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Abstract

The relationship between diabetes mellitus and liver disease is bidirectional, both supporting and accelerating the development of each other. The key pathogenic mechanism is insulin resistance (IR). The main factor leading to IR is accumulation of fat in the liver. The hepatic fat predominately comes from three sources:

- Dietary fat,
- De-novo lipogenesis due to high insulin level and
- Fatty acid generation from adipose tissue lipolysis.

Fat in the liver impairs insulin signaling, leading to IR. Liver is the largest metabolic organ leading to IR. The resultant IR worsens hyperinsulinemia, which affects various metabolic processes in the liver. The IR prevents glucose transport from blood to liver, thus leading to poor trapping in liver and consequent rise in blood sugar. In addition, increased free fatty acids inhibit the insulin action on liver, and insulin-induced suppression of glucagon is impaired, thus leading to increased production of hepatic glucose which has a major contribution in fasting hyperglycemia. Evidence suggests that improvement in fatty liver reduces IR and prevents development and/or improvement of diabetes mellitus. There are numerous observational studies suggesting that fatty liver is an independent risk factor for development of diabetes. Chronic liver disease is associated with development of diabetes (secondary diabetes). Glucose intolerance can be seen in about 80% of patients, and diabetes in about 30% of patients with chronic liver disease. Thus, fatty liver may be considered the main organ responsible for IR and T2DM. Diabetes should be considered a reversible metabolic state due to excess intra-organ fat, especially fatty liver.

Introduction

The interest in relationship between chronic liver disease and diabetes mellitus has increased since last decade. Chronic liver disease particularly NAFLD is associated with diabetes mellitus. In the United States, NAFLD is the most common cause of chronic liver disease and affects between 80–100 million individuals.¹ According to an estimate in India, approximately 30% of the population is having NAFLD and its prevalence approaches to 64% in diabetics.² The association is based on insulin resistance (IR), which is the common underlying mechanism for both T2DM and NAFLD. The relationship between diabetes mellitus and liver disease is bidirectional, both supporting and accelerating the development of each other. What remains unclear is the chicken-egg conundrum—which comes first? In other words, does diabetes lead to fatty liver or fatty liver causes diabetes? An understanding of this requires a deep study of the physiology and pathogenesis of both conditions and developing clear concepts. Although IR is the common pathogenetic mechanism for both these conditions; however, it is the liver which is the key player for IR.
Liver is the Main Organ Producing IR

Being the largest metabolic organ of human body, it plays an important role in glucose metabolism. It is the site for glycogenesis, glycogenolysis, and gluconeogenesis. It has an immense capacity to store sugar in times of excess and push out glucose into circulation in deficient condition. Therefore, in states of fasting or hypoglycemia, liver releases glucose into the circulation by glycogenolysis and/or gluconeogenesis. On the other hand, it is also the main organ which prevents rapid rise of blood glucose after food ingestion. Whatever glucose is absorbed from the intestines it goes through the portal vein to the liver where, almost all of it is retained. The rise in prandial plasma glucose reflects only a minor component of the absorbed glucose. It is pertinent to note that the first glycemic abnormality in T2DM is postprandial hyperglycemia, which may actually indicate insufficient trapping of glucose by the liver. The insufficient trapping of glucose in the liver is due to the liver mediated IR. The main factor leading to IR is accumulation of fat in the liver. This brings us to the basic question as to what causes fatty liver (Flowchart 1). High carbohydrate/high fat diet increases insulin production, which pushes sugar from blood into liver. The liver cells are filled up with stored glycogen. The hepatic fat predominately comes from three sources:

- Dietary fat,
- De-novo lipogenesis due to high insulin level, and
- Fatty acid generation from adipose tissue lipolysis.

In addition the role of absorbed fructose is also important. Fructose unlike glucose can only be metabolized by the liver and not by other tissues. In fatty liver, there is already high hepatic glucose/glycogen; hence, fructose can only be converted into fat which adds to the fatty pool. Fatty acid accumulation occurs in the liver cells which would normally be oxidized to produce energy. However, the oxidative stress and mitochondrial dysfunction in fatty liver prevents oxidation. The fatty acid is therefore esterified into triglycerides and stored in the liver cells. Fat in the liver impairs insulin signaling, leading to IR. The resultant IR worsens hyperinsulinemia, which affects various metabolic processes in the liver. First, it stimulates the enzyme hexokinase, which phosphorylates glucose. In addition, it also activates the enzymes phosphofructokinase and glycogen synthase, which are involved in glycogen synthesis. When glycogen stores are saturated, the excess glucose is then shunted to fatty acid synthesis, which further adds to liver fat.

The liver mediated IR is a manifestation of the inherent ability of liver to protect itself from ongoing onslaught of further sugar/fat accumulation in liver cells, which is likely to cause cell disintegration. The stored fat is therefore transported out from the cell in the form of free fatty acid and VLDL, which causes tissue IR in various organs (Fig. 1). The IR prevents glucose transport from blood to liver, thus leading to poor trapping in liver and consequent rise in blood sugar.

Increased Hepatic Glucose Output in Diabetes

It is also well known that hepatic glucose output is increased in T2DM, and it has a major contribution in fasting hyperglycemia. Increased free fatty acids inhibit the insulin action on liver, and insulin-induced suppression of glucagon is impaired, thus leading to increased production of hepatic glucose excessive release of glucose from liver further increases blood sugar levels although the levels may still be maintained within the normal range due to compensatory high pancreatic beta cell production of insulin.

Phases of T2DM and the Role of Pancreatic Fat

It is well known that in diabetics, there is a prolonged period of 12–14 years of IR with compensatory hyperinsulinemia keeping the blood sugar within the normal range with gradually increasing HbA1c to prediabetic levels. Then comes the pancreatic beta cell failure resulting in reduced...
insulin production causing overt diabetes (Fig. 2). The question is what causes beta cell failure? Various theories in literature have been suggested especially the burnout theory due to persistent insulin overproduction by the pancreatic beta cells leading to cell death causing reduced insulin production. If this was so then T2DM would clearly be an irreversible condition. On the contrary, there is evidence of increase in insulin secretion post-bariatric surgery or following a hypocaloric diet.\textsuperscript{3,4} Such interventions have the ability to reverse diabetes completely. Hence, a more plausible explanation would be that the beta cells have been rendered metabolically inactive due to reversible factors. Evidence suggests that fatty acids prevent beta cell proliferation. In the genetic model, Zucker diabetic fatty rats rapid increase in pancreatic fat leads to development of diabetes. When food intake is restricted in this model, diabetes did not develop. This also suggests that a significant

Fig. 1: Sources and fate of free fatty acids in liver

Fig. 2: Two phases of type 2 diabetes
mass of beta cells is not permanently damaged but became metabolically inactive. Thus, pancreatic fat (PF) accumulation is an important precursor for development of diabetes. The amount of PF is greater in diabetics and increases with the duration of diabetes. Patients with PF have a higher prevalence of T2DM than non-PF controls (12.6% vs. 5.2%) and T2DM was independently associated with PF. A cohort of patients with biopsy proven NASH had more PF in diabetics compared to patients without diabetes. The fatty liver cells are overdistended with fat which is then transported to different organs including the pancreas as free circulating fatty acids and VLDL particles which lead to tissue IR and PF accumulation. There is evidence to suggest this cross talk between the fatty liver and PF. Fat in pancreas may lead to metabolic suppression of beta cells causing pancreatic failure and reduced insulin production leading to T2DM. This hypothesis appears attractive but needs to be evidence based. There are studies on post-bariatric surgery patients demonstrating lowering of pancreatic triglyceride content with simultaneous increase in insulin secretion. Bariatric surgery leads to fat mobilization from various tissues and liver/pancreas are the earliest targets of mobilization leading to reduction in liver and PF causing improvement in insulin sensitivity and insulin production. Hence, improvement in blood glucose in post-bariatric surgery patients occurs early even before body weight loss and this improvement in blood glucose has linear correlation with reduction in fat content of liver and improved sensitivity to insulin and the normalization of fasting blood glucose which occurred within 7 days. PF content reduction occurred in 8 weeks and was accompanied by restoration of first phase insulin.

**Evidence Suggesting Fatty Liver Leads to T2DM**

Over the past 15 years there have been numerous observational studies suggesting that fatty liver is an independent risk factor for development of diabetes (Table 1).

**Secondary Diabetes is Related to Liver Disease**

Liver is the most important organ for regulation of blood sugar. It is therefore, a simple understanding that chronic liver disease is associated with impaired glucose tolerance and development of diabetes. Glucose intolerance can be seen in about 80% of patients, and diabetes in about 30–60% of patients with chronic liver disease. Apart from fatty liver disease, other conditions like hemochromatosis, cystic fibrosis, chronic liver disease due to alcohol abuse, chronic hepatitis C, and glycogen storage disorders are also associated with development of diabetes.


### TABLE 1

Observational studies of the association between NAFLD and T2DM

<table>
<thead>
<tr>
<th>Study</th>
<th>Study population</th>
<th>Length of follow-up (diagnosis)</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fan et al. (2007) Chinese study</td>
<td>Age and sex matched 1,146 individuals with and without NAFLD</td>
<td>7 years, ultrasound based NAFLD diagnosis</td>
<td>Higher incidence of T2DM in NAFLD group (OR 4.6, 95% CI 3.0–7.1)</td>
</tr>
<tr>
<td>Shibata et al. (2007) Japanese study</td>
<td>3,189 male ≥ 40 years age</td>
<td>8 years, ultrasound based NAFLD diagnosis</td>
<td>NAFLD significantly increases the risk of T2DM (HR 5.5, 95% CI 3.6–8.5)</td>
</tr>
<tr>
<td>Kim et al. [2008] South Korean study</td>
<td>5,372 individuals</td>
<td>5 years, ultrasound based NAFLD diagnosis</td>
<td>NAFLD was independent risk factor for T2DM (HR 1.51, 95% CI 1.04–2.20).</td>
</tr>
<tr>
<td>Yamada et al. (2010) Japanese study</td>
<td>12,375 individuals</td>
<td>5 years, ultrasound based NAFLD diagnosis</td>
<td>Fatty liver is independent risk factor for development of T2DM (OR 1.91, 95% CI 1.56–2.34)</td>
</tr>
<tr>
<td>Sung et al. (2011) South Korean Study</td>
<td>11,091 individuals</td>
<td>5 years, ultrasound based NAFLD diagnosis</td>
<td>Increased risk of T2DM in NAFLD (OR 2.05, 95% CI 1.3–3.1)</td>
</tr>
<tr>
<td>Bae et al. (2011) South Korean Study</td>
<td>7,849 individuals</td>
<td>5 years, ultrasound based NAFLD diagnosis</td>
<td>Increased risk of T2DM in NAFLD (HR 1.33, 95% CI 1.07–1.66)</td>
</tr>
<tr>
<td>Sung et al. (2012) South Korean Study</td>
<td>12,853 individuals</td>
<td>5 years, ultrasound based NAFLD diagnosis</td>
<td>NAFLD was independently associated with incident T2DM (OR 2.42, 95% CI 1.7–3.36)</td>
</tr>
<tr>
<td>Ekstedt et al. (2006) Swedish study</td>
<td>Retrospective study, 129 individuals</td>
<td>13.7 years, liver biopsy based NAFLD diagnosis</td>
<td>At follow-up, 58% of patients developed T2DM and 20% developed impaired glucose tolerance</td>
</tr>
<tr>
<td>Alessandro Mantovani, et al. (2018) Meta-analysis</td>
<td>19 observational studies (296,439 individuals)</td>
<td>Median 5 years</td>
<td>NAFLD associated with two fold increase risk of diabetes</td>
</tr>
<tr>
<td>Sung et al. (2019) South Korean Study</td>
<td>70,303 adults</td>
<td>3.3 years</td>
<td>Diabetes risk increased with increasing insulin resistance (HR-6.6)</td>
</tr>
</tbody>
</table>

### Flowchart 2: Triumvirate pathology of T2DM

The traditional triumvirate features in the pathogenesis of diabetes, viz. IR, diminished insulin release from pancreatic islet beta cells and increased hepatic glucose output (Flowchart 2) gave way to the ominous octet proposed by deFronzo in his Banting Lecture a decade back. However, it is imperative to note that the triumvirate features had the liver contributing to categorically all the features. The octet may provide the treating physicians with different ways to tackle the treatment of diabetes, but it will be pertinent to understand that the liver-pancreas axis is involved in most of the features of the octet. Thus, liver is an important organ involved in glucose homeostasis and plays an important role in the pathogenesis of T2DM. In fact, reversal of fatty liver may help ameliorate IR, and may aid in the prevention of development of type 2 diabetes. Thus, fatty liver may be considered the main organ responsible for IR and T2DM. Diabetes should be considered a reversible metabolic state due to excess intra-organ fat especially fatty liver.

### Conclusion

The traditional triumvirate features in the pathogenesis of diabetes, viz. IR, diminished insulin release from pancreatic islet beta cells and increased hepatic glucose output (Flowchart 2) gave way to the ominous octet proposed by deFronzo in his Banting Lecture a decade back. However, it is imperative to note that the triumvirate features had the liver contributing to categorically all the features. The octet may provide the treating physicians with different ways to tackle the treatment of diabetes, but it will be pertinent to understand that the liver-pancreas axis is involved in most of the features of the octet. Thus, liver is an important organ involved in glucose homeostasis and plays an important role in the pathogenesis of T2DM. In fact, reversal of fatty liver may help ameliorate IR, and may aid in the prevention of development of type 2 diabetes. Thus, fatty liver may be considered the main organ responsible for IR and T2DM. Diabetes should be considered a reversible metabolic state due to excess intra-organ fat especially fatty liver.
References

Nonalcoholic fatty liver disease (NAFLD) and its complications are growing with increasing prevalence of obesity. Multiple factors and pathways are involved in pathogenesis of disease. In the absence of effective pharmacotherapy that addresses all or most of the components of disease and reverses the inflammation and fibrosis, primary approach to treat NAFLD focuses on promoting weight loss through diet and lifestyle interventions. The choice of therapy is dependent on degree of overweight, comorbidities, and patient preferences. This chapter will review the dietary therapy and lifestyle changes of NAFLD.

**Introduction**

Nonalcoholic fatty liver disease (NAFLD) and its complications are growing with increasing prevalence of obesity worldwide. Under the umbrella of NAFLD, there are two histological phenotypes:

- Steatosis (nonalcoholic fatty liver, NAFL) and
- Steatosis with inflammation, ballooning and fibrosis (nonalcoholic steatohepatitis, NASH).

NAFLD often occurs concomitantly with other end organ diseases like diabetes, hypertension, coronary artery disease, and chronic kidney disease. These are often connected to common biology linked to metabolic stress and systemic inflammation. So term NAFLD is proposed to rename as metabolic dysfunction associated fatty liver disease (MAFLD) to give clearer concept of liver manifestations of this multisystem disease. 

Natural history of disease is influenced by various factors like age, sex, ethnicity, diet, hormonal status, genetic, epigenetic factors, gut microbiome, alcohol, and metabolic status and leads to heterogeneous clinical phenotype.

