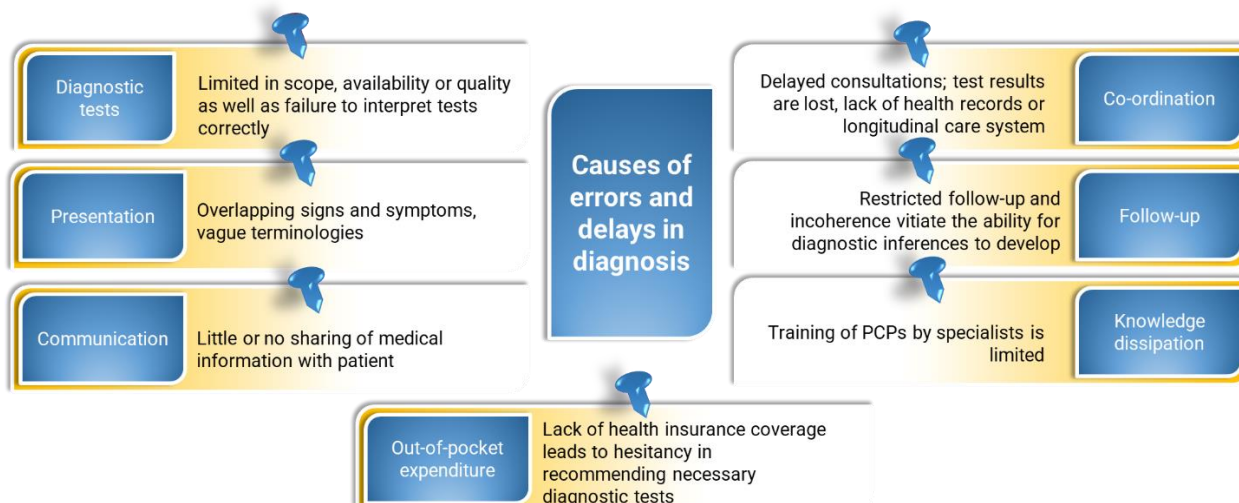


Figure 2. Causes of Errors and Delays in Diagnosis<sup>10,11,12,18</sup>

### Methodology

Literature published in English and the supporting concept of gastrovigilance for GI and hepatic conditions were included. From a wide range of GI conditions, the list included in this article was narrowed down by a group of senior gastroenterologists from India. A draft of the summary of literature supporting the concept of gastrovigilance for GI and hepatic conditions was shared with experts after a virtual/expert group deliberation. In this paper, we have included common challenges in managing these conditions in Indian clinical practice along with their proposed solutions.

### Gastroesophageal Reflux Disease (GERD)

#### Definition, Prevalence in India

GERD is defined as a syndrome due to reflux of gastric content into the oesophagus, resulting in symptoms more than once a week or more than a month and/or complications.<sup>19</sup> As per a recent meta-analysis, the pooled prevalence of GERD in the Indian population is 15.6 (5%-28.5%).<sup>20</sup>

#### Challenges in Diagnosis and Treatment

Among the various obstacles, incorrect diagnosis is an important one that impacts the successful treatment of GERD patients in clinical practice.<sup>21</sup> These challenges, along with probable causes and their remedies based on best practices and guideline recommendations, have been elucidated in **Table 1**.

Table 1. GERD- Challenges in Diagnosis and Treatment: Evidence-based practical approach

Challenges in Management		Evidence-based practical approach
Diagnosis/Treatment	Reasons Identified/ Clinical Evidence	
Lack of awareness of presenting symptoms other than heartburn and regurgitation, increased risk of misdiagnosis	GERD can manifest as atypical extra-oesophageal manifestations such as chest pain, dental erosions, chronic cough, laryngitis or asthma. For, e.g. <ul style="list-style-type: none"> <li>GERD was reported as a cause of chronic cough in ~ 40% of patients<sup>22,23</sup></li> <li>15.5% of patients with GERD had a nocturnal cough<sup>24</sup></li> <li>~ 75% of cases, GERD-related cough may present with no GI symptoms<sup>23</sup></li> </ul>	<ul style="list-style-type: none"> <li>Clinical practitioners should be aware that the relationship between cough and GERD is bilateral. For e.g. 48% of patients had a positive symptom association probability for cough preceded by reflux, 56% had a positive symptom association probability for reflux preceded by cough, and 32% had both.<sup>25</sup></li> <li>Use impedance/pH manometry in patients with chronic cough<sup>25</sup></li> <li>24-h impedance-pH monitoring off PPI is currently the gold standard for diagnosis of GERD<sup>24</sup></li> </ul>
	High prevalence of GERD in patients with NCCP in Indian studies <sup>26</sup> <ul style="list-style-type: none"> <li>22.4% of subjects with GERD had chest pain as compared to 4% of non-GERD</li> </ul>	Initially evaluated with upper GI endoscopy, with further testing (esophageal manometry, pH recording) only in those with normal endoscopy. <sup>26</sup>