**Aim and objectives of dietary restriction and exercise:**

Patients with NAFLD/MAFLD are metabolically unhealthy with imbalance between calorie intake and expenditure that leads to obesity, insulin resistance, and other metabolic disorders. Obesity doubles the prevalence of NASH and its progression to cirrhosis, liver failure, and hepatocellular carcinoma (HCC). Prior to development of cirrhosis, clinical outcomes of disease are mostly related to cardiovascular system. With the advancement of fibrosis stage or cirrhosis development, liver-related outcomes increase exponentially. The ideal goal of treatment is to subside inflammation, regression of fibrosis, and cirrhosis with simultaneously addressing concomitant metabolic disorders and cardiovascular mortality.

Histology based data have showed that weight loss is the only modality at present that has favorable impact on reducing hepatic as well as extrahepatic complications. In a prospective study of 293 patients, degree of weight loss was independently associated with improvements in all NASH-related histological parameters. Nevertheless, in the study just 10% of patients reached a 10% weight loss and 70% of the cohort did not lose 5% of total body weight (Fig. 1). Approximately 22 kcal/kg (±20%) is required to maintain a kilogram of body weight in a normal-weight
adult. An average deficit of 500 kcal/day should result in an initial weight loss of about 0.5 kg/week. Both lean body mass and body fat decreases with weight loss and reach plateau after 3–6 months. Further caloric restriction and increased physical activity required to overcome this plateau effect. Aim of weight loss is to preserve muscle mass and decrease visceral fat.

Types of diet: Planning a diet requires the selection of caloric intake and then choice of foods according to local culture and palatability. Replacement of food by low-calorie meals containing 250–350 kcal/package in form of nutrition bars, frozen food, and prepackaged meals resulted in early initial weight loss, which then was maintained over long term (4 year follow-up). The Mediterranean diet includes consuming high level of monounsaturated fat relative to saturated fat; moderate consumption of alcohol, mainly as wine, a high consumption of vegetables, fruits, legumes, and grains, a moderate consumption of milk and dairy products, mostly in the form of cheese, and a relatively low intake of meat and meat products. Adherence to the Mediterranean dietary pattern leads to a significant decrease in liver fat and insulin resistance among overweight patients with NAFLD.

Dietary Composition

Carbohydrate: Low- and very low-carbohydrate (60–130 gm and <60 gm, respectively) diets have been more effective for short-term weight loss than low-fat diets, but not for long-term weight loss, compared with a low-fat diet. Restriction of carbohydrates less than 50 gm/day cause rapid weight loss, due to breakdown of glycogen, ketosis development, and fluid loss. In addition, very low-carbohydrate diets are associated with a small increase in energy expenditure. Side effects may be more with low-carbohydrate diet like constipation, headache, muscle cramps, diarrhea, weakness, and rash. There is some data to suggest that low-carbohydrate diet have early weight independent effect on liver steatosis and insulin resistance but after more than 7% weight loss this benefit is similar like hypocaloric low-fat diet.

A low-carbohydrate diet may be planned either by reducing the total amount of carbohydrate or by consuming foods with a lower glycemic index (GI) or glycemic load. High-glycemic-load foods increase postprandial glycemia and insulinemia, particularly in patients with insulin resistance. Since the duration of post-meal satiety is related to postprandial glycemia, low-GI foods have been hypothesized to reduce hunger signals and delay the onset of the next meal. Meals with high GI were found to be associated with high-grade liver steatosis (assessed by ultrasound), particularly in insulin-resistant subjects.

Fructose: Fructose mainly derived from table sugar (50% fructose) and corn syrup (55% fructose). High intake of sugar-sweetened foods in general contributes to weight gain and high liver fat due to their high-energy density, glycemic load, and palatability. Fructose role has been implicated in alteration of gut microbiome, increasing gut permeability, endotoxemia and hyperuricemia. Soft drinks contain caramel coloring rich in advanced glycation end products, which increases insulin resistance and liver injury.

Fat: The quality of fat consumed and its food sources appear to be more important for health than total fat intake. Trans fatty acids and saturated fatty acids have been associated with metabolic derangement (increase LDL, low HDL), and an elevated cardiovascular risk. Saturated fat promotes visceral and liver fat deposition. Assessment of dietary pattern in NASH patients showed higher saturated fat and cholesterol intake and lower polyunsaturated fatty acids (PUFA), fiber, vitamin C and E consumption.

Monounsaturated fatty acids (oleic acid, palmitoleic acid in canola and olive oil) consumption favors accumulation of fat in adipose tissues rather than the liver in animal models. In type 2 diabetic patients, an
isocaloric diet enriched in MUFA compared with a diet higher in carbohydrate and fiber was associated with a significant fat reduction in liver (measured by proton magnetic resonance spectroscopy) despite a stable weight in both groups. Polyunsaturated fatty acids (n-6: linoleic acid, arachidonic acid and n-3: α-linolenic acid, eicosapentaenoic acid, docosahexaenoic acid) are abundant in fish oil. Low intake n-3 fatty acids and higher n-6/n-3 ratio is found in NAFLD patients than healthy controls. It is associated with a proinflammatory state and increased lipogenesis leading to steatosis. Conversely, n-3 PUFAs down-regulate sterol regulatory element binding protein 1c (SREBP-1c) and up-regulate peroxisome proliferator activated receptor α (PPAR-α) that would favor fatty acid oxidation and reduce steatosis. PUFA Supplementation is effective in reducing total liver fat but not beneficial in histological improvement in terms of inflammation and fibrosis.

High cholesterol consumption (>500 mg/day) was associated with higher risk of cirrhosis or liver cancer, instead of total fat consumption.

**Protein:** High-protein diets have been recommended for the treatment of obesity because they are more satiating and stimulate thermogenesis. Higher-protein diets may improve weight maintenance. Total red meat and processed red meat intake are both positively associated with risk of coronary artery disease.

Fiber has several beneficial metabolic effects, including increased satiety, increased incretin secretion, reduced absorption rate of CHO and proteins, modulation of gut microbiota, and increased fermentation products, such as butyrate.

Increased coffee consumption has been associated inversely with the risk of cirrhosis or progression of fibrosis but not with steatosis. In epidemiological studies, coffee consumption is associated with a lower risk of metabolic syndrome. Animal studies suggest, coffee exerts its effects by reducing hepatic fat accumulation, systemic and liver oxidative stress and liver inflammation. Drinking coffee reduces HCC risk. For the majority of healthy adults, consuming less than 400 mg of caffeine a day appears to be safe.

**Intermittent Fasting**

Intermittent fasting strategies, including alternate-day fasting (25% of total energy consumed on “fast” days and 125% consumed on “feast” days) and time-restricted feeding (TRF) (cessation of eating by a certain time each day) have been used as approaches to weight loss. Short-term TRF trials have shown that the alignment of the feeding period with circadian rhythms may result in weight loss and improve metabolic parameters. The mechanisms by which intermittent fasting affect health may include improved insulin sensitivity and anti-inflammatory effects.

**Summary of diet recommendations for NASH:**
- Calorie restriction (500–1000 kcal/day)
- Low-carbohydrate (<40%) diet—replace calories with PUFA, MUFA
- Low-fat diet—replace calories with low-GI foods
- Reduce trans FA (<1%), saturated fats (<7%), and cholesterol (<200 mg/day)
- Proteins from fish, poultry, nuts, and legumes & restrict unprocessed red meats (<300 g/week), processed meats (<2/week)
- Increase the intake of cereal-derived non-soluble fiber (whole grain) (25 g/day)
- Vegetables (3–5 servings/day), fruits (2–4 servings/day), nuts (4 servings/week), olive oil, and low-fat dairy products.

**Physical Activity**

Sedentary behavior is a component of reduced life expectancy. The energy expenditure is sum of resting metabolic rate (RMR), the thermic effect of feeding (TEF), and physical activity. Exercise (aerobic and resistance) is planned form of physical activity. While it may be difficult to lose weight with exercise alone, exercise programs added to moderate to severe caloric restriction have additional effect upon weight loss. If a patient burn 100 calories during exercise each day (700 calories per week), it would take almost 5 weeks to utilize the energy (3,500 calories) in half kg of fat. Exercise alone, in the absence of any change in body weight or composition, may enhance peripheral insulin sensitivity and glucose homeostasis mediated by insulin-receptor up regulation in muscle tissue, enhancing whole-body lipid oxidation, decreased hepatic triglyceride accumulation and lower hepatic FFA uptake (Fig. 2). Increased physical activity attenuates the diet-induced loss of muscle mass, which in turn increases physical functioning and insulin sensitivity. Both aerobic or resistance exercise are effective in reducing liver
The addition of resistance exercise to weight-loss programs can help prevent the reduction in muscle and bone mass. Patients with poor cardiorespiratory reserve may better tolerate resistance exercise. Weight training results in greater increases in fat-free mass. The recommendation by American Heart Association of intense cardiorespiratory activity (aerobic & resistance) for at least 150 minutes (preferably 300 minutes) per week, or at least 75 minutes (preferably 150 minutes) is adapted by EASL for NASH patients. The clinician needs to be aware for identifying high-risk patients who may require a more thorough evaluation before beginning an exercise program. The major hurdle is obtaining long-term compliance—especially in individuals who are not accustomed to regular intense exercise.

**Conclusion**

The primary approach to treat NAFLD focuses on the control of the underlying risk factors like diabetes, hyperlipidemia, obesity, and other comorbidities through diet and lifestyle changes. After the initial weight-loss phase, the weight-maintenance phase is key for preventing long-term complications. Strategies to enhance long-term adherence to lifestyle interventions, with a multidisciplinary approach should be included.

**References**

Non-Pharmacological Management of NAFLD/NASH (Diet, Exercise, and Role of Intermittent Fasting)


40. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;65(6):1388-402.
Acute pancreatitis is a common disease, major etiologies being gallstones or alcohol ingestion. Diagnosis is based on clinical symptoms, elevated pancreatic enzymes, and imaging findings. Revised ATLANTA classification (2013) has defined the types, severity, organ failure, and complications of acute pancreatitis. Majority of patients have self-limiting disease while some may develop severe disease, causing organ failure and complications such as pseudocyst or wall-off necrosis (WON). Treatment involves early enteral nutrition, intravenous fluids, analgesics, with avoidance of use of antibiotics. Endoscopic and/or surgical interventions are required in case of complicated unresolving pancreatic collections.

**Introduction**

Acute pancreatitis (AP) is a common gastrointestinal tract (GIT) disease causing enormous physical, emotional, and socioeconomic human burden. The first clinical description of AP was given by Dutch anatomist Nicholaes Tulp in 1652. Incidence of AP varies from 30–80/100,000 population. In India, approximately 74% of patients of AP are men with the mean age being 40 years, which is a younger age group compared to other parts of the world.

**Definitions**

ATLANTA classification defining the severity and complications of AP was first described in 1992. Since then there has been continuing research in this field and has resulted in improvement of knowledge about the disease process, and hence management of AP. Also, there has been a major improvement in imaging modalities, which has helped to classify and define disease severity and complications in a clarified way as a part of revised ATLANTA classification proposed in 2013. This revision includes assessment of the severity clinically and provides objective terms to define the local complications of AP, which are described as follows.

**Definitions and Classification: Proposed to be Used in Clinical and Research Communications**

**Diagnosis of AP**

The diagnosis of AP requires two out of following three features:

- Pain abdomen suggestive of AP (acute onset severe, persistent, epigastric pain, aggravated with food intake, and radiating to the back);
- Pancreatic enzymes activity (serum lipase and serum amylase) more than three times elevated than normal range; and
- Imaging findings on contrast-enhanced computerized tomography (CECT), magnetic resonance imaging (MRI), or trans abdominal ultrasonography, showing characteristic changes of AP.
Routinely use of CECT in patients of AP is unjustified, as the diagnosis is apparent and most patients have a mild, non-complicated course. But if there is lack of improvement after 48–72 hours (e.g., persistent pain, nausea, fever, inability of start oral feeds), imaging using CECT or MRI is recommended for assessment of local complications such as peripancreatic fluid collection or pancreatic necrosis.

**Onset of AP**

The onset of AP is defined by the time when the typical abdominal pain first begins and not by the time when patient first seeks hospital care. This time of onset of pain abdomen is crucial to define the further complications of AP.

**Types of AP**

AP can be subdivided into two types based on presence or absence of necrosis:

- *Interstitial pancreatitis*—in the absence of pancreatic necrosis, the edematous pancreas in mild disease, is defined as interstitial pancreatitis;
- *Necrotizing pancreatitis*—in about 5–10% of patients, AP evolves to produce necrosis of pancreatic parenchyma, the peripancreatic tissue or both.

Pancreatic necrosis is defined as focal or diffuse areas of nonviable parenchyma which is 30% of the pancreas or 3 cm in size.

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**Complications**

**Organ Failure—Definition**

Organ failure is defined based on the assessment of three major organ systems:

- Cardiovascular
- Respiratory, and
- Renal. Modified Marshall scoring system (Table 1) is used to define organ failure.

**Local Complications—Definition**

The concept of local complications following AP was defined by the Original ATLANTA classification (1992). Since then with the advancement of the understanding of pathophysiology and improvement of imaging has led to better characterize the local complications as acute peripancreatic fluid collection, pancreatic pseudocyst (Fig. 1), acute necrotic collection, and walled-off necrosis (Fig. 2) based on the presence and absence of necrosis and time from the onset of pain abdomen, each of which has been defined by the revised ATLANTA classification (2013) (Table 2). Gastric outlet obstruction, splenic vein and portal vein thrombosis are some of the other local complications of AP.

**Systemic Complications—Definition**

Any exacerbation of previous comorbid conditions such as chronic lung disease, or coronary artery disease, by AP is defined as systemic complications.

---

### TABLE 1

**Modified Marshall scoring system**

<table>
<thead>
<tr>
<th>Organ systems</th>
<th>Scores</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory (FiO₂/PaO₂)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;400</td>
<td>301–400</td>
<td>201–300</td>
<td>101–200</td>
<td>≤100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal (creatinine mg/dL)</td>
<td>&lt;1.4</td>
<td>1.4–1.8</td>
<td>1.9–3.6</td>
<td>3.6–4.9</td>
<td>&gt;4.9</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular (systolic BP mm Hg)</td>
<td>&gt;90</td>
<td>&lt;90, fluid responsive</td>
<td>&lt;90, not fluid responsive</td>
<td>&lt;90, pH&lt;7.3</td>
<td>&lt;90, pH&lt;7.2</td>
<td></td>
</tr>
</tbody>
</table>

**FiO₂ calculation for non-ventilated patients**

<table>
<thead>
<tr>
<th>Supplemental oxygen (L/min)</th>
<th>FiO₂ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Room air</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
</tr>
<tr>
<td>6–8</td>
<td>40</td>
</tr>
<tr>
<td>9–10</td>
<td>50</td>
</tr>
</tbody>
</table>
The disease process of AP is not fixed and can vary from patient to patient. Arbitrarily the disease course can be divided into two overlapping phases with two peaks of mortality: Early and Late phase. These two phases are considered separately.

**Early Phase**
The early phase involves first week of disease presentation, but may sometimes be prolonged into the second week also. During the early phase, manifestations are due to the response to local pancreatic inflammation and injury. Pancreatic inflammation, in turn, activates cytokine cascade, which clinically manifests as systemic inflammatory response syndrome (SIRS) (Table 3). There is an increased risk of developing organ failure if SIRS is persistent. The presence and duration of organ failure in the early phase determines the severity of AP. If the organ failure resolves within 48 hours, it is defined as “Transient organ failure,” and if it persists for more than 48 hours, it is defined as “Persistent organ failure.” Multiorgan failure (MOF) is defined when more than one organ develops failure.

**Late Phase**
By definition, the late phase occurs only in patients with moderately severe or severe AP. It is characterized by the persistence of local complications or systemic signs of inflammation.

**Severity of AP—Definition**
It is prudent to define and distinguish patients of AP based on severity. The ATLANTA classification has defined three major types of severity—mild, moderate, and severe AP (Table 4).

**Etiology**
The most common causes of AP are gallstones (40-70%) and alcohol (25-35%). Other etiologies being post ERCP (5%), post trauma, especially in children (1%), idiopathic (25%), and miscellaneous (5%). Alcohol-related
pancreatitis usually manifests as a spectrum, ranging from distinct episodes of AP to chronic pancreatitis causing irreversible changes silently.

**Risk Stratification and Predicting Severe AP**

For initial management and hospitalization, laboratory investigations and imaging studies can be useful but are unreliable to predict the severity of AP. Laboratory investigations like hematocrit, blood urea nitrogen (BUN), creatinine or CRP in the 1st 48 hours can be normal. Also, cross sectional imaging cannot determine severity early in disease course as necrosis is usually absent on admission and may take 2–3 days to develop. Thus, as there is an absence of any definite test to determine the severity of AP, clinical assessment of third space fluid losses, shock and signs and symptoms suggestive of organ dysfunction is of paramount importance.

**Management (Flowchart 1)**

**Pain Management (Analgesia)**

Abdominal pain is the presenting and distressing symptom in patients with AP. Effective and successful analgesia is an important component of the management of AP. An added desirable effect of the analgesic could be its impact on the underlying inflammatory process. Both opioid analgesics and nonsteroid anti-inflammatory agents (NSAIDs) have been used in patients with AP for pain relief. However, the evidence for their efficacy and safety profile is limited. The concern with NSAIDs is adverse events such as gastrointestinal bleeding and acute kidney injury. Opiates have shown by a randomized controlled trial to have better analgesic effect and safety profile compared to NSAIDs for AP. Nalbuphine (an opioid with μ receptor antagonism) is a latest armamentarium useful for AP pain.

**Fluid Resuscitation—Importance of Intravenous Hydration**

Multiple factors are responsible for often causing hypovolemia in patients affected by AP, such as vomiting, third space loss, decreased oral intake, diaphoresis, and increased respiratory losses. Besides, inflammation of pancreas causes pancreatic edema and microcirculatory effects causing decreased blood flow, which in turn causes cell death, pancreatic tissue necrosis and pancreatic enzymes release, activating further numerous inflammatory cascades.

In AP, there is a median fluid loss of 3.2 liters. The fluid should be given as 15–20 mL/kg bolus dose followed by 1.5–3 mL/kg/hour, depending on the response for the first 12–24 hours. Although the most effective approach to early fluid resuscitation has yet to be determined, studies have suggested that lactated Ringer’s maybe the preferred solution for initial hydration. Owing to its bicarbonate content and stable pH, this isotonic solution, when compared to normal saline, may prevent the development of metabolic acidosis, which can complicate care in patients receiving large-volume resuscitation using isotonic saline. Also, there are theoretical advantages in stabilizing the pancreas by preventing acidosis, which increases degranulation, enzyme release. The goal of fluid therapy is to achieve a mean arterial BP of minimum 70 mm Hg, hematocrit of 40–42, urine output—0.5–1 mL/min. Monitoring of fluid therapy can be done using invasive methods like central venous pressure, stroke volume, arterial pressure wave-form, and noninvasive methods like IVC diameter: <1.5 cm or >50% index-deficit, lung ultrasound for fluid overload. Elderly patients and those with history of cardiac and/or renal disease should be taken carefully resuscitated.
Antibiotics—Role in AP Management
Routine use of prophylactic antibiotics in patients with mild AP and also severe AP is not recommended. Also, in patients having sterile necrosis, the use antibiotics to prevent the evolution of infection is not recommended. After 7–10 days of hospital stay, in patients with lack of improvement and having persistent fever and increasing WBC counts, infected pancreatic or peripancreatic necrosis should be suspected. Serum procalcitonin may be helpful as a useful marker. In these patients, there are two ways to manage: (a) CT-guided fine needle aspiration (FNA) with culture sensitivity can be used to start suitable
antibiotics, or (b) Empirical use of antibiotics can be done after obtaining necessary blood or urine culture sensitivity for disease causing agents, without CT-guided FNA. Infected necrosis warrants use of antibiotics which can penetrate the necrosis, such as carbapenems, quinolones, and metronidazole, as per the local pattern of sensitivity of organisms. Timely use of antibiotics in such cases can delay or sometimes avoid interventions, hence reducing morbidity and mortality. Evidence of extra-pancreatic infections like urinary tract infections, cholangitis, catheter-acquired infections, bacteremia, and pneumonia necessitates antibiotics. Routinely antifungal agents along with antibacterial agents (used for prophylaxis or treatment) are not recommended.

**Nutrition in AP**

Traditionally patients having AP were kept nil per mouth (NPO) to theoretically provide rest to the organ. Multiple experimental and clinical studies have subsequently shown that bowel rest causes mucosal atrophy and increases infectious complications due to bacterial translocation from the gut. Also, studies have shown that early enteral feeding in the course of AP reduces hospital stay, and hence decreased morbidity. In mild AP, if there is absence of vomiting, and if abdominal pain has improved, oral feeds should be started as soon as possible. Oral feeds in mild AP are introduced as a low-fat, low-residue, light diet as the patient improves clinically. Polymeric feeds (feeds containing all major nutrients) are preferred consisting of 25–30 kcal/kg with 1.2–2 gm/kg protein. In mild as well as severe AP, total parenteral nutrition ideally should be avoided as it increases chances of infectious complications and other peripheral or central line-related complications.

Use of nasogastric tube for enteral nutrition appears to be safe; however, the use of nasojejunal tube is typically preferred to avoid gastric phase of pancreatic stimulation. Nasogastric tube placement is far easier compared to the nasojejunal tube (requires fluoroscopic guidance for placement and is expensive), which is advantageous for patients in intensive care unit (ICU) treatment. In patients presenting as severe AP, on initial assessment, should be started on enteral tube feeding as a part of primary therapy. In the late phase of AP (2nd–3rd week) maintaining nutrition is critical, the target should be to provide 1500–2000 kcal diet.

**Endoscopic Retrograde Cholangiopancreatography (ERCP)—Role in AP**

As per the latest recommendations, patients with concurrent AP and acute cholangitis with high clinical suspicion of choledocholithiasis should undergo ERCP with biliary stenting within 24 hours of admission as a therapeutic procedure. Usually, in patients with gallstone pancreatitis who lack laboratory or clinical evidence of ongoing biliary obstruction, magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasound (EUS) rather than ERCP should be used to screen for choledocholithiasis.

Also, ERCP on one hand, it can be a therapeutic modality for biliary pancreatitis, while on the other hand, it can be an important and preventable etiology of AP. The risk of post-ERCP pancreatitis is around 5%. Three methods to reduce the risk of post-ERCP pancreatitis, especially severe AP include:
- Pancreatic duct stents
- Use of guidewire for cannulation
- Rectal NSAIDs (diclofenac suppository) pre-procedure.

**Infected Pancreatic Necrosis**

The step-up approach is recommended with conservative treatment in ICU 1st followed by percutaneous drainage, which is followed by minimally invasive necrosectomy. Primarily conservative management results in mortality comparable to surgery in patients with infected pancreatic necrosis. If necrosectomy is required, endoscopic step-up approach should be preferred.

**Conclusion**

The diagnosis and optimal management of AP requires a systematic approach and multidisciplinary decision-making. Regardless of pancreatitis severity, recommended medical management includes goal-directed intravenous fluid resuscitation, early enteral feeding, avoidance of antibiotics as prophylaxis and urgent ERCP for patients with acute biliary pancreatitis complicated by cholangitis. Hence to conclude the first 24–48 hours are critical, and hence triaging of these patients on first presentation to hospital is an important approach to enable appropriate level of care.
References

Abstract

Functional gastrointestinal disorders (FGIDs), common problems in GI practice, are diagnosed by symptom-based criteria, such as the most recent iteration by the Rome Foundation, called Rome IV criteria and limited laboratory investigations. However, in presence of alarm symptoms, which may suggest presence of organic diseases, more thorough investigations may be needed. Different FGIDs may overlap in a single patient. The two common subtypes of FGIDs, such as irritable bowel syndrome (IBS) and functional dyspepsia (FD), are elaborated in this chapter. Treatment of FGIDs would depend on its subtypes, such as diarrhea- or constipation-predominant IBS or epigastric pain and postprandial distress syndrome subtypes of FD. The treatment also depends on severity of the condition, presence of psychological comorbidity, biological factors, etc.

Introduction

Physicians and Gastroenterologists often encounter patients with functional gastrointestinal disorders (FGIDs) in their clinical practice. Patients with FGIDs are diagnosed based on the symptom-based criteria. FGIDs are characterized by the presence of chronic gastrointestinal (GI) symptoms (at least during the last 3 months with onset at least 6 months previously) in the absence of identifiable structural lesions explaining these symptoms on investigations including GI endoscopy. It is, however, noteworthy that though the routine investigations, including GI endoscopy, do not pick-up organic lesions in patients with FGIDs, more sensitive tests may pick-up subtle structural abnormalities and molecular aberrations that may explain their symptoms. Hence, in the recent time, it has been considered that many of these disorders may be “micro-organic” in nature, challenging the concept that these disorders are entirely functional or psychogenic. Rome Foundation, which formulates diagnostic and treatment algorithm for FGIDs, released its fourth iteration of Rome criteria in April 2016. Experts of Rome Foundation correctly decided to underscore term “functional” and consider the gut to be more important than brain in the pathogenesis; hence, the new name for these disorders has been “Disorders of Gut-Brain Interaction (DGBI).”

FGIDs are chronic disorders that are not fatal but cause considerable impairment of quality of life, work absenteeism, burden to the society, health care, economy, and family. Considering the high frequency of these disorders in the global population, the magnitude of the problem of FGIDs cannot be underestimated. Hence, knowledge about the diagnosis and management of these disorders at primary and secondary care settings are essential issues that need to be deliberated. Accordingly, this chapter will briefly discuss the current classification of FGIDs, the diagnostic criteria, and management of common forms of FGIDs, for example, irritable bowel syndrome (IBS) and functional dyspepsia (FD). The current classification of FGIDs (Rome IV) is presented in Table 1.
**TABLE 1**

Different categories of functional gastrointestinal disorders according to the most recent iteration of Rome Foundation (Rome IV classification)

<table>
<thead>
<tr>
<th>Category</th>
<th>Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Esophageal disorders</strong></td>
<td>- Functional chest pain - Functional heartburn - Reflux hypersensitivity - Globus - Functional dysphagia</td>
</tr>
<tr>
<td><strong>Gastroduodenal disorders</strong></td>
<td>- Functional dyspepsia - Postprandial distress syndrome (PDS) - Epigastric pain syndrome - Belching disorders - Excessive supragastric belching - Excessive gastric belching - Nausea and vomiting disorders - Chronic nausea vomiting syndrome (CNVS) - Cyclic vomiting syndrome (CVS) - Cannabinoid hyperemesis syndrome (CHS) - Rumination syndrome</td>
</tr>
<tr>
<td><strong>Bowel disorders</strong></td>
<td>- Irritable bowel syndrome (IBS) - IBS with predominant constipation (IBS-C) - IBS with predominant diarrhea (IBS-D) - IBS with mixed bowel habits (IBS-M) - IBS unclassified (IBS-U) - Functional constipation - Functional diarrhea - Functional abdominal bloating/distention - Unspecified functional bowel disorder - Opioid-induced constipation</td>
</tr>
<tr>
<td><strong>Centrally mediated disorders of gastrointestinal pain</strong></td>
<td>- Centrally mediated abdominal pain syndrome (CAPS) - Narcotic bowel syndrome (NBS)/opioid-induced GI hyperalgesia</td>
</tr>
<tr>
<td><strong>Gallbladder and sphincter of Oddi (SO) disorders</strong></td>
<td>- Biliary pain - Functional gallbladder disorder - Functional biliary SO disorder - Functional pancreatic SO disorder</td>
</tr>
<tr>
<td><strong>Anorectal disorders</strong></td>
<td>- Fecal incontinence - Functional anorectal pain - Levator ani syndrome - Unspecified functional anorectal pain - Proctalgia fugax - Functional defecation disorders - Inadequate defecatory propulsion - Dyssynergic defecation</td>
</tr>
<tr>
<td><strong>Childhood functional GI disorders: Neonate/Toddler</strong></td>
<td>- Infant regurgitation - Rumination syndrome - Cyclic vomiting syndrome (CVS) - Infant colic - Functional diarrhea - Infant dyschezia - Functional constipation</td>
</tr>
</tbody>
</table>
In the above classification, the different FGIDs are considered as pure disorders. However, in practice, more than two-thirds of patients present overlapping symptoms of multiple FGIDs. The various categories of bowel disorders such as IBS, functional diarrhea, and functional constipation often overlap with upper GI disorders such as FD and gastroesophageal reflux disease (Fig. 1A). In an earlier study on 3,426 adult population of rural northern India, overlap of FD-IBS was commoner (4.1%) than IBS alone (2.7%) though FD was the most common form of FGID (15%; Fig. 1B). Overlap disorders often have a more severe illness, may require combination treatment, and may have a worse prognosis. In this chapter, the diagnosis and treatment of two common FGIDs (FD and IBS) are briefly discussed. It is important to note that several management principles of pure FGIDs, such as those of FD and IBS, would apply to overlap disorders. For example, a patient with constipation-predominant IBS and postprandial distress syndrome subtype of FD is expected to benefit from treatment with a pan-GI prokinetic drug such as prucalopride along with fundic relaxant such as acotiamide.