	subjects of these, 31% had pain >once/week <sup>24</sup>	Symptomatic improvement with PPI is seen in most patients. <ul style="list-style-type: none"> <li>85% of patients had symptomatic relief with a 2-week course of PPI therapy<sup>26</sup></li> </ul>
No established consensus regarding the definition of refractory GERD in terms of symptom burden <sup>27</sup>	Degree of therapeutic response, and PPI dose at which failure occurs is mostly a patient-driven phenomenon <sup>27</sup>	More India-specific data required
Acid-suppressive therapy in the treatment of undiagnosed chronic cough is not effective <sup>28</sup>	An Indian study reported that 10.4% of patients with chronic cough related to GERD and ~80% of physicians treated these empirically with PPI. <sup>29</sup>	In such patients, only treat with PPI when objective evidence of GERD (endoscopy or physiological monitoring) to avoid delay in referral <sup>19</sup>
Delay in referral	Non-responders to 4 weeks of PPI therapy continue its use	After 4 weeks, invasive investigations should be performed in patients with alarm <sup>a</sup> symptoms and those with refractory GERD. <sup>19,30</sup>
Failure to identify specific GI disorders such as GERD, FD, IBS or malabsorption	Use of nonspecific terminology 'indigestion.'	Use endoscopic and histopathological examination, which can differentiate among the types of GERD such as NERD, EE and BE <sup>31</sup>
Achalasia misdiagnosed as GERD.	Overlapping clinical presentation and diagnostic work-up Heartburn reported in 13.2–68.0% of patients with achalasia <sup>32</sup>	Avoid performing oesophageal manometry in all patients undergoing surgical fundoplication <sup>33</sup>
Delaying referrals for older patients and those with alarm symptoms of <i>H. pylori</i> infection	Development of refractory disease	Prompt referral for endoscopy and further investigations Tailored approach
Underestimated symptom severity	Poor agreement between patients and physicians <sup>34,35</sup>	Strengthen physician-patient relationship <sup>36,37</sup>
Injudicious use of PPIs- inappropriately used in ~ 50% of cases <sup>38</sup>	Long-term use of PPI has been associated with a multitude of adverse events <sup>39,40,41</sup>	After complete symptomatic relief, Physicians should advise the patients to stop PPIs and monitor their clinical condition <sup>19</sup>

<sup>a</sup>dysphagia, odynophagia, GI bleeding, anorexia, and weight loss

### Dyspepsia and *H. pylori* Infection Definition, Prevalence in India

Dyspepsia is defined as predominant epigastric pain lasting at least 1 month, which may be associated with any other upper GI symptom such as epigastric fullness, nausea, vomiting, or heartburn.<sup>42</sup>

There is a wide variation in the prevalence of dyspeptic symptoms (7.6 to 49%) among the Indian population due to the lack of uniform criteria used for the diagnosis. Similarly, a recent meta-analysis

of global data found a variation in pooled prevalence according to Rome I criteria (17.6%) and Rome IV criteria (6.9%).<sup>43</sup>

### Challenges in Diagnosis and Treatment

Overlap of symptoms, lack of uniform criteria used for diagnosis and wide variation in occurrence due to ethnicity, and frequently changing epidemiology are the predominant challenges in the management of dyspepsia. The details have been outlined in **Table 2**.

**Table 2. Dyspepsia- Challenges in Diagnosis and Treatment: Evidence-based practical approach**

Disease condition	Challenges in Management		Evidence-based practical approach
	Diagnosis/Treatment	Reasons Identified	
Dyspepsia	<ul style="list-style-type: none"> <li>7%-45% of patients remain un-investigated for dyspepsia<sup>44</sup></li> <li>11%-29.9%, for FD.<sup>44</sup></li> </ul>	<ul style="list-style-type: none"> <li>&gt;25% of individuals have overlapping symptoms between dyspepsia and GERS<sup>b45</sup></li> <li>&gt;70% of patients with dyspeptic symptoms have no underlying cause detected at endoscopy, so not a good predictor.<sup>46</sup></li> </ul>	Patients with alarm symptoms should be referred for an endoscopy <sup>1</sup>
<i>H. pylori</i> infection	Accounts for 15% of the total cancer burden and ~ 89% of gastric cancers. <sup>47</sup>		



Disease condition	Challenges in Management		Evidence-based practical approach
	Diagnosis/Treatment	Reasons Identified	
	Ethnic variation: <ul style="list-style-type: none"> <li>Esophagitis is more prevalent in the Western populations than in Asians (25% vs 3%)</li> <li>PUD<sup>c</sup> (6% vs 11%)<sup>1,46</sup></li> </ul>		Update knowledge and understanding regarding the local/regional prevalence.
Dyspepsia and <i>H. pylori</i>	Epidemiology changes frequently over a period of time. <sup>48</sup>		
<i>H.pylori</i>	Over-testing, overmedication, initiating drugs without understanding resistance rates of antibacterial agents: Complications and resistant infection	<ul style="list-style-type: none"> <li>Lack of knowledge regarding established recommendations among Physicians and GPs<sup>49,50,51</sup></li> <li>India-specific guidelines lacking</li> <li>No clear distinction/recommendation on the ideal candidate and time of treatment (huge infected population 49.94% to 83.30%)<sup>52</sup></li> </ul>	Local sensitivity reports should guide the choice of antimicrobials.
	Debatable whether all those infected need treatment, especially in resource constraint settings and asymptomatic individuals <sup>53</sup>	<ul style="list-style-type: none"> <li>Treatment is associated with significant side effects and costs.</li> </ul>	?
	Dyspeptic patients <ul style="list-style-type: none"> <li>Tested positive</li> <li>Not tested</li> </ul>	<ul style="list-style-type: none"> <li></li> </ul>	The algorithm should be followed.