**Functional Dyspepsia**

“Dyspepsia” is a Greek word that refers to “bad digestion.” As per Rome IV criteria, FD is diagnosed using the symptom-based criteria that are listed in Table 2. However, if a patient fulfills the symptom-based criteria, he should be considered as having uninvestigated dyspepsia. Subsequently, a few investigations, including upper GI endoscopy, are required before a diagnosis of FD is made. However, in the absence of alarm features discussed later in this chapter, an empirical trial of drug-treatment may be instituted after due consideration by the physician on a case-to-case basis. A firm diagnosis of FD, however, requires an upper GI endoscopy. Though currently, most international recommendation warrant tests for Helicobacter pylori and its eradication, if present, its universal acceptability in the Indian scenario is subject to debate based on the limited available data (Flowcharts 1A and B).
TABLE 2 Rome IV criteria for the diagnosis of functional dyspepsia (FD)

**Functional dyspepsia**

**Diagnostic criteria**
1. One or more of the following:
   a. Othersome postprandial fullness
   b. Othersome early satiation
   c. Othersome epigastic pain
   d. Othersome epigastic burning

No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms

Must fulfill criteria for PDS and/or EPS.
Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS) are the two subtypes of FD. In practice, however, patients rarely present with pure EPS or PDS, but most patients have overlapping symptoms. The criteria, as suggested by the Rome IV Committee for diagnosis of EPS and PDS, are presented in Table 3.

**Management of FD**

Management of the patients with dyspepsia as per the Rome IV system is presented in Flowcharts 1A and B. One must not forget to look for alarm features (age >45 years, history of GI bleeding, weight loss, family history of gastric cancer, anemia, etc.). Patients with a history of alarm features must undergo thorough investigations including upper GI endoscopy and CT scan of the abdomen (in patients with a family history of gastric cancer and a high degree of clinical suspicion of gastric cancer) before considering dyspepsia to be functional. It is also important to note that the age cut off of 45 years may vary depending on the local epidemiology of gastric cancer. International societies, including experts in the Rome IV committee, suggested that *H. pylori* infection, if present on appropriate testing, should preclude the diagnosis of FD. If eradication of infection improves dyspeptic symptoms, the condition should instead be called *H. pylori*-associated dyspepsia. The applicability of this international guideline in India, however, may be viewed with skepticism. Though Indian literature on this issue is scanty, yet considering the high frequency of *H. pylori* infection in Indian adults, this strategy may not be practicable. Treatment of FD depends on its subtype. Whereas EPS, an uncommon subtype is treated with proton pump inhibitors and when unresponsive, antidepressants, PDS is treated with prokinetics, fundic relaxants, and psychotropic agents. Overlap syndrome is treated with combined therapeutic agents. Table 4 lists the drugs available currently in the Indian market for the treatment of two subtypes of FD.

**Irritable Bowel Syndrome**

**Diagnosis of IBS**

IBS is one of the common FGIDs seen in clinical practice both by the Gastroenterologists and the Physicians. IBS was variously called earlier, albeit inappropriately, as spastic colitis, chronic amebiasis, etc. In the past, the diagnosis of IBS could only be made once extensive investigations failed to find a cause for the chronic lower GI symptoms. Manning and Thompson, for the first time, introduced the criteria-based diagnosis of IBS in 1978. Since then, the Rome Foundation brought in several iterations of Rome criteria for the diagnosis of IBS. Manning’s criteria encourage a positive diagnosis of IBS without the need for multiple unnecessary investigations to exclude organic diseases before diagnosing IBS.

However, it is essential to note that in the study by Manning and Thompson, organic disorders excluded were peptic ulcer disease, inflammatory bowel disease, gastroesophageal reflux disease, gallstones, and carcinoma of the colon and not the conditions which closely mimic IBS such as lactose intolerance, celiac disease, microscopic colitis, small intestinal bacterial overgrowth, fecal evacuation disorder, collagenous colitis and microscopic, etc. Hence, over-reliance on such symptom-based criteria to exclude every organic disorder (some of which are rather micro-organic) may result in overlooking such conditions. Another limitation of the Manning criteria is the lack of due consideration for the duration of symptoms. As some of the organic disorders are expected to have a short duration of symptoms, the importance of time of illness cannot be overestimated. However, despite these limitations, Manning’s criteria remain quite useful and popular in practice not only among Gastroenterologists but also among Physicians. In addition to the higher sensitivity of Manning’s criteria as compared to the various iteration of Rome criteria in India, the simplicity of the former is a significant reason for its popularity.
Flowcharts 1A and B: Rome IV algorithm for management of functional dyspepsia

**Upper abdominal symptoms such as post-prandial fullness, early satiation, epigastric pain and burning, nausea, vomiting, belching, ruminating**

- History, physical examination
  - Uninvestigated nausea, vomiting, belching, ruminating
    - No
    - Yes
      - **Alarm features?**
        - No
        - Uninvestigated dyspepsia
          - Consider empirical therapy
        - Yes
          - UGI endoscopy
            - Positive
              - Consider Hp test and repeat
            - Negative
              - Symptoms resolved
        - No
          - Secondary dyspepsia
            - Yes
              - Symptoms resolved
            - No
              - Treatment as needed
      - No
        - Other diagnostic tests as indicated
          - No
            - Abnormality identified
              - Yes
                - Secondary dyspepsia
              - No
                - Abnormality identified
                  - Yes
                    - Eradication therapy
                  - No
                    - Functional dyspepsia
        - Yes
          - Abnormality identified

**Functional dyspepsia**

- Post-prandial distress syndrome (PDS)
  - Yes
    - Prokinetics
  - No
    - Chronic symptoms
      - Adequate relief
        - No
          - Anti-depressant
            - Yes
              - Long-term management
            - No
              - Refer for histopathologic, functional testing, experimental therapy
        - Yes
          - Delayed gastric emptying
            - Antiemetic, prokinetics
              - Yes
                - Increased fundic tone
                  - 5 HT A1 agonist
                    - Yes
                      - Ant-depressant, combination
                    - No
                      - Montelukast, H1, H2 blocker, combination
                  - Hypersensitivity
                    - Anti-depressant, combination
                      - Yes
                        - Long-term management
                      - No
                        - Refer for histopathologic, functional testing, experimental therapy
              - No
                - Reflux
                  - Yes
                    - Ant-depressant, combination
                      - Yes
                        - Long-term management
                      - No
                        - Refer for histopathologic, functional testing, experimental therapy
                  - No
                    - Refer for histopathologic, functional testing, experimental therapy
              - No
                - Delayed gastric emptying
                  - Yes
                    - Antiemetic, prokinetics
                      - Yes
                        - Increased fundic tone
                          - 5 HT A1 agonist
                            - Yes
                              - Ant-depressant, combination
                            - No
                              - Montelukast, H1, H2 blocker, combination
                          - Hypersensitivity
                            - Anti-depressant, combination
                              - Yes
                                - Long-term management
                              - No
                                - Refer for histopathologic, functional testing, experimental therapy
                      - No
                        - Refer for histopathologic, functional testing, experimental therapy
                  - No
                    - Refer for histopathologic, functional testing, experimental therapy
          - Epigastric pain syndrome (EPS)
            - Anti-secretory drugs
              - Yes
                - Long-term management
              - No
                - Refer for histopathologic, functional testing, experimental therapy
    - Chronic symptoms
      - Anti-secretory drugs
        - Yes
          - Long-term management
        - No
          - Refer for histopathologic, functional testing, experimental therapy
      - Delayed gastric emptying
        - Antiemetic, prokinetics
          - Yes
            - Increased fundic tone
              - 5 HT A1 agonist
                - Yes
                  - Ant-depressant, combination
                - No
                  - Montelukast, H1, H2 blocker, combination
              - Hypersensitivity
                - Anti-depressant, combination
                  - Yes
                    - Long-term management
                  - No
                    - Refer for histopathologic, functional testing, experimental therapy
            - No
              - Refer for histopathologic, functional testing, experimental therapy
          - No
            - Refer for histopathologic, functional testing, experimental therapy
        - No
          - Refer for histopathologic, functional testing, experimental therapy
  - No
    - Chronic symptoms
      - Anti-secretory drugs
        - Yes
          - Long-term management
        - No
          - Refer for histopathologic, functional testing, experimental therapy
      - Delayed gastric emptying
        - Antiemetic, prokinetics
          - Yes
            - Increased fundic tone
              - 5 HT A1 agonist
                - Yes
                  - Ant-depressant, combination
                - No
                  - Montelukast, H1, H2 blocker, combination
              - Hypersensitivity
                - Anti-depressant, combination
                  - Yes
                    - Long-term management
                  - No
                    - Refer for histopathologic, functional testing, experimental therapy
            - No
              - Refer for histopathologic, functional testing, experimental therapy
          - No
            - Refer for histopathologic, functional testing, experimental therapy
      - No
        - Refer for histopathologic, functional testing, experimental therapy

Bx, biopsy; Hp, helicobacter pylori; UGI, upper gastrointestinal
TABLE 3  Rome IV criteria for the diagnosis of epigastric pain and postprandial distress syndromes7

Postprandial distress syndrome

- **Diagnostic criteria:** Must include one or both of the following at least 3 days per week:
  - Bothersome postprandial fullness (i.e., severe enough to impact on usual activities)
  - Bothersome early satiation (i.e., severe enough to prevent finishing a regular-size meal)
- No evidence of organic, systemic, or metabolic disease that is likely to explain the symptoms on routine investigations (including at upper endoscopy)

*Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis

- Supportive remarks
  - Postprandial epigastric pain or burning, epigastric bloating, excessive belching, and nausea can also be present
  - Vomiting warrants consideration of another disorder
  - Heartburn is not a dyspeptic symptom but may often coexist
  - Symptoms that are relieved by evacuation of feces or gas should generally not be considered as part of dyspepsia
  - Other individual digestive symptoms or groups of symptoms, e.g., from gastroesophageal reflux disease and the irritable bowel syndrome may coexist with PDS

Epigastric pain syndrome

- **Diagnostic criteria:** Must include at least 1 of the following symptoms at least 1 day a week:
  - Bothersome epigastric pain (i.e., severe enough to impact on usual activities)
  - Bothersome epigastic burning (i.e., severe enough to impact on usual activities)

*Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis

- Supportive remarks
  - Pain may be induced by ingestion of a meal, relieved by ingestion of a meal, or may occur while fasting
  - Postprandial epigastric bloating, belching, and nausea can also be present
  - Persistent vomiting likely suggests another disorder
  - Heartburn is not a dyspeptic symptom but may often coexist
  - The pain does not fulfill biliary pain criteria
  - Symptoms that are relieved by evacuation of feces or gas generally should not be considered as part of dyspepsia
  - Other digestive symptoms (such as from gastroesophageal reflux disease and the irritable bowel syndrome) may coexist with EPS

TABLE 4  Drugs available currently in Indian market for treatment of two subtypes of FD

<table>
<thead>
<tr>
<th>Epigastric pain syndrome</th>
<th>Postprandial distress syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>Fundic relaxants</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>Acotiamide</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>Buspirone</td>
</tr>
<tr>
<td>Dexlansoprazole</td>
<td>Mirtazapine</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>Prokinetics</td>
</tr>
<tr>
<td>Ilaprazole</td>
<td>Metoclopramide</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>Domperidone</td>
</tr>
<tr>
<td>Dexrabeprazole</td>
<td>Mosapride</td>
</tr>
<tr>
<td>Potassium competitive</td>
<td>Itopride</td>
</tr>
<tr>
<td>acid blocker</td>
<td>Levosulpiride</td>
</tr>
<tr>
<td></td>
<td>Cinitapride</td>
</tr>
<tr>
<td></td>
<td>Prucalopride</td>
</tr>
<tr>
<td></td>
<td>Visceral neuromodulators</td>
</tr>
</tbody>
</table>

TABLE 5  Rome IV criteria for IBS9

**Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with two or more of the following criteria:**

- Related to defecation
- Associated with a change in frequency of stool
- Associated with a change in form (appearance) of stool

*Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis

BOX 1  The Manning criteria that suggest a positive diagnosis of irritable bowel syndrome if any four of the listed six symptoms are present8

- Onset of pain associated with more frequent bowel movements
- Onset of pain associated with more loose bowel movements
- Relief of pain with defecation
- Abdominal distension
- Sense of incomplete evacuation
- Passage of mucus

Currently, Rome IV criteria (Table 5), developed after several iterations through Rome I, II, and III criteria, are used to diagnose IBS.

**Alarm Features**

Alarm features also called “red flags,” suggest the possible presence of an organic disease warranting investigations
before the diagnosis of IBS is made. Alarm features include the age of onset at or more than 45 years, anemia, blood in the stools, unintended weight loss, nocturnal symptoms, fever, abdominal mass, and a family history of colorectal cancer. As mentioned earlier, the age cut off of 45 years may vary depending on the local epidemiology of gastric cancer.

For clinical trials, all patients should have at least full blood counts, erythrocyte sedimentation rate, C-reactive protein, and limited colonoscopic examination, and other investigations, if indicated.9

Multidimensional Clinical Profile

There has been a significant paradigm shift in the management of FGIDs after the introduction of a multidimensional clinical profile (MDCP) in the Rome IV algorithm in 2016. Currently, experts, including the author, are in the process of generating a plausibility consensus in relation to organic issues on FGIDs. According to MDCP, in addition to assigning the patients to a diagnostic category, it is essential to evaluate the patients as a whole rather than only a diagnostic label. Sir William Osler wrote that it is better to treat the patient who has the disease rather than treating the disease. MDCP necessitate the physician to assess several critical issues in addition to the categorical diagnosis of FGIDs such as IBS (Box 2).10

A component of MDCP includes subtyping (Fig. 2) of FGIDs; for example, constipation-predominant or diarrhea-predominant IBS (IBS-C, and IBS-D, respectively), EPS or PDS subtypes of FDE, etc. As described in the treatment of these disorders, such subtyping is the cornerstone for the choice of appropriate drugs to treat these disorders.9 Moreover, those with alternating (change in symptoms over weeks to months) and mixed type is more difficult to treat and may require pathophysiology modifying measures such as an attempt at manipulating gut microbiota.

Table 6 and Figure 3 list the biological factors that may contribute to two subtypes of IBS, namely diarrhea-predominant and constipation-predominant IBS.4

Treatment

In addition to pharmacological treatment, dietary modification (low FODMAP diet) and management of psychological issues may help in relieving symptoms and improving the quality of life. To address these issues, dieticians and psychologists are essential members of the team to manage these patients. Treatment would depend on the predominant symptoms: diarrhea, constipation, or pain/gas/bloat (Figure 3, Table 7).4

Initial treatment for patients with IBS should include various combinations of antispasmodic, laxative, and antidiarrheal agents as they are quite safe and relatively inexpensive.12 Antispasmodics, which reduce abdominal pain by reducing muscle spasm, include antimuscarinics, smooth-muscle relaxants, and anticholinergics.12 Common adverse effects include dry mouth, dizziness, blurred vision, confusion, urinary retention, and constipation, which are associated with anticholinergics. Bulking agents are commonly prescribed drugs, especially for IBS-C.11 However, bulking agents may even aggravate abdominal pain and bloating.12 For the control of diarrhea, loperamide has the best quality of evidence but has not been shown to improve abdominal pain or distension.