<sup>b</sup> gastric oesophagus reflux syndrome <sup>c</sup> peptic ulcer disease

### Irritable Bowel Syndrome (IBS)

#### Definition, Prevalence in India

Patients with IBS should report symptoms of abdominal pain at least once weekly (on average) in association with a change in stool frequency, a change in stool form, and/or relief or worsening of abdominal pain related to defecation.<sup>54</sup>

Population-based studies have shown the prevalence of IBS between 4.2%-7.5% in India compared to a global pooled prevalence of 11.2%.<sup>55</sup> However, epidemiology, clinical

presentation, and management of IBS may vary in different geographical regions due to differences in diet, gastrointestinal infection, sociocultural and psycho-social factors, religious and illness beliefs, symptom perception and reporting.<sup>55</sup>

#### Challenges in Diagnosis and Treatment

Awareness of alarm symptoms of IBS is crucial to facilitate early diagnosis.<sup>56</sup> Diagnosing IBS can be challenging and uncertain for several reasons, as depicted in **Table 3**.

**Table 3. IBS- Challenges in Diagnosis and Treatment: Evidence-based practical approach**

Challenges in Management		Evidence-based practical approach
Diagnosis/Treatment	Reasons Identified	
Diagnosis is difficult: 10% of patients are misdiagnosed, and 3% remain misdiagnosed ≥5 years. <sup>57</sup>	<ul style="list-style-type: none"> <li>No consistent biological marker for IBS</li> <li>Symptoms difficult to quantify objectively</li> <li>Many organic conditions can masquerade as IBS</li> </ul>	Rely on clinical symptoms
Rome IV and Manning criteria are available yet inaccurate diagnosis	<ul style="list-style-type: none"> <li>Only 2-36% of Physicians aware of these tools</li> <li>0%-21% use them<sup>58</sup></li> </ul>	
Patients in IBD remission complaining of IBS-like symptoms	Symptoms as "true IBS" or subclinical IBD are insufficient as they do not account for all available observations <sup>59,60,61</sup>	<ul style="list-style-type: none"> <li>More research required<sup>62</sup></li> <li>Individualised and case-based approach</li> </ul>
Treatment challenge		
The role of lactose or gluten dietary restriction is questionable	No high-quality evidence. <sup>63</sup>	Await results of ongoing research.

Challenges in Management		Evidence-based practical approach
Diagnosis/Treatment	Reasons Identified	
Suitability (or otherwise) of probiotics	Limited familiarity	Need for more objective, evidence-based guidance
Widespread claims	Advertisement/ Commercial campaigns <sup>1</sup>	Use specific probiotics known to relieve lower GI symptoms in IBS and prevent diarrhoea associated with antibiotics and <i>H. pylori</i> eradication therapy. <sup>64</sup>
Medications are largely ineffective in symptom management, and diet remains first-line, but benefits are questionable.	Limited evidence for a beneficial role. <sup>63,65</sup>	Long-term and non-pharmacological approaches to help the patient adjust to their chronic illness

### Inflammatory Bowel Disease (IBD)

#### Definition, Prevalence in India

IBD is a broad term that includes conditions characterised by chronic inflammation of the gastrointestinal tract. IBD includes Crohn's Disease (CD) and Ulcerative Colitis (UC).<sup>66</sup> A comparison of incidence and prevalence rates with other countries suggests that among Asian countries, the disease burden is highest in India.<sup>67</sup> With a population of more than 120 million, the total IBD population in India is among the largest globally.<sup>67</sup> A multicenter study from India has reported An increasing incidence of CD, with the number of patients diagnosed per year increasing from < 16 patients

in 2000 to 57 in 2006.<sup>68</sup> A population study found the incidence of UC to be 6.02/100,000.<sup>69</sup> A recent multicenter, cross-sectional, prospective national registry showed that the UC:CD ratio was 5.1:1 in India across four zones.<sup>70</sup>

#### Challenges in Diagnosis and Treatment

For physicians, both early diagnosis and proper treatment are a real challenge in their effort to ensure the best quality of life in patients with IBD. **Table 4** Moreover, recognition of extra-intestinal manifestations of IBD, such as arthralgia, uveitis and erythema nodosum, which could increase the possibility of early diagnosis, could help avoid unnecessary referrals to other specialities.<sup>71</sup>

**Table 4. IBD- Challenges in Diagnosis and Treatment: Evidence-based practical approach**

Challenges in Management		Evidence-based practical approach		
Diagnosis/ Treatment	Reasons Identified			
Differentiating between CD and UC is challenging	Overlapping signs and symptoms eg. In UC, blood in stool is common; in severe CD cases, the possibility of bleeding <sup>72,73</sup>	Look for differentiating clinical details:		
		Parameter	CD	UC
		Affects	Mouth, anus, all layers of the intestine	Rectum and colon
		Abdominal pain	Right lower abdomen with/without an accompanied palpable mass <sup>d</sup>	Tenderness in the left iliac fossa of the suprapubic area
	>50% with deficiency	Folate, vitamin D	Iron	
	Accurate diagnosis based on Endoscopic and histological examinations <sup>72,73</sup>	Focus on clinical presentation <sup>72,73</sup>		
Differentiate between CD and ITB (India-specific)	ITB is a close mimic of CD, and it is often difficult to differentiate the two based on clinical, endoscopic, histological, and radiological characteristics. <sup>67</sup>	<p>In a patient with a diagnostic dilemma of CD and ITB after all investigations, a therapeutic ATT trial should be prescribed, and then the patient should be follow-up based on the clinical and endoscopic response to it.</p> <ul style="list-style-type: none"> <li>38% of all patients with CD had a good clinical response to 6 months of ATT, and &lt; 5% had mucosal healing in comparison to ITB, where all patients showed clinical as well as endoscopic response<sup>67</sup></li> </ul>		

ITB- Intestinal TB, ATT-Antitubercular therapy, <sup>d</sup> finding that could be difficult to differentiate from an attack of acute appendicitis

Optimal management of IBD requires a multidisciplinary approach with many key players involving Physicians, GEs, surgeons, radiologists, pathologists, psychologists, rheumatologists and dietitians.<sup>74,75</sup> The Physicians play an active role in managing IBD via monitoring patient's treatment compliance and, if necessary, making dose adjustments in close cooperation with the specialist.<sup>76</sup> Recognising risk factors, monitoring the patient for prevention and treatment of osteoporosis, infections using necessary vaccinations, and regular laboratory investigations is necessary since IBD management involves chronic therapy with aminosaliclates, corticosteroids, or immunosuppressive drugs.<sup>75,77,78</sup>

### Chronic constipation (CC)

#### Definition, Prevalence in India

Constipation is one of the major gastrointestinal disorders diagnosed in clinical practice.<sup>79</sup> Primary constipation includes constipation-predominant irritable bowel syndrome (IBS-C), functional constipation, slow transit constipation like myopathy, neuropathy, and functional defecation disorders. 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).<sup>79,80,81,82</sup>

Limited data from available studies indicate chronic constipation as a common health problem in India, challenging the general belief of its uncommonness due to a high-fibre diet and vegetarianism. Studies from India have reported a prevalence ranging from 8.6% to 24.8%.<sup>83,84,85,86</sup> While studies excluding India suggested a global prevalence of chronic constipation to be 14%.<sup>87</sup>

#### Challenges in Diagnosis and Treatment

There are several challenges with chronic constipation, including the definition and identifying the pathophysiology. The average daily stool frequency is higher than the Western population, so the definition from Western countries may not apply to the Indian population (< 3/week vs 14/week) to diagnose CC.<sup>84,88</sup> Further, uncertainty about which treatment to use and when is still a challenge in clinical practice.<sup>89</sup> **Table 5**

**Table 5. Chronic Constipation- Challenges in Diagnosis and Treatment: Evidence-based practical approach**

Challenges in Management		Evidence-based practical approach
Diagnosis/Treatment	Reasons Identified	
Lack of clear assessment	Use of nonspecific/vague terminology at both patient and physician levels, e.g. "attempts at defecation" or "fragmented defecation." E.g. Feeling of incomplete evacuation reported by 98.8% of Indian patients <sup>90</sup>	Investigate all attempts to defecate to obtain a clear diagnosis: <ul style="list-style-type: none"> <li>• Primary evaluation: Gather a detailed medical history and physical examination (focus on anal examination).</li> <li>• Obtain 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.</li> <li>• Changes in living conditions, medicaments, lifestyle changes, duration, and onset of symptoms are also relevant.<sup>79</sup></li> <li>• Base diagnosis on predefined symptoms and the Rome criteria.<sup>79</sup></li> <li>• Subsequently, use the latest technologies<sup>79</sup></li> </ul>
Difficult to differentiate IBS-constipation and chronic constipation	Overlap symptom	Relief of abdominal pain or discomfort by defecation differentiates IBS from chronic constipation as per the Rome IV criteria <sup>79</sup>
Uncertainty in the choice of treatment alternatives due to questionable efficacy	Almost half of the affected patients report a lack of complete relief from their symptoms. <sup>79</sup>	To improve the management of ambulatory patients with chronic constipation, combined therapies should be initiated early, and a long-term step-down strategy to the lowest satisfactory regimen should be implemented. <sup>79</sup> Cases refractory to medical treatment should be referred for further diagnostic evaluations to assess alarm symptoms: colonic transit time and anorectal dysfunction. If pharmacologic treatment fails, surgery is the option. <sup>79</sup>

## Celiac disease (CeD)

### Definition, Prevalence in India

Celiac disease is estimated to affect about 1% of the world's population. It is thought to be unusual not only in India but also in Asia.<sup>91</sup> Studies from India have found a prevalence of 8.53/1,000 in the northern, 4.66/1,000 in the northeastern, and 0.11/1,000 in the southern part of India. Thus, CeD

is more common than is recognised in India, affecting primarily the wheat-consuming population.