Several visceral neuromodulators, which also have central nervous system effect, such as tricyclic antidepressants, serotonin reuptake inhibitors (SSRI), and serotonin-norepinephrine reuptake inhibitors (SNRI), relieve abdominal pain, diarrhea, insomnia, and depression. These drugs are useful in the treatment of IBS even in the absence of psychiatric illness.12 Another approach to treating IBS is psychotherapy.12 Aims of psychotherapy include reframing maladaptive beliefs, reduction of over-responsiveness to stress, reduction of maladaptive psychological responsiveness, and modification of maladaptive behaviors. Hypnotherapy is one of the essential tools in psychotherapy. The essence of hypnotherapy is to create a relaxing and calming environment and allowing the patient to refocus away
Fig. 2: Bristol stool types and method of sub-typing of IBS according to Rome IV system. IBS subtypes should be established according to stool consistency, using the Bristol stool form scale. Whether 25% of the stools are constipating types (I and II) or 25% of the stools are diarrheal types (VI or VII) determine IBS subtypes according to Rome IV criteria.

Another novel approach to the treatment of IBS is targeting the gut microbiota dysbiosis and small intestinal bacterial overgrowth (SIBO). Rifaximin, a broad-spectrum poorly absorbed antibiotic, has been found useful in the treatment of non-constipating IBS. Rifaximin works against Gram-negative bacteria, Gram-positive bacteria, and anaerobes and also has anti-inflammatory activity. In the famous TARGET study, a 2-week treatment with rifaximin (550 mg thrice daily) resulted in 41% non-constipating IBS patients reporting improvement as compared to 30% placebo-treated patients. However, symptoms recur in most patients within 2–3 months. This study is essential as it brings a novel concept of treating a “functional disorder,” which is now believed to result from altered gut microbiota, with an antibiotic.

Dietary modification is an essential component of the treatment of patients with IBS. Symptoms exacerbation due to intolerance to different nutritional ingredients is not uncommon among patients with FGIDs, including IBS. Worsening of symptoms following intake of curry and

<table>
<thead>
<tr>
<th>Types of IBS</th>
<th>Contributing physiological dysfunctions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation-predominant IBS</td>
<td>• Fecal evacuation disorder</td>
</tr>
<tr>
<td></td>
<td>• Slow transit</td>
</tr>
<tr>
<td>Diarrhea-predominant IBS</td>
<td>• FODMAP sensitivity including lactose or fructose intolerance</td>
</tr>
<tr>
<td></td>
<td>• Bile acid malabsorption</td>
</tr>
<tr>
<td></td>
<td>• Non-celiac wheat sensitivity</td>
</tr>
<tr>
<td></td>
<td>• Small intestinal bacterial overgrowth</td>
</tr>
<tr>
<td></td>
<td>• Post-infectious</td>
</tr>
</tbody>
</table>

TABLE 6: Different physiological factors that may cause or exacerbate symptoms of patients with two subtypes of irritable bowel syndrome

IBS: irritable bowel syndrome, FODMAP: fermentable oligo-dimonsaccharides and polyols.
**Figure 3:** Pathophysiological mechanisms of constipation and diarrhea-predominant irritable bowel syndrome (IBS-C and D) and possible therapeutic agents to target these abnormalities. It is important to note that the therapeutic agents work in functional constipation and IBS-C and functional diarrhea and IBS-D comparably. (Source: Reproduced from Reference 4)

<table>
<thead>
<tr>
<th>Putative therapeutic targets of pathophysiological factors in IBS-C</th>
<th>Putative therapeutic targets of pathophysiological factors in IBS-D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary &amp; lifestyle modification</td>
<td>Food fermentation products</td>
</tr>
<tr>
<td>Less dietary fibre &amp; water intake</td>
<td>Elimination diet including lactose</td>
</tr>
<tr>
<td>Fleet bile acid inhibitor (libuxibat)</td>
<td>Increased bile acids</td>
</tr>
<tr>
<td>Reduced bile acids</td>
<td>Cholestyramine</td>
</tr>
<tr>
<td>Rifaximin probiotics</td>
<td>Cholestispol</td>
</tr>
<tr>
<td>Methanogens</td>
<td>Cholestevetlam</td>
</tr>
<tr>
<td><strong>Osmotic Agents and secretagogue</strong></td>
<td>Gut microbiota</td>
</tr>
<tr>
<td>- Osmotic laxatives</td>
<td>Rifaximin Probiotics</td>
</tr>
<tr>
<td>- Lubiprostone</td>
<td>Fecal microbiome transplant</td>
</tr>
<tr>
<td>- Linaclotide</td>
<td><strong>Anti-motility agents</strong></td>
</tr>
<tr>
<td>Sbw motility</td>
<td>- Loperamide</td>
</tr>
<tr>
<td><strong>Pro-motility serotonergic agents</strong></td>
<td>- Diphenoxylate</td>
</tr>
<tr>
<td>- Cisapride (withdrawn)</td>
<td>- Anti-cholinergic including tricycles</td>
</tr>
<tr>
<td>- Mosapride</td>
<td>- Asimadoline</td>
</tr>
<tr>
<td>- Tegaserod (withdrawn)</td>
<td>- Eloxadoline</td>
</tr>
<tr>
<td>- Prucalopride</td>
<td><strong>Anti-serotonergics</strong></td>
</tr>
<tr>
<td>Low serotonin</td>
<td>- Alosetron</td>
</tr>
<tr>
<td>Fecal evacuation disorders</td>
<td>- Citalopram</td>
</tr>
<tr>
<td>Inflammation Mast cell</td>
<td>- Ramoxetone</td>
</tr>
<tr>
<td>Mesalamine Mast cell stabilizer</td>
<td>- Ondasetron</td>
</tr>
</tbody>
</table>

**Source:** Reproduced from Reference 4
TABLE 7 Current symptom-based management of irritable bowel syndrome

<table>
<thead>
<tr>
<th>Symptom</th>
<th>First line</th>
<th>Second line</th>
<th>Future</th>
</tr>
</thead>
</table>
| Constipation | • Fiber  
• Osmotic laxative, including polyethylene glycol  
• Lactulose/Lactitol  
• Stool softener, e.g., docusate | • Bisacodyl  
• Sodium picosulfate  
• Tegaserod (withdrawn)  
• Lubiprostone  
• Linaclotide  
• Prucalopride (5-HT4 agonist) | Elobixibat (ileal bile acid transporter inhibitor) |
| Diarrhea | • Loperamide  
• Diphenoxylate | • Alosetron  
• Ramotsetron  
• Ondansetron  
• Bile acid sequestrant (cholestyramine, colestipol)  
• Rifaximin  
• Clonidine | |
| Bloating | Treat constipation | • Probiotic  
• Antibiotic (rifaximin) | |
| Pain | | • Antispasmodics  
• Anticholinergics  
• Mebeverine  
• Pinaverium  
• Otilonium bromide  
• Antidepressant  
  – Tricyclic antidepressants  
  – SSRI  
  – RI | |

SSRI: serotonin re-uptake inhibitor, RI: reuptake inhibitor

chili is not unusual in Asia.14,15 Though malabsorption of lactose is as common among patients with IBS as healthy subjects, the patients reported symptoms following the ingestion of this disaccharide than the controls, possibly due to visceral hypersensitivity. Lactose is a component of Fermentable Oligo-, Di-, Monosaccharide, and Polyol (FODMAP) foods. All the high FODMAP foods lead to pathophysiological effects, such as production of osmotically active substances, and gas causing flatulence, distension, and pain, somewhat similar to lactose, among the patients with IBS. Hence, avoidance of high FODMAP foods improves symptoms of IBS.16 FODMAP diet chart is available from http://spreadhealth.in/New%20Folder/High%20&%20low%20FODMAP%20foods.pdf.

Conclusion

FGIDs, including IBS and FD, are common in medical practice. These disorders have multiple pathophysiological basis. Multimodality treatment directed to the subtypes and underlying pathophysiological factors is often successful in managing these patients.

References

Abstract
Variceal bleed is a clinically significant event in the natural history of cirrhosis, and provides opportunity to treat and correct the underlying cause in the first decompensation. With advancement in critical care, endoscopic variceal band ligation and use of vasoactive agents had improved the management of acute variceal bleed in last few decades. However, refractory variceal bleed is difficult to manage, requires specialized care, and has poorer prognosis. Transjugular intrahepatic portosystemic shunt (TIPS) is reserved for patients with high risk for treatment failure and refractory variceal bleed. Primary and secondary prophylaxis by non-selective beta blocker is another important development in the medical management of esophageal varices and variceal bleed.

Introduction
Upper gastrointestinal bleed (UGIB), one of the common medical emergencies, can be broadly divided into variceal and non-variceal UGIB. Varices are the abnormally dilated submucosal veins in gastrointestinal tract usually developed as a complication of portal hypertension to decompress the portal system. The collaterals gradually increase in size due to various factors and the most important factor is progressive rise in portal pressure and consequent increase in flow through these collaterals.

Approximately half of the patients with cirrhosis have esophageal varices and one-third of all the patients with varices will bleed in their natural course of the disease. In India, the proportion of patients with variceal bleed among all the cases of UGIB presenting to emergency varies widely between 12% and 55% based on region of study. The esophageal varices are the most common source of variceal bleed followed by gastric varices. Cirrhosis is the most common cause of the variceal bleed in >90% of the cases. The overall 6-week rebleeding rate at 6 weeks is 24-30%, whereas 6-week mortality of variceal bleed in cirrhosis is 12–22%. The following sections will be the overview of the management of the esophageal variceal bleed in accordance with the recent guidelines. We will not discuss the management of gastric and ectopic varices.

Risk Stratification (Fig. 1)
Cirrhosis can be stratified according to Child-Pugh-Turcotte (CTP) stage or MELD. Higher the score, more severe is the disease. For clinical point of view, it is broadly classified into compensated and decompensated cirrhosis, and later is characterized by variceal bleed, ascites, or hepatic encephalopathy. The higher the number of the decompensation events, the worse is the prognosis.

Hepatic venous pressure gradient (HVPG) >10 mm Hg is associated with clinically significant portal hypertension (CSPH), where esophageal varices start to appear; and HVPG >12 mm Hg is associated with bleeding risk. HVPG responders (reduction in HVPG by ≥20% of the baseline value or absolute HVPG <12 mm Hg by NSBBs) are associated with lower risk of rebleed; however, in routine
clinical practice HVPG measurement is not feasible due to its cost and invasiveness.4

Management of Acute Variceal Hemorrhage (Flowchart 1)
Acute variceal hemorrhage (AVH) is to be suspected and treatment should be started immediately in all cases of UGI bleed in known cirrhotics or patient with high-risk of cirrhosis without waiting for the confirmation by endoscopy. The main cause of death in AVH is not uncontrolled bleeding, but due to additional decompensation and complications resulting from acute bleed. The management of AVH will be discussed here.

Immediate Management
Assessment of the airway and circulatory function should be done first and orotracheal intubation should be considered in any obtunded patient or in patients with massive hematemesis with high-risk of aspiration. Intravenous access with two large-bore cannula should be secured for careful volume resuscitation. Blood samples should be sent for complete blood counts, liver function test, blood urea and creatinine, and for cross-matching.

The volume resuscitation is done by the crystalloids; and a “restrictive” packed red blood cell (PRBC) transfusion strategy (i.e., target range for the post-transfusion hemoglobin level of 7–9 g/dL), which is associated with significant lower early rebleeding and mortality rates in patients with cirrhosis compared to liberal transfusion strategy.7 However, cases with cardiovascular comorbidities, ongoing bleeding, and hemodynamic instability require higher hemoglobin target and it should be individualized considering the patient conditions.

In a recent randomized control trial, thromboelastography-guided blood-product transfusion strategy was associated with reduced blood-product transfusion to
correct coagulopathy without compromising hemostasis in cirrhotic patients. There is no recommendation for use of platelet transfusion, intravenous vitamin K, or tranexamic acid to halt the acute ongoing variceal bleed. Transfusion of fresh frozen plasma or factor VIIa to correct INR is not recommended.

Any one of the vasoactive drugs (Table 1) and antibiotic prophylaxis should be initiated at the earliest prior to esophagogastroduodenoscopy (EGD). These vasoactive drugs cause splanchnic vasoconstriction and reduce the portal pressure. Even in patients on noradrenaline infusion for hypotension, one of the vasoactive drugs should be continued. Intravenous antibiotic prophylaxis (ceftriaxone 1 g/24 hourly) prevent the infectious complications and reduce mortality. A nasogastric tube placement is usually not recommended and prokinetic administration can enhance the gastric mucosa visualization during endoscopy (erythromycin 250 mg IV 30–120 minutes before endoscopy, if no QT prolongation on electrocardiography).

**Endoscopic Treatment**

There is no need to hurry for EGD to achieve hemostasis. While the first and foremost step is hemodynamic resuscitation and stabilization before sending the patients for endoscopic hemostasis. EGD can be safely performed between 6–24 hours after presentation to the emergency, but it should be individualized if there is evidence of active ongoing bleed despite vasoactive drugs, hemodynamic instability due to blood loss despite resuscitation, actively
vomiting fresh blood, or persistent fresh blood from nasogastric tube.\textsuperscript{10}

Endoscopic variceal obliterator techniques commonly used are endoscopic variceal band ligation (EVL), the preferred technique; and the endoscopic variceal sclerotherapy (EST). Once EVL is done, next session will be planned after 2–4 weeks till complete eradication of varices. Once eradicated, next screening endoscopy will be after 3–6 months and then every 6–12 months.

**Role of TIPS**

Monitor for rebleed (recurrence of hematemesis/drop in hemoglobin/hypotension due to bleed after endoscopic hemostasis) and assessment for high-risk factors for treatment failure should be done. In patients with high-risk of treatment failure [Child C (with CTP score ≤13) or Child B with active bleeding on endoscopy despite vasoactive drug therapy], evidence showed that the early transjugular intrahepatic portosystemic shunt (TIPS) done within 24–72 hours of presentation after first endoscopy was associated with lower treatment failure and mortality rates compared to standard therapy.\textsuperscript{11} So, guidelines recommend "early or pre-emptive TIPS" in acute variceal bleed at high-risk of treatment failure after combined vasoactive drugs and endoscopic therapy.

**Post-endoscopic Hemostasis Management**

Vasoactive drugs should be continued for 3–5 days and antibiotic prophylaxis should be given for 5–7 days. Assessment for any other decompensation should be done and treated accordingly. Non-selective beta blockers (NSBBs) (Table 2) should be started before hospital discharge after the discontinuation of vasoactive agents unless the patient undergoes TIPS.

At our center, in hemodynamically stable patient, we keep the patient fasting for 4–6 hours after endoscopic hemorrhage followed by liquid diet for 24–48 hours and then the solid food is allowed. There are some concerns for increase in splanchnic blood flow and increase in portal pressure after enteral nutrition. Some guidelines advocate withholding of enteral nutrition for at least 48–72 hours after an episode of AVH.\textsuperscript{12} Avoid placing a nasogastric tube after EVL for first few days to avoid the risk of dislodging the newly placed bands. However, if there is indication for nasogastric tube placement, a tube can be gently placed by an experienced clinician.