### Challenges in Diagnosis and Treatment

The predominant challenges include difficulty in diagnosis and patient adherence to dietary restrictions. **Table 6**

**Table 6. Celiac disease- Challenges in Diagnosis and Treatment: Evidence-based practical approach**

Challenges in Management		Evidence-based practical approach
Diagnosis/Treatment	Reasons Identified	
50% to 90% of patients undiagnosed <sup>92</sup>	Mild, nonspecific symptoms Bacterial overgrowth or cereal intolerance	A high index of suspicion for CeD and considering a differential diagnosis in many clinical situations is important:
Remain untreated	Misidentification of underlying aetiology Elderly symptoms are non-intestinal and attributed to age-related comorbidities. <sup>95</sup>	<ul style="list-style-type: none"> <li>○ Subject patients with chronic/intermittent diarrhoea, persistent/unexplained GI symptoms [nausea and vomiting], prolonged fatigue, recurrent abdominal pain, cramping/distension, sudden/unexpected weight loss and unexplained iron-deficiency anaemia) to serological test for immunoglobulin A anti-tissue transglutaminase antibody<sup>1</sup></li> <li>○ Consider non-immunological mechanisms in patients with wheat or cereal intolerance causing a systemic or local allergic response.<sup>93</sup></li> <li>○ Adherence to guidelines may reduce misdiagnosis.<sup>94</sup></li> </ul>
	Treatment challenge	
Diet control therapy is impracticable.	Expensive Socially isolating diet Inadequate symptom control or intestinal damage	Patient education and support should be provided. The importance of risk reduction for complications (e.g. malignancy) with a gluten-free diet should be explained. <sup>96</sup>

## GI cancers (Colorectal Carcinoma, Gastric Cancer, Esophageal Cancer)

### A. Colorectal Cancer

#### Definition, Prevalence in India

In India, the annual incidence rate for colorectal cancer ranges between 4.1 to 4.4 per 100,000.<sup>97,98</sup> Colorectal cancer (CRC) in India is distinct compared to that in Western countries. Patients from India are younger, and a higher proportion of signet ring carcinomas is noted; more sites are anorectal compared to colonic reported worldwide.<sup>99</sup> Besides, patients usually present at an advanced stage. These differences, at least in part, could be attributed to insufficient access to healthcare and socioeconomic factors.<sup>99</sup>

#### Challenges in Diagnosis and Treatment

Early detection (Dukes' A and B) represents the only chance for increasing 5-year survival rates. Evidence from countries with effective CRC prevention programs shows that early endoscopic detection and removal of preexisting colorectal polyps diminish the incidence of neoplasm. Further, CT colonoscopy (CTC) is the gold standard for managing bowel pathology. Nevertheless,

widespread screening and technical expertise for CTC is inadequate in India, resulting in advanced disease stage at presentation.<sup>100,101</sup>

### B. Gastric Cancer

#### Definition, Prevalence in India

As per the National Cancer Registries (NCR)—population-based tumor registries and Hospital-based cancer registries, the prevalence of gastric cancer (GC) ranges from 0.5/100,000 in Western India to 12.2/100,000 in Southern to 64.2/100,000 in Eastern Indian population.<sup>102</sup> Thus, though the prevalence of gastric cancer is low compared to Western counterparts, there is immense regional diversity. Besides, the majority of patients are at an advanced stage of presentation which poses a significant challenge.<sup>102</sup>

#### Challenges in Diagnosis and Treatment

Preventing the formation of premalignant lesions, either by reducing (eliminating) risk factors or by surveillance and management of premalignant (precancerous) conditions, should be the ideal practice. However, early diagnosis and treatment remain challenging. **Table 7**



**Table 7. GI Cancers: Challenges in Treatment and Diagnosis with Solutions**

Disease Condition	Challenges in Management		Evidence-based practical approach
	Diagnosis/Treatment	Reasons Identified	
CRC	CRC screening is not widespread	<ul style="list-style-type: none"> <li>Poor compliance due to lack of awareness of symptoms and risk factors</li> <li>High perceived health, psychological and access barriers in Asia</li> </ul>	<p>Screening in primary care is key, so clinicians should persuade/counsel* people to participate in screening programs, particularly &gt;50 years of age.<sup>103,104,105</sup></p> <p>Use CRC screening promotion scripts</p> <p>Train physicians enabling them to</p> <ul style="list-style-type: none"> <li>provide safe screening using colonoscopy</li> <li>detect cancer and precancerous lesions<sup>101,106,107,108,109</sup></li> </ul>
GC	Early diagnosis is difficult, and suboptimal investigations by physicians <sup>110,111</sup>	<ul style="list-style-type: none"> <li>Nonspecific symptoms<sup>112</sup></li> </ul>	Identifying patients with high-risk factors should be a part of routine clinical practice.
	Referral for advanced investigation - challenging <sup>113</sup>	<ul style="list-style-type: none"> <li>Dyspepsia is a common early symptom.</li> </ul>	Referral for endoscopy for all patients (≥ 45 years) with new onset dyspepsia Consider upper and lower GI investigations in all postmenopausal female and all male patients with IDA. <sup>114</sup>
	Delayed detection of gastric and oesophageal adenocarcinoma on endoscopy <sup>115,116</sup>	<ul style="list-style-type: none"> <li>Early malignancy within the gastric mucosa may be healed with acid suppression therapy<sup>117</sup></li> </ul>	Avoid PPI therapy before endoscopy, particularly in patients > 45 years. <sup>117</sup>
EC	Diagnosis is often delayed by 1-11 months from the onset of symptoms. <sup>118,119</sup>	<ul style="list-style-type: none"> <li>Lack of identification of risk factors</li> <li>Relying on limited symptoms such as dysphagia.<sup>1</sup></li> </ul>	Refer patients presenting with progressive dysphagia and weight loss for urgent endoscopy. Consider detecting precancerous change in smokers, alcoholics and patients with other aerodigestive cancers due to common risk factors. <sup>120</sup> Consider Endoscopic screening for BE in patients with chronic GERD due to multiple risk factors <sup>e 121,122</sup>

<sup>e</sup> ≥ three risk factors: age 50 or older, white race, male sex and obesity).

### C. Esophageal Cancer

#### Definition, Prevalence in India

Squamous cell carcinoma (SCC) is currently the most common type of oesophageal cancer (EC) in the Indian subcontinent, with the distal third of the oesophagus being the most common site. Approximately 47,000 new cases are reported each year in India.<sup>123</sup> About 1 in 300 patients with Barrett's oesophagus (BE) are estimated to develop EC annually.<sup>121</sup> There has been an association between adenocarcinoma and BE due to chronic inflammation from GERD.<sup>121,122</sup>

#### Challenges in Diagnosis and Treatment

Nonspecific complaints like progressive dysphagia and weight loss, limited risk factors for identification delay the diagnosis.<sup>1,118,119</sup> **Table 7**

#### Hepatic Disorders

##### A. Viral Hepatitis

Viral hepatitis is a cause for major healthcare burden in India and is now paralleled as a threat to the trio of HIV/AIDS, malaria and tuberculosis.<sup>124</sup> While Hepatitis A virus (HAV) and Hepatitis E virus (HEV) cause both sporadic infections and epidemics

of acute viral hepatitis (AVH), Hepatitis B virus (HBV) and Hepatitis C virus (HCV) cause chronic hepatitis. Though earlier prevalent in young children, currently there has been a sero-epidemiological shift in HAV infection in India, with increasing incidence of infection in the adult and adolescents (aged 15–24 years: 4.6%) when compared to subjects aged population compared with children (5–14 years: 3.1%).<sup>125,126</sup> HEV is a major aetiology for AVH in the paediatric population and is reported to be responsible for over 70% of cases of acute hepatitis.<sup>127</sup> During an HEV epidemic, the secondary attack rate among the household contacts is estimated to be lower than HAV (0.7–2% vs 50-75%).<sup>128</sup> During an outbreak, pregnant women are at a greater risk of getting infected (12-20% and developing acute liver failure compared to the non-pregnant population (10-22% vs 1-2%).<sup>129</sup>

India has "intermediate to high endemicity" for Hepatitis B surface antigen and an estimated 40 million chronic HBV-infected people, constituting nearly 11% of the global burden. The population

prevalence of chronic HBV infection in India is around 3-4 %. The estimated prevalence of HCV infection in India is about 1–1.9%.<sup>124</sup>

### B. Non-viral Hepatitis

#### Definition, Prevalence in India

Non-viral hepatitis can be caused by exposure to some medications, drugs, alcohol, toxins or autoimmune disease. 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. The drugs causing drug-induced liver injury (DILI) tend to differ geographically based on specific disease states.<sup>130</sup> In India, it is intensified by the widespread use of traditional and complementary medicines.<sup>130</sup> The actual incidence of DILI in India is not known but is

probably higher than in Western countries. The idiosyncratic form of DILI includes ~99% of all DILI cases in India, and intrinsic DILI, as it occurs in acetaminophen/paracetamol hepatotoxicity, accounts for <1% of cases.<sup>130</sup> Autoimmune hepatitis (AIH) prevalence in India is around 5% of all patients with chronic liver disease.<sup>131</sup>

#### Challenges in the Diagnosis and Treatment of Hepatitis

Clinicians should maintain a high index of suspicion for non-viral hepatitis in the differential diagnosis of acute hepatitis in patients presenting with compatible clinical findings.<sup>132</sup> **Table 8** Patient exposure history should be collected in a more detailed manner to identify the aetiology for non-viral hepatitis.<sup>132</sup> Awareness of differential diagnosis and identification of prognostic risks associated with the condition could be an approach for managing patients.