**Management of Refractory Bleed or Treatment Failure**

Treatment failure occurs in 10–15% of the patients with AVH despite treatment and associated with high

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**TABLE 1** Vasoactive drugs used in acute variceal hemorrhage (adapted from AASLD 2016 Practice Guidance\textsuperscript{4})

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommended dose</th>
<th>Predominant mechanism of action</th>
<th>Significant adverse effects and contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatostatin</td>
<td>Initial IV bolus 250 µg (can be repeated in the first hour if ongoing bleeding)</td>
<td>Splanchnic vasoconstriction due to inhibition of vasodilatory hormones</td>
<td>Major adverse events are rare</td>
</tr>
<tr>
<td></td>
<td>followed by continuous IV infusion of 250–500 µg/hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duration: 2–5 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Octreotide (somatostatin analogue)</td>
<td>Initial IV bolus of 50 µg (can be repeated in first hour if ongoing bleeding)</td>
<td>Similar to somatostatin</td>
<td>Major adverse events are rare. Category B drug in pregnancy</td>
</tr>
<tr>
<td></td>
<td>followed by continuous IV infusion of 50 µg/hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duration: 2–5 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terlipressin (vasopressin analogue)</td>
<td>Initial 48 hours: 2 mg IV every 4 hours until control of bleeding followed by 1 mg IV every 4 hours to prevent rebleeding</td>
<td>Mesenteric arteriolar vasoconstriction</td>
<td><strong>Common adverse events:</strong> abdominal pain, hypertension, and hyponatremia <strong>Contraindications:</strong> history of ischemic disease of heart, brain, gut or peripheral limb; and in pregnancy Use with caution in elderly and hypertension</td>
</tr>
<tr>
<td></td>
<td>Duration: 2–5 days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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\textsuperscript{10} Endoscopic variceal obliterator techniques commonly used are endoscopic variceal band ligation (EVL), the preferred technique; and the endoscopic variceal sclerotherapy (EST). Once EVL is done, next session will be planned after 2–4 weeks till complete eradication of varices. Once eradicated, next screening endoscopy will be after 3–6 months and then every 6–12 months.

\textsuperscript{11} So, guidelines recommend "early or pre-emptive TIPS" in acute variceal bleed at high-risk of treatment failure after combined vasoactive drugs and endoscopic therapy.

\textsuperscript{12} Avoid placing a nasogastric tube after EVL for first few days to avoid the risk of dislodging the newly placed bands. However, if there is indication for nasogastric tube placement, a tube can be gently placed by an experienced clinician.
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<th>Drug</th>
<th><strong>Recommended dose</strong></th>
<th><strong>Predominant mechanism of action</strong></th>
<th><strong>Significant adverse effects and contraindications</strong></th>
</tr>
</thead>
</table>
| **Oral non-selective beta blockers (Propranolol or Nadolol)** | **Initiation dose:** 20–40 mg BD for propranolol and 10–20 mg OD for nadolol  
**Dose titration:** Adjust every 2–3 days to achieve maximally tolerated dose or therapy goal achieved  
**Maximal daily dose:**  
For propranolol: 320 mg/day if no ascites and 160 mg/day if ascites present  
For nadolol: 160 mg/day if no ascites and 80 mg/day if ascites present  
**Therapy goal:** Resting heart rate of 55–60 beats/minute and systolic blood pressure should not be < 90 mm Hg | Reduce portal venous inflow by splanchnic vasoconstriction (by β2-blockade and unopposed α-adrenergic activity) and decrease cardiac output (by β1-blockade) | Common adverse events: fatigue, lightheadedness, and shortness of breath  
**Contraindications:** decompensated heart failure, advanced heart block, severe sinus bradycardia, aortic valve disease, advanced peripheral arterial disease, obstructive pulmonary disease, insulin-dependent diabetes  
-In spontaneous bacterial peritonitis, refractory ascites, and severe circulatory dysfunction like hyponatremia (Na⁺ <130 meq/L) and hepatorenal syndrome, the dose of NSBB should be reduced or withheld temporarily till circulatory dysfunction or sepsis improves |
| **Carvedilol** | **Initiation dose:** 3.125 mg OD  
**Dose titration:** Adjust every 3 days to 6.25 mg BD  
**Maximal daily dose:** 12.5 mg/day (except in patients with persistent arterial hypertension)  
**Therapy goal:** Systolic blood pressure should not be < 90 mm Hg | Non-selective beta-blocker (reduce portal blood flow) with additional anti-α1-adrenergic action (reduce intrahepatic resistance) | Common adverse events: orthostatic hypotension, dizziness and fatigue  
**Contraindications:** decompensated heart failure, advanced heart block, obstructive airway disease, and severe bradycardia  
To be avoided in decompensated cirrhosis as it can worsen ascites and renal dysfunction |
Tamponade as Bridge Therapy
If the rebleeding is persisting despite first endoscopy or the rebleed is massive (hemodynamic instability, blood transfusion or 3 g/dL drop in hemoglobin) or the second endoscopic attempt fails, balloon tamponade (Sengstaken–Blakemore tube) or self-expandable metal stent (SEMS) can be used as bridge therapy till definite portal decompressive therapies is available. The balloon tamponade can achieve hemostasis in ~80% cases and should be used for maximum of 24 hours, but it is associated with severe complications such as aspiration and esophageal rupture. SEMS is effective and safer alternative than balloon tamponade for control of bleeding and can be left in place for up to 7 days.

Rescue or Salvage TIPS
This can effectively control bleeding in more than 90% of refractory esophageal variceal bleeding cases, but the mortality rate remains high (30–50%) as well as the risk of encephalopathy. So, the patients with high-risk of rebleed are to be identified and offered aggressive strategies (like early TIPS) to prevent treatment failure. Surgical shunts are rarely performed nowadays, may be done in good surgical candidate (child A cirrhosis), when TIPS is not technically feasible.

Patients who Recovered from Recent Variceal Bleed and Secondary Prophylaxis
Untreated patients who recover from first episode of bleed are at high-risk of rebleed (55–67% in first year) and mortality (25–50%). So, initiation of secondary prophylaxis against rebleed is essential before hospital discharge. Patients with indication for liver transplantation should be referred for the same. The patients who underwent TIPS as a part of AVH management do not require additional therapy for rebleed prevention.

All guidelines recommend combination of NSBB (propranolol or nadolol) with EVL as first-line management for secondary prophylaxis. NSBBs (Table 2) form the cornerstone of combination therapy; meta-analysis showed an improvement in survival with the addition of NSBBs to EVL, while the addition of EVL to NSBBs has no survival benefit. NSBBs can be used as monotherapy if patients are unable or unwilling to undergo EVL. Currently neither HVPG-guided therapy nor TIPS is recommended for secondary prophylaxis. Unless contraindicated, TIPS is the recommended treatment in patients with recurrent bleed despite combination therapy and also in patients who are intolerant to NSBBs (EVL alone cannot be used as secondary prophylaxis) and especially if patient has ascites also.

Screening and Primary Prophylaxis for Varices
All cirrhotics should undergo variceal screening by endoscopy. However, EGD can be avoided in patients whose liver stiffness on transient elastography (TE) is <20 kPa with platelet count >1,50,000/µL (TE-based criteria); or serum albumin >3.6 g/dL and platelets >1,20,000/mm³ (platelet-albumin criteria). There is no role of prophylaxis in cirrhosis with no varices or low-risk varices. Primary prophylaxis must be initiated in all cirrhosis with varices at high-risk of rupture. High-risk varices are small varices with red color signs, small varices in CTP C cirrhosis and medium or large varices irrespective of CTP class. The choice between NSBBs (Table 2) and EVL depends on variceal size, patient preference, and local resources. A recent network meta-analysis showed that NSBBs are associated with lower mortality compared to EVL.

Conclusion
Acute variceal bleed is an important prognostic event in the natural history of cirrhosis. It is a medical emergency with high mortality and must be managed with resuscitation, vasoactive drugs, prophylactic antibiotics, and endoscopic treatment. Non-selective beta blocker plays a crucial role in the primary and secondary prophylaxis. TIPS has role in refractory bleed and prevention of rebleed in high-risk patients.

References
CHAPTER 129

Hepatorenal Syndrome: Current Diagnosis and Management

Shri Krishna Gautam

Abstract

HRS is a life threatening complication of advanced liver disease. It is considered as development of renal failure in patients with pre-existing liver disease but without any underlying renal dysfunction. The term HRS first emerged in the year 1932 in a group of postoperative patients of biliary tract surgery. The Pathophysiology of HRS is poorly understood, three essential components play vital role in Pathophysiology of HRS:

- Arterial vasodilatation in the splanchnic and systemic circulation,
- Renal vasoconstriction, and
- Cardiac dysfunction. Spontaneous bacterial peritonitis is an important risk factor for development of HRS. About one third of patient of spontaneous bacterial peritonitis develop HRS.

Most common presentation of HRS is asymptomatic followed by decrease in urine output. Due to acute kidney injury (AKI), glomerular filtration rate decreases (GFR) and the blood urea nitrogen (BUN) level increases which may result in hepatic encephalopathy as the initial clinical presentation of HRS. Based on clinical features and prognosis HRS is of two types: Type 1 HRS and Type 2 HRS.

HRS requires a very aggressive management considering its poor prognosis. There are three treatment options available for management of HRS:

- Medical therapies are the mainstay of treatment of HRS consisting of vasoconstrictor agents like: Terlipressin, Noradrenaline, and Midodrine plus Octreotide.
- Transjugular intrahepatic portosystemic shunt (TIPS) placement, and
- Liver transplantation.

Therefore, HRS is a life threatening complication of liver cirrhosis. In addition to increased knowledge regarding liver cirrhosis, portal hypertension, ascites as well as HRS, new pharmacological treatments like administration of terlipressin and albumin have proven vital role in improving the short-term outcome of HRS. The other medical treatments using different pharmacological principles such as endothelin antagonists, adenosine-receptor antagonists, and N-acetylcysteine may also help in minimizing renal vasoconstriction and improving renal function, but liver transplant remains to be the mainstay of the treatment.

Introduction

Hepatorenal syndrome (HRS) is a life-threatening complication of advanced liver disease. It is considered as development of renal failure in patients with pre-existing liver disease but without any underlying renal dysfunction. The term HRS first emerged in the year 1932 in a group of postoperative patients of biliary tract surgery. International ascites club has formulated diagnostic guidelines for HRS in 1994, which were modified in 2007.

Diagnostic Criteria for HRS

See Box 1.
The pathophysiology of HRS is poorly understood, three essential components are:

- Arterial vasodilatation in the splanchnic and systemic circulation,
- Renal vasoconstriction, and
- Cardiac dysfunction.

Several cytokines are involved which alter the renal blood flow and glomerular microvasculature. Important among them are cysteiny1 leukotrienes, thromboxane A2, F2-isoprostanes, and endothelin-1. Knowledge about these vasoactive compounds is also important from therapeutic and preventive point of view.

**Arterial Vasodilatation in the Splanchnic and Systemic Circulation**

Splanchnic vasodilatation is the hallmark of portal hypertension seen in chronic liver disease. Several vasodilators like nitric oxide, glucagon, carbon mono oxide, prostacyclin are released which are responsible for these vasodilatory response.\(^6,7\) In the initial stages, cardiac compensatory mechanism tends to counter the vasodilation.\(^8\)

**Renal Vasoconstriction**

Due to splanchnic vasodilatation and renal vasoconstriction there is activation of the renin-angiotensin-aldosterone system (RAAS). The clear pathway is not known but cytokines like endothelins, prostaglandins, kallikreins, and F2 isoprostanes are considered to cause renal vasoconstriction.\(^9,11\)

These hemodynamic changes in renal microvasculature and splanchnic vasodilatation compromises renal blood flow leading to fall in glomerular filtration rate.\(^5\)

So, HRS is initially a functional renal syndrome, which later progresses to an organic disease.

**Cardiac Dysfunction**

The development of cirrhotic cardiomyopathy leads to impairment of cardiac function, which may further lead to a relative impairment of the compensatory increase in cardiac output secondary to vasodilatation.

**Risk Factors of HRS**

Spontaneous bacterial peritonitis is an important risk factor for development of HRS.\(^12-14\)

About one third of patient of SBP develops HRS.\(^12\) The outcome of HRS is very poor. Median survival time of all patients with HRS is approximately 3 months only.\(^15\) High MELD scores and type 1 HRS further worsen the prognosis. Type 1 HRS patients if not treated have very poor outcome with median survival of approximately 1 month.\(^16\)

**Clinical Features and Classification of HRS**

Most common presentation of HRS is asymptomatic followed by decrease in urine output. Due to acute kidney injury (AKI), glomerular filtration rate (GFR) decreases and the blood urea nitrogen (BUN) level increases which may result in HE as the initial clinical presentation of HRS.

Based on clinical features and prognosis, HRS is of two types (type 1 and type 2).\(^3\)

**Type 1 HRS**

Type 1 HRS has worse prognosis than type 2 HRS. There is very rapid deterioration in renal function in type 1 HRS. Typically, the level[0l] of serum creatinine rises to a value higher than 2.5 mg/dL within 2 weeks or less. Most of time type 1 HRS has a triggering event. These triggers interfere with the renal blood flow.\(^7\) Some of the common triggers are bacterial infections,18 GI bleeding, surgery, and acute hepatic injury.\(^1,19\)

Among bacterial infections, SBP is the most important trigger event to develop HRS.\(^20,21\) There are certain predisposing factors like high levels of inflammatory markers, severe circulatory depression prior to the onset of acute kidney injury, which may lead to the development of HRS.

**Risk Factors of Type 1 HRS**

- Spontaneous bacterial peritonitis
- Severe circulatory depression
- High levels of inflammatory markers

**Diagnosis of HRS**

- Cirrhosis with ascites
- Serum creatinine 1.5 mg/dL (133 lmmol/L)
- Absence of shock
- Absence of hypovolemia as defined by no sustained improvement of renal function (creatinine decreasing to 133 lmmol/L) following at least 2 days of diuretic withdrawal (if on diuretics), and volume expansion with albumin at 1 g/kg/day up to a maximum of 100 g/day
- No current or recent treatment with nephrotoxic drugs
- Absence of parenchymal renal disease as defined by proteinuria 0.5 g/day, no micro hematuria (50 rbc/high powered field), and normal renal ultrasonography

**Type 2 HRS**

Type 2 HRS has less severity and worse prognosis than type 1 HRS. The primary features are persistent decrease in urine output and ascites.

**Risk Factors of Type 2 HRS**

- Spontaneous bacterial peritonitis
- Drug-induced kidney injury
- Acute hepatic failure

**Management of HRS**

Management of HRS is supportive and involves hydration, diuretics, and albumin. In type 1 HRS, nephrotoxic drugs should be avoided.

**Prognosis of HRS**

The prognosis of HRS is poor. Median survival time of all patients with HRS is approximately 3 months only. High MELD scores and type 1 HRS further worsen the prognosis. Type 1 HRS patients if not treated have very poor outcome with median survival of approximately 1 month.\(^16\)
of infection, and adrenal insufficiency, which have more chances of development of HRS.

### Type 2 HRS

Type 2 HRS is more slowly progressive than type 1 HRS, but still carries a median survival of only approximately 6 months. Typically patient presents with pre-existing resistant ascites with mild renal dysfunction (serum creatinine < 2.5 mg/dL). Type 2 HRS patient can progress into type 1 HRS after a triggering event.