**Table 8. Hepatitis- Challenges in Diagnosis and Treatment: Evidence-based practical approach**

Challenges in Management		Evidence-based approach
Diagnosis/Treatment	Reasons Identified	
HBeAg-, with low levels of HBV DNA but significantly high levels of ALT and AST and established liver disease <sup>133,134</sup>	Usually, HDV occurs in a setting where hepatitis B viremia is low	Check for HDV coinfection, which is important for risk stratification
Antiviral therapy may reduce the risk of HCC development but not eliminate it. <sup>135</sup>	Presence of high-risk factors: cirrhosis, older age (>40 years), male sex, family history, coexisting liver disease, chronic coinfections (e.g. with other hepatitis viruses or HIV) and a high level of HBV DNA <sup>136,137</sup>	Ensure appropriate screening and surveillance in terms of the timing of initiation and its frequency for patients with HBV. <sup>137</sup>
Misdiagnosis of parenchymal cyst as necrotic HCC in patients with cirrhosis <sup>138</sup>	Fibrous and regenerative tissue in cirrhosis complicates liver imaging occurs, by altering the appearances of many benign lesions <sup>138</sup>	Ensure lesions fulfil all of the criteria for parenchymal cysts.
High risk of false-positive diagnosis of malignancy in patients with cirrhosis	High incidence and prevalence of HCC among patients with cirrhosis creates a high risk of suspicion and bias <sup>138</sup> All HCCs do not have a typical appearance	Enhanced radiological imaging interpretation skills Consider the impact of confounding factors/risk factors prior to final diagnosis
Deciding the time for treatment initiation is challenging <sup>139</sup>	Starting early carries a risk of potential long-term side effects of therapy	Consider an individualised approach and assess based on the presence of risk factors
	Delaying treatment until the later stages of chronic infection increases the risk of complications.	
Differentiating between acute and chronic hepatitis	Initial clinical manifestations are similar	Assess based on aminotransferase levels <ul style="list-style-type: none"> <li>• Acute hepatitis: Marked elevations &gt;5XULN or &gt; 500 IU/L (1000's)</li> <li>• Chronic hepatitis/non-hepatic: typically elevated &lt;5X times ULN or &lt;500IU/L<sup>140,141</sup> (2-10XULN)</li> <li>• Exclude non-hepatic causes of pregnancy, lactic acidosis, sepsis, and cardiac dysfunction.</li> </ul>

Challenges in Management		Evidence-based approach	
Diagnosis/Treatment	Reasons Identified		
Ascertaining the aetiology of AH is critical but challenging	Clinical signs and symptoms, ranging from asymptomatic elevated LFTs to ALF requiring LT	Obtain a detailed history: <sup>141</sup> <ul style="list-style-type: none"> <li>• duration of the presenting illness</li> <li>• travel history</li> <li>• assess for high-risk activities like IV drug use, alcohol consumption</li> <li>• sexual history</li> <li>• prior blood-product transfusion history</li> <li>• recent food intake</li> <li>• Recent, current prescription and OTC drug history</li> </ul>	
Recognising the aetiology of acute hepatitis <sup>141</sup>	Initial clinical manifestations are similar <sup>141</sup>	<b>Histopathology</b>	<b>Inference</b>
		Central to central bridging necrosis and minimal inflammatory cell infiltrates <sup>141</sup>	DILI: acetaminophen overdose
		Intranuclear viral inclusions and surrounding neutrophils <sup>141</sup>	Acute viral hepatitis
		Portal inflammation and interface hepatitis <sup>142</sup>	Autoimmune hepatitis
		Diffuse microvesicular steatosis, Mallory bodies, fibrosis, or cirrhosis <sup>143</sup>	Alcohol-related liver injury
		Iron accumulation with hepatocellular hemosiderin pigment and increased hepatic copper concentrations <sup>144</sup>	Hereditary hemochromatosis and Wilson's disease
		Concentric rings of fibrosis - onion skin fibrosis <sup>145</sup>	Primary sclerosing cholangitis

### C. Non-alcoholic steatohepatitis (NASH)

#### Definition, Prevalence in India

A diagnosis of NASH is made when the presence of hepatic steatosis in >5% of hepatocytes in the absence of alcohol abuse or any other hepatic disease accompanied by ballooning and inflammation in the liver is detected.<sup>146,147</sup> It is a progressive stage of NAFLD which may lead to cirrhosis, hepatic malignancy or fibrosis.<sup>146,148</sup> It is currently the second commonest indication for liver transplantation in India.<sup>149,150</sup> The prevalence of NAFLD ranges from 9% to 32% in India.<sup>151,152</sup> The wide variation in NAFLD prevalence across India could be attributed to the urban-rural divide.<sup>153,154</sup>

#### Challenges in Diagnosis and Treatment

Non-invasive detection of NASH and accurate determination of fibrosis stage remain key diagnostic challenges.<sup>155</sup> **Table 9** Correctly diagnosing and staging NAFLD and distinguishing

the subset of NASH patients 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.<sup>156</sup>

#### Gallstones

##### Definition, Prevalence in India

In India, the prevalence of gallstones is approximately 4%, whereas it is 10% in the Western world.<sup>157</sup> The prevalence of asymptomatic gallstones is relatively high in central India.<sup>157</sup>

##### Challenges in Diagnosis and Treatment

The challenge is a diagnosis of asymptomatic gallstones and a dilemma with treatment. Recommendations for initial and periodic follow-up screening are also inadequate. **Table 10**

**Table 9. NASH- Challenges in Diagnosis and Treatment: Evidence-based practical approach**

Challenges in Management		Evidence-based approach
Diagnosis/treatment	Reasons Identified	
Non-invasive detection of NASH and accurate determination of fibrosis stage remain key diagnostic challenges. <sup>155</sup>	<ul style="list-style-type: none"> <li>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.<sup>155</sup></li> <li>Serum aminotransferases have poor predictive value for NASH.</li> <li>Serum (ALT) &gt;2X ULN or (&gt;70 U/L): 50% sensitivity and 61% specificity for NASH.</li> <li>NAFLD patients with normal ALT levels does not exclude NASH</li> </ul>	<p>Liver biopsy remains the only validated method of diagnosing NASH and staging fibrosis<sup>158</sup></p> <p>During initial screening presence of one or more metabolic risk factors along with hepatic steatosis (fat &gt;5% to 10% of the liver parenchyma) should raise clinical suspicion for NAFLD.<sup>159</sup></p>