### Prevention of HRS

HRS has a very poor prognosis and very high mortality rate. So prevention of HRS is an important aspect in management of patients of chronic liver disease. Most important strategy is to prevent depletion of intravascular volume. Important causes of volume depletion are over diuresis, diarrhea due to lactulose, variceal bleed, and large volume paracentesis.

Use of nephrotoxic drugs should be avoided. Beside these prevention of infection and its prompt treatment is also very important for prevention of HRS.

### Treatment of HRS

HRS requires a very aggressive management considering its poor prognosis. There are three treatment options available for management of HRS:

- M2 mediated therapies,
- Transjugular intrahepatic portosystemic shunt (TIPS) placement,
- Liver transplantation.

Aim of medical therapy is to maintain intravascular volume. Vasoconstrictors are used to counter splanchnic vasodilatation. Colloid infusion is done for volume expansion. Aim of the medical therapy is to act as a bridge until definitive treatment of liver disease is done or until the triggering event (SBP, UGI bleed) has subsided.

### Medical Therapy

- Non-specific medical therapy:
  - Vitals monitoring and maintaining fluid balance is very important. Monitoring of blood pressure, central venous pressure, urine output helps in maintaining fluid balance.

- Infection control: prophylactic antibiotic therapy should be given if indicated for prevention of SBP. Sepsis should be identified early using culture of blood, urine, and ascetic fluid. There is no role of antibiotic without proven infection.

- Diuretic has to be stopped to prevent depletion of intravascular volume.

- Specific therapies:

  - **Vasoconstrictors**: Aim is to reverse the splanchnic vasodilatation to maintain the renal blood flow vasopressin analogues are most commonly used for vasoconstriction. Terlipressin has been studied extensively in HRS patients. The dose of terlipressin is 1 mg every 4–6 hours. It can be increased up to 2 mg every 4–6 hours after 3 days if there is no improvement in renal function (fall in serum creatinine by at least 25% of baseline). Terlipressin is discontinued if serum creatinine comes below 1.5 mg/dL with improvement in renal function there is increase in urine volume, blood pressure, and serum sodium concentration. Improvement is slow and can take up to 14 days for renal function to become normal. Duration is shorter with lower serum creatinine at the time of starting terlipressin. Reoccurrence after stopping terlipressin is rare. Terlipressin is effective in reoccurrence.

  - **Midodrine plus octreotide**
  - **Noradrenaline**

Better response is observed in patients with baseline serum bilirubin less than 10 mg/dL. Also patients who show reduction in mean arterial pressure of more than 5 mm Hg after 3 days of medical therapy have favorable response to medical therapy. Reoccurrence after stopping terlipressin is rare. Terlipressin is effective in reoccurrence.

Common side effects of terlipressin include cardiovascular and ischemic complications. So terlipressin is avoided in patients with known cardiovascular and ischemic conditions. Patients of HRS are given albumin along with terlipressin to maintain intravascular volume. Albumin is given in a dose of 1 g/kg body weight.

Terlipressin shows improvement in renal function in patients of type 2 HRS also, but there are limited studies in patients of type 2 HRS.

There are other vasopressors that are used in type 1 HRS:

- Midodrine plus octreotide
- Noradrenaline
Midodrine is an alpha adrenergic receptor agonist. It is an oral drug started at a dose of 2.5 mg tds and can be increased up to 12.5 mg. Octreotide is started with a dose of 100 microgram tds and can be increased up to 200 microgram tds. There are only few studies with midodrine and octreotide.26

Noradrenaline (0.5–3 mg/h) is a vasopressor drug. Increased arterial pressure helps to maintain adequate blood flow to kidneys.27 Comparative studies between noradrenaline and other vasoconstrictors drugs are the area of research. Noradrenaline is given as continuous infusion with an aim to keep systolic blood pressure above 110 mm Hg.

There have been few studies on prevention of HRS. Short-term treatment (4 week) with pentoxifylline (400 mg three times a day) in a randomized double-blind study was shown to prevent the development of HRS in patients with severe alcoholic hepatitis. In a recent study, long-term treatment with pentoxifylline was not associated with an improved survival but with reduced frequency of some complications of cirrhosis, including renal failure, yet the 7w was not the primary endpoint of the study. Finally, norfloxacin (400 mg/day) reduced the incidence of HRS in advanced cirrhosis.

Transjugular Intrahepatic Portosystemic Shunt (TIPS)

TIPS has been used for treatment of portal hypertension associated with cirrhosis.28 TIPS helps to control ascites along with improvement in renal function in patients of HRS.

Renal replacement therapy: Hemodialysis is used in patients of HRS. Indication of hemodialysis is similar to any cause of acute renal failure.29,30 There are no separate studies to see results of hemodialysis in HRS patients. Comparison of renal replacement therapy and medical therapy for HRS is an area of further evaluation.

Liver Transplantation

Treatment of choice for both types of HRS is liver transplantation.31 Liver transplantation success rate is about 65% in patients of type 1 HRS.31 Renal failure subsides after liver transplantation. Patients who remain on renal support therapy for more than 12 weeks should be considered for combined liver kidney transplantation.

Therefore, HRS is a life-threatening complication of liver cirrhosis. In addition to increased knowledge regarding liver cirrhosis, portal hypertension, ascites as well as HRS, new pharmacological treatments like administration of terlipressin and albumin have proven vital role in improving the short-term outcome of HRS. The other medical treatments using different pharmacological principles such as endothelin antagonists, adenosine-receptor antagonists and N-acetylcysteine may also help in minimizing renal vasoconstriction and improving renal function,22,33 but liver transplant remains to be the mainstay of the treatment. The multiple aspects in the pathophysiological process will likely be targeted by the future treatment of HRS.

References

CHAPTER 130

Hepatic Encephalopathy: Management

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Abstract

Hepatic encephalopathy is defined as brain dysfunction caused by liver insufficiency and/or portosystemic shunting; its clinical manifestations include spectrum of neurological or psychiatric dysfunction ranging from subclinical alterations to deep coma. The development of hepatic encephalopathy correlates with the severity of liver disease. Hepatic encephalopathy is classified into overt hepatic encephalopathy, which is characterized by neurologic and neuropsychiatric dysfunctions detected by clinical examination and bedside tests or minimal hepatic encephalopathy, characterized by normal mental status and normal neurologic examination but abnormalities on psychometric testing. Early detection and rectification of precipitating factors is most important in the management. The first-line therapy is still lactulose which is effective in minimal, overt and recurrent hepatic encephalopathy. Rifaximin is equally effective to lactulose and is better tolerated. Branch chain amino acids have a beneficial effect on hepatic encephalopathy in protein intolerant patients. Probiotics and L-ornithine L-aspartate are also useful in the management of hepatic encephalopathy. Combinations of rifaximin and lactulose have shown promising results in the treatment of overt and recurrent hepatic encephalopathy. Embolization of large portosystemic shunts and liver transplantation are effective treatment in few and highly selected patients. Nutritional therapy and fecal microbiota transplantation are emerging treatment options but data is limited.

Introduction

Hepatic encephalopathy (HE) is identified by indiscriminate neurological and psychiatric manifestations, which adversely impacts the life of patients and their family members. The requirement of multiple hospital admissions due to HE is a matter of great concern for the healthcare sector. HE has been categorized based on preexisting liver disorder, gravity of the clinical features, the trends over time, and triggering/precipitating factors (Table 1). Type A HE is a consequence of acute liver failure, type B of large portosystemic shunts (PSS), and type C of liver cirrhosis. Type C is the most common. The scope of HE scales from not easily observable clinical features characterized as minimal hepatic encephalopathy (MHE), overt neuropsychiatric features characterized as overt hepatic encephalopathy (OHE) to comatose state. Overt HE is observed in 10–14% of cirrhotic patients at the time of diagnosis. Forty percent of patients with cirrhosis encounter at least one outbreak and many encounter frequent outbreaks of HE. In cirrhotic patients the prevalence of MHE is 20–80%. In patients with cirrhosis HE is a marker of poor prognosis, with up to 85% 1-year mortality. The available literature on pathogenesis suggest that an increase in ammonia concentration is implicated and a role for inhibitory neurotransmission through gamma aminobutyric acid (GABA) receptors in the central nervous system along with changes in central neurotransmitters and circulating amino acids.
Overt Hepatic Encephalopathy Management

Management of OHE includes finding and resolving any triggering factor, to reduce blood ammonia level with lactulose or rifaximin and the proper setup for its treatment. The severity of OHE is graded from I to IV, based on the clinical features (Table 2). The treatment depends on the severity of OHE. Patients with grade I HE may be managed on outpatient basis, if caregivers are available to look for signs of worsening and to bring the patient to the hospital if required. Hospital admission of a patient with grade II HE depends on the degree of lethargy and confusion. If the patient is not able to take the treatment or if caregivers are not available for monitoring the patient, the patient needs to be admitted to the hospital. Patients with more severe HE (grades III and IV) require hospital admission for management, ideally in the intensive care unit and intubation should be considered for airway protection. All patients with HE should receive supportive care, which includes balanced nutrition, avoiding dehydration and electrolyte abnormalities, and providing a safe environment. Disoriented and agitated patients need extra care to prevent falls. Judicious use of restraints is a safe option than sedative drugs, as patients with advanced cirrhosis and HE are vulnerable to over sedation with drugs. If at all medications are required, haloperidol is a better and safe option than benzodiazepine.6 Nutritional support includes 35–40 kcal/kg energy with 1.2–1.5 g/kg protein per day. Cirrhotic patients are usually malnourished and restriction of protein can increase mortality, so patients with HE should not restrict their protein intake.7,8 Grades I and II HE patients can take their diet orally, but patients with severe HE are usually unable to receive oral nutrition. These patients should be fed through Ryle’s tube along with necessary medications. All HE patients are advised to take small portions at regular intervals with a late-night snack of complex carbohydrates, as fasting further promotes the production of glucose from amino acids, which leads to ammonia production.9 Vegetable proteins are preferred as they improve nitrogen balance and mental status. Addition of branched-chain amino acids (BCAA) to a low-protein diet should be considered for patients intolerant to protein. Usually patients with transjugular intrahepatic portosystemic shunt (TIPS) or surgical PSS have severe HE and use of vegetable protein or protein restriction with BCAA supplementation is beneficial in these patients. The algorithm for management of HE has been shown in Flowchart 1.
**Acute Episode of Overt Hepatic Encephalopathy Management**

The treatment of acute HE starts with finding and management of triggering factors and the reduction of blood ammonia level. Treatment of precipitating factors combined with standard ammonia lowering therapy is associated with a rapid reversal of HE. Common precipitating factors are constipation, gastrointestinal bleeding, infections (including spontaneous bacterial peritonitis, urinary tract infection, and respiratory tract infection), renal failure, hypokalemia, metabolic alkalosis, hypovolemia, hypoxia, hypoglycemia, and use of sedatives. Blood ammonia concentration is reduced with lactulose, lactitol, rifaximin, and other ammonia lowering agents. Lactulose is administered in the dose of 30–45 mL (20–30 gm) two to four times per day and it should be adjusted so that it results in two to three soft stools per day. Lactitol powder of 67–100 gm diluted in 100 mL of water represents an equivalent dose. It is recommended to administer lactulose or lactitol enemas (1–3 L of a 20% solution) in patients who cannot take it orally. For patients who have not improved within 48 hours or who are unable to take lactulose or lactitol, rifaximin is the next option. The recommended dose of rifaximin is 400 mg orally thrice daily or 550 mg twice daily. Both the doses are equally effective. The safety and tolerability of rifaximin has been proved for up to 2 years. As a rule, antibiotics

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**Flowchart 1: Algorithm for management of hepatic encephalopathy**

BCCA, branch-chain amino acids; BRTO, balloon occluded retrograde transvenous obliteration; FMT, fecal microbiota transplantation; HE, hepatic encephalopathy; LOLA, L-ornithine L-aspartate; MHE, minimal hepatic encephalopathy; PSS, portosystemic shunts.
are added rather than substituted to nonabsorbable disaccharides. In a study, complete reversal of HE was observed more with combination of lactulose and rifaximin compared to lactulose alone (76% vs. 50.8%, p=0.004) along with decreased mortality (23.8% vs. 49.1%, P < 0.05). Hence, combination therapy is recommended in the management of HE. If the precipitating factor has been resolved and there is no recurrence of HE for next 3 months, the rifaximin can be discontinued. Neomycin, vancomycin, and metronidazole are other alternatives of rifaximin but rifaximin is preferred as it has less side effects. L-ornithine L-aspartate (LOLA) and branch-chain amino acids (BCCA) are the next in consideration for patients who do not respond to conventional therapy.

Hepatic Encephalopathy—Primary and Secondary Prophylaxis

Lactulose and rifaximin are proved to be equally effective in patients with acute variceal bleed for primary prophylaxis of HE. In a study, HE developed in a smaller number of cirrhotic patients with variceal bleed in lactulose group compared to placebo group (14% vs. 40%, p=0.03). In another study, lactulose and rifaximin were equally effective. Secondary prophylaxis of HE is defined as preventing another episode of HE in patients who had a previous episode of HE. In secondary prophylaxis chronic therapy with lactulose or lactitol is indicated and if HE recurs on lactulose therapy, combination therapy including lactulose and rifaximin should be considered. A published study revealed the efficacy of lactulose in prevention of HE recurrence compared to placebo (19.6% vs. 46.8%, p=0.001). Recurrence of HE can also be prevented with the help of probiotics, glycerol phenylbutyrate (PB), BCAA, and LOLA. Patients with refractory HE may have large spontaneous PSS. Refractory HE in these patients can be prevented by PSS embolization and balloon occluded retrograde transvenous obliteration (BRTO) of large spontaneous splenorenal shunts. Fecal microbiota transplantation (FMT) also prevents recurrence of HE, improve cognition and dysbiosis without major side effects in patients with cirrhosis. Liver transplant is the last resort in patients with decompensated cirrhosis who present with recurrent HE despite of being on above therapy.

Management of Minimal Hepatic Encephalopathy

Patients with MHE have poor quality of life, increased risk of OHE, require frequent hospitalization, and have high mortality. The available treatment options for MHE are disaccharides (lactulose, lactitol), rifaximin, probiotics, and nutritional support. In a study that compared a nutritional therapy of 30–35 kcal/kg and 1.0–1.5 g vegetable protein/kg with no dietary intervention in 120 cirrhotic patients with MHE, the rate of reversal of MHE was higher in those receiving nutritional therapy (71.1% vs. 28.8%, p=0.001). Prevention of OHE and improvement in quality of life was also observed with nutritional therapy.

Drugs Used in Management of Hepatic Encephalopathy

Nonabsorbable Disaccharides

Lactulose and lactitol are nonabsorbable disaccharides used as first-line treatment for HE. Lactulose reduces formation and absorption of ammonia from the gut by altering the microbiota, increases nitrogen excretion in the feces and reduces production of toxic short chain fatty acids. It works as an osmotic purgative, prebiotic, and also leads to gut acidification. A Cochrane data base review proved the efficacy of lactulose in HE management compared to placebo or no intervention. Efficacy of lactulose has been seen in the management of MHE, OHE, and recurrent HE. It is also effective in reducing the risk of variceal bleeding, spontaneous bacterial peritonitis, hepatorenal syndrome, liver failure, and mortality. Lactulose is well tolerated, and the main side effects include abdominal cramps, diarrhea, and flatulence. About 70–80% patients of HE responds to lactulose. Lactitol is as effective as lactulose, is more palatable, and have less side effects.