**Table 10. Gall stones-Challenges in Diagnosis and Treatment: Evidence-based practical approach**

Challenges in Management		Evidence-based approach
Diagnosis/Treatment	Reasons Identified	
Gall stones found incidentally on USG. Dilemma to choose the correct treatment <sup>160</sup>	Asymptomatic Advising cholecystectomy	Advise cholecystectomy only if symptoms can be attributed to gallstones Patients with calcification in the gall bladder wall and those with a family history of cancer of the gall bladder should undergo cholecystectomy even if they are not symptomatic for gallstone disease/ multiple polyps with stone
Poor routine periodic follow-up imaging	Lack of recommendation	Obtain appropriate history and advise periodic screening using USG to avoid undetected gallstones resulting in long-term complications to patients (cholecystitis, bile duct infection and jaundice, pancreatitis or cancer of the gallbladder) in patients with older age group, female gender, high cholesterol level, family history of gallstones, sickle cell disease, increased BMI and comorbidities like diabetes or hypertension for early detection of gallstones formation.
Missing history of comorbidities like diabetes, increased risk of gallstone formation and reduced gall bladder wall contractility due to neuropathy. <sup>161</sup>	Inadequate awareness regarding its association among patients and Physicians	

### Importance of Patient-Physician Interaction/Relationship

The patient-physician relationship and patient participation are the cornerstone of care in managing several GI and hepatic diseases like IBD, UC, GERD and NASH. The Chronic nature of most diseases often demotivates the patient and affects outcomes. Patient education or counselling is effective only when the clinician provides adequate time to understand concerns/questions and provide satisfactory responses. Therefore, reassuring patients to voice their diagnostic concerns or fears is essential. Since most of these diseases necessitate dietary and lifestyle modifications, a clear understanding of these details is necessary to design a patient-centric approach to ensure adherence and improve outcomes. Therefore, there is a need to improve communication strategies for enhancing disease outcomes and improving health-related QoL. There is a need to empower patients so that they transition from passive care recipients to partners in care. Implementing longitudinal-care plans and patient follow-up outside the consultation is specifically important in primary care due to the

nonspecific presentation and progression of serious diseases eventually.<sup>162</sup>

### Methods to Improve Screening

Similar to Western countries screening should be performed primarily by physicians. Subjects should be selected based on risk score stratification, which also requires adequate disease knowledge among clinicians. Innovative strategies to maximise adherence to screening recommendations need to be deciphered. Some of these which have been evaluated and found to be successful include use of electronic reminders, best practice alerts, electronic medical record (EMR) prompts.<sup>163,164</sup> For the section of the population not generally engaged with primary care, other testing opportunities such as testing in emergency room departments, retail pharmacies, and prenatal clinics should be explored. Nevertheless, though these settings appear reasonable for screening, completing the follow-up steps in the cascade of care is questionable. Thus, robust and persistent screening practices could play a major role in preventing aggressive form of disease states by adopting timely measures.

Moreover, these methods could identify subtle symptoms and attenuate the disease progression at early stages, which has a better prognosis, especially in liver cirrhosis, CRC, and GC. These are associated with poor survival rates due to presentation in advanced stages and limited treatment alternatives. Thus, screening based on risk stratification could enhance the window for prevention and early diagnosis, even in asymptomatic or the presence of nonspecific signs and symptoms, which is indeed a major challenge in most of the diseases discussed. This shall also help in the optimisation of the referral process.

### Conclusions

GI and hepatic disorders are highly prevalent and are associated with significant mortality and morbidity. Although many evidence-based consensus for individual conditions are available, the effective management of GI and hepatic disorder relies on effective diagnosis and monitoring of the conditions. Differential diagnosis plays a major role in reducing diagnostic errors and helps reduce long-term malignancy risk in patients with GI and hepatic disorders. Early diagnosis in cases of FGID plays a crucial role in detecting associated overlapping GI conditions. Physicians have a primary role compared to gastroenterologists for diagnosis and treating the

patient with early symptoms. However, evidence suggests that the lack of awareness and knowledge of diagnosis among Physicians and limited facilitation of diagnostic resources in clinical settings leads to inefficient treatment of patients. Therefore, optimising knowledge access in primary care is needed.

Moreover, there are also gaps between patient and clinician communications which lead to poor patient education. An in-depth understanding of symptoms and differential diagnosis can result in improved diagnosis and better treatment outcomes. Besides the large population, sociodemographic profiles and challenges in health expenditure are major obstacles to implementing guideline-based screening and diagnostic approaches.

### Acknowledgements

Medical writing support is provided by Miss Seema Kalel at Intersect Kommunications in Mumbai, India, and is funded by Pfizer.

### Disclosure

None of the authors have any conflicts of interest to declare. All authors received an honorarium from Pfizer for their services as a member of the expert group meeting. Dr. Pratyusha, Dr. Akshay, and Dr. Charles are employees of Pfizer Ltd.



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