Nonabsorbable Antibiotics

Ammonia lowering effect has been observed with use of antibiotics such as metronidazole, vancomycin, neomycin, paromomycin, and rifaximin as they have activity against urease-producing gut bacteria. As rifaximin has minimal systemic absorption, broad spectrum, and less adverse events, it is most commonly used. Rifaximin effectively...
prevented the recurrence of HE when used as an add-on therapy for refractory HE, despite on appropriate lactulose therapy. \textsuperscript{11} Rifaximin is effective in recovery from HE, secondary prophylaxis, and in reducing the mortality as shown in a meta-analysis. \textsuperscript{34} It also enhances the performance and health-related quality of life in patients with MHE. \textsuperscript{35,36} Rifaximin had similar efficacy to nonabsorbable disaccharides for acute and chronic HE, and somewhat better tolerated. Although neomycin and metronidazole have been used for the management of HE, data are very old and inadequate.\textsuperscript{37–39} These antibiotics also have serious adverse events, like neomycin can cause nephrotoxicity, ototoxicity, malabsorption, and metronidazole can lead to peripheral neurotoxicity.

**Branch Chain Amino Acids**

Cirrhotic patients show reduce blood level of BCCA (leucine, isoleucine, valine). The BCCA have a role in skeletal muscle protein synthesis and detoxification of ammonia. High ammonia level decreases protein synthesis by diminishing the mTOR signaling in cirrhotic patients, this effect is prevented by BCAAs. A Cochrane data base review showed that BCAAs have a favorable effect on HE in cirrhotic patients.\textsuperscript{40} Both oral and intravenous preparations are effective. The BCCA helps in muscle building in all cirrhotic patients with sarcopenia along with favorable effects on HE which lead to improvement in quality of life. There is no benefit of BCAA supplementation in protein-tolerant patients. A recent randomized trial on 116 patients who had an episode of HE in the past, found no benefit of BCAA on the prevention of recurrent HE, although supplementation appeared to improve MHE and muscle mass.\textsuperscript{39} Based on these results, dietary BCAA supplementation is indicated only in severely protein-intolerant patients.

**L-Ornithine L-Aspartate**

LOLA promotes ammonia detoxification as it works as metabolic substrates for urea cycle in liver and glutamine synthesis in skeletal muscle thus reduces blood ammonia levels. There was improvement in HE, reduction in venous ammonia level, recovery time and duration of hospital stay with use of intravenous LOLA along with lactulose.\textsuperscript{37} A Cochrane data base review revealed favorable effect of LOLA on HE in cirrhotic patients and reduced mortality.\textsuperscript{41} This effect was observed with both oral and intravenous preparations.\textsuperscript{32} Prophylactic LOLA infusion proved to be effective in decreasing venous ammonia concentration in patients who underwent TIPS placement.\textsuperscript{43} LOLA is ineffective in patients acute liver failure.

**Probiotics**

Prebiotics and probiotics reduce blood ammonia concentrations by promoting colonization of acid-resistant, non-urease producing bacteria. The most efficacious species for HE appears to be Lactobacilli and Bifidobacterium. Use of probiotics improves recovery in HE, but when compared with lactulose they failed to show a benefit in significant outcomes as shown in a meta-analysis.\textsuperscript{44} Probiotics are effective in MHE, OHE, and prevention of recurrent HE.\textsuperscript{27}

**Other Therapies**

**Large Spontaneous Portosystemic Shunts Embolization**

Improvement in OHE and recurrence of HE has been observed with embolization of these shunts and BRTO of splenorenal shunt without deteriorating ascites, variceal bleed, and portal hypertensive gastropathy.\textsuperscript{21,22}

**Polyethylene Glycol**

Polyethylene glycol (PEG) solution results in increase excretion of ammonia in the stool by its purgative action thus it helps in HE management. Although the efficacy of PEG has been proved in a study, more such studies are required for the same.\textsuperscript{45}

**Acarbose**

Acarbose enhances the growth of gut saccharolytic bacterial flora and diminishes proteolytic flora that produces ammonia, mercaptans, and benzodiazepine-like substances. Improvement in HE and reduction in ammonia level has been observed with use of acarbose.\textsuperscript{46}

**Ammonia Lowering Agents**

Ammonia lowering agents like PB, ornithine phenylacetate (OPA), and benzoate binds to ammonia and leads to excretion of nitrogen by urinary non-urea excretion. To date there is no definite evidence for OPA and PB for the management of HE. Sodium benzoate had similar efficacy
to lactulose in the management of HE in a small study. Further studies are required to prove their efficacy.

**Flumazenil**

Use of flumazenil shows reduction in the GABA/benzodiazepine receptor complex activity thus reversing the neurological inhibition in HE. The short-term (minutes) favorable effect of flumazenil on HE has been proved in a meta-analysis but it does not have any effect on recovery, mortality, and quality of life. Flumazenil may be useful, in patients who received benzodiazepines.

**Zinc**

Zinc has a role in few patients with recurrent HE, but more studies are required to prove its efficacy.

**Newer Therapies**

**Fecal Microbiota Transplant**

In cirrhotic patients there is reduced level of favorable bacterial families like Lachnospiraceae and Ruminococcaceae and rise of the pathogenic Enterobacteriaceae, Streptococcaceae. Fecal microbiota transplant prevents HE recurrence, improves cognitive function, and decreases frequent hospitalization as shown in a randomized pilot trial.

**Albumin**

Albumin has anti-inflammatory properties; it binds and clears many toxic substances, which accumulate in liver failure. Lactulose with albumin has been proved to be more effective than lactulose alone in treatment of HE (75% vs. 53.3%, p=0.03).

**Other Experimental Therapy**

Glutamine synthetase replacement, Liposome supported peritoneal dialysis, Melatonin, L-carnitine, Glutamatergic antagonist, serotonin antagonist, opioid antagonist, and spherical carbon (AST-120).

**Conclusion**

Early detection and correction of precipitating factors is utmost important in the management of HE. The most commonly used therapy is still lactulose, which is effective in MHE, OHE, and recurrent HE. Efficacy of rifaximin is similar to lactulose in the treatment of HE with less side effects. In protein intolerant patients, BCCA have a favorable effect on HE. Probiotics and LOLA also have favorable effects in the treatment of HE. Nutritional therapy and FMT are emerging therapies for HE treatment but the data are limited. Combination of rifaximin and lactulose is more effective in the management of overt and recurrent HE. Liver transplant, embolization of large PSS, and BRTO of splenorenal shunts are effective management options in highly selected patients.

**References**


Abstract

This chapter discusses the current understanding of the gut microbiome in Indian population. It also highlights the differences of the Indian gut microbiome from other populations. Most of the earlier studies involved small to relative moderate sample size from specific geographic locations of India. An ideal study to evaluate the core gut microbiota of healthy Indians should involve a large homogeneous population across the country and use the same technology and data analytics tools. The LogMPIE (Landscape of gut microbiome-Pan India Exploration) is such a study. This study confirmed the most predominant organisms in the Indian gut are Prevotella copri and Faecalibacterium prausnitzii.

Introduction

The microbial ecosystem within the human body has established a symbiotic relationship that results in mutually beneficial metabolic and protective functions. Depending on the mode of delivery, the human gut gets colonized earliest from the maternal vaginal or skin flora. Even though organisms had been demonstrated in amniotic fluid, studies have even raised the possibility of colonization even before birth as organisms have been demonstrated in the first meconium. However, this observation is currently under scrutiny. Recent studies have also reported similarity between the ancient microbiome to the modern human gut microbiome, especially with modern rural population. It is now known that the gut microbiome is shaped throughout life in a dynamic manner by factors such as mode of delivery, diet patterns (vegan, fiber-rich, or meat-based), use of food preservatives and emulsifiers, environmental antimicrobial peptides, lifestyle behavior, such as alcohol intake, use of antibiotics and probiotics host genetics, and surrounding biodiversity.

Indian Gut Microbiota and Its Determinants

Mode of Delivery and Early Diet

It was shown by Pandey et al. that the fecal microbiota of vaginally born infants was dominated by Acinetobacter sp., Bifidobacterium sp., and Staphylococcus sp. On the contrary, the infants born by cesarean delivery conspicuously lacked Bifidobacterium, which is a crucial organism required for milk digestion. In a subsequent study, Kabeerdoss et al. reported a dynamic evolution of organisms in the infant gut, with the most dominant being Lactobacilli and Enterobacteriaceae. This was significantly higher than in infants born by cesarean delivery on the first day of life but equaled thereafter. After 3 months
of birth, an abundance of *Bifidobacterium* was higher in stools of the vaginally born infants while there was a progressive increase in abundance of the *Bacteroides-Prevotella* group in these infants from birth to 3 months of life. Meanwhile, exclusively breast-fed infants had a higher abundance of *Enterobacteriaceae* compared to those who were additionally fed with supplemental cow’s milk.10

**Age**

Balamurugan et al. reported the first Indian study on 130 children and adolescents that demonstrated a dynamic change in the gut bacterial composition.11 The study cohort was fairly homogeneous and predominantly consumed a lactovegetarian diet with infrequent meat intake. *Bifidobacterium longum* showed predominance from the age of 2–3 years but declined rapidly after reaching adulthood. Similarly, *Lactobacillus acidophilus* was predominant in the 2–3 years age group but progressively declined as age progressed toward adulthood. On the other hand, the *Bacteroides-Prevotella-Porphyromonas* group which was low in early childhood constituted the major organisms in later childhood and adolescence. The study by Marathe et al. also suggested a change in the gut microbiota with progressing age.12

**Habitat and Geography**

A multicenter study13 from urban and adjacent rural Delhi and Pune reported *Prevotella*, *Megasphaera*, *Faecalibacterium*, *Lactobacillus*, *Ruminococcus*, and *Roseburia* as the most dominant organisms. Interestingly, the gut microbiota in these individuals could be divided into two groups on the basis of the absolute counts of *Prevotella* and *Megasphaera*. The microbial diversity was significantly higher among the urban individuals.

Another subsequent study14 that evaluated the gut microbiota in rural and urban Ballabgarh (sea level) and Ladakh (11,500 ft above sea level) demonstrated region-specific differences in bacterial diversity. The genus and species level diversity were least in the rural Ladakh region while in individuals from urban Ballabgarh had high alpha and beta diversity, while individuals from the rural region had high alpha but low beta diversity.14 The genus *Parabacteroides*, *Blautia*, *Brevundimonas*, *Pelomonas*, and *Megamonas* were significantly higher in the Ballabgarh rural cohort. On the other hand, while *Lactobacillus* was abundant in the Ballabgarh urban cohort, *Bacteroides*, *Vibrio*, *Eggerthella*, and *Pseudomonas* were high in both the Ballabgarh cohorts.

The region-specific variation in the gut microbiota in this study was also associated with enrichment of xenobiotic metabolizing pathways in the Ballabgarh rural and urban cohorts compared to the Ladakh population, implying higher exposure to industrial chemical and drugs in the Ballabgarh populations.

Another recent study15 that evaluated the gut microbiota in Bhopal (Central India) and Kerala (South India) identified two distinct clusters of organisms. Cluster 1 was enriched in organisms from the genera *Prevotella* while Cluster 2 was enriched with species from the genus *Bifidobacterium*, *Ruminococcus*, *Clostridium*, and *Faecalibacterium*. Location-wise distribution revealed *Prevotella* and *Megasphaera* to be predominant in Central Indian cohort while the others including *Bacteroides* were more abundant in the South Indian cohort. Moreover, the authors also reported three characteristics fecal metabolomic clusters among the study cohorts. The Central Indian cohort abounded in metabolites such as palmitic acid, stearic acid, and valeric acid, while in the South Indian cohort, there was a significant enrichment of BCAAs (especially isoleucine), cadaverine, propionate, and lauric acid.

**Ethnicity**

Since tribal populations are closely attached to nature and their lifestyle is largely determined by agriculture, fishing, hunting, tribe specific dietary patterns, culture, and traditions, they are likely to harbor an evolutionarily conserved gut microbiota. India harbors the largest tribal population in the world and thus constitutes the ideal for evaluation of the “normal” gut microbiota. In the first and so far, the largest study on the Indian tribal gut microbiota,16 we evaluated healthy tribal volunteers belonging to 15 tribes of Mongoloid or Proto-Australoid decent dispersed over different geographic locations across Northeast and Southern India. The genus *Prevotella* contributed to 40% of the genus across all tribes. The other genera that constituted the core microbiota irrespective of geography and ethnicity included *Faecalibacterium*, *Eubacterium*, *Clostridium*, *Blautia*, *Collinsella*, *Ruminococcus*, and *Roseburia*. In addition to these genera, *Bacteroides*, *Dialster*, and *Veillonella* were found to abound the tribes from Manipur while *Bacteroides*, *Dialster*, *Bifidobacterium*, and
Lactobacillus abounded in the tribes from Sikkim. Tribes from Manipur had the least abundance of Bifidobacterium. Correlational analyses within the core microbiota revealed that Prevotella had a negative correlation with Bacteroides, Faecalibacterium, and Clostridium in the Telangana tribes, with Faecalibacterium, Bacteroides, and Roseburia in the Manipur tribes, and with Bacteroides, Clostridium, Ruminococcus, and Blautia in the tribes from Sikkim. Tribes from Sikkim had a significantly lower abundance of Enterobacter compared to tribes from Assam, Telangana, and Manipur.

### Dietary Factors

Diet has been established as a major factor that shapes the human gut microbiota. In the foregoing sections of this review, even though there were variations in the gut microbiota according to geography and habitat, a closer look actually converges these variations to dietary patterns. Overall, Prevotella, which is responsible for complex plant-derived polysaccharide degradation, was dominant in a majority of the study populations implicating this as a signature genus in Indians.13,15-17

The study from Ballabgarh and Ladakh14 also suggested that cooking oil and ghee could impact the Indian gut microbial composition. For instance, individuals from Ladakh consumed predominantly sunflower oil, which has a high concentration of linoleic acid that is known to be degraded by Roseburia. Similarly, Sporobacter was also abundant in individuals consuming sunflower oil; while Collinsella was specifically predominant in individuals who consumed clarified butter (ghee).

In the tribal study by Dehingya et al.,16 the gut microbiota was similar between tribes from Assam and Telangana despite the geographic and ethnic differences. Therefore, it appears likely that the carbohydrate and dietary fiber-rich diet (including rice, whole grain, vegetables, fruits, legumes, tubers) determines the core microbiota, which is predominant in Prevotellaceae, Ruminococcaceae, Lachnococcaceae, and Enterobacteriaceae, which are enriched in carbohydrate metabolizing enzymes. In the Lepcha, Nepali, and Bhutia tribes from Sikkim the abundance of Bifidobacterium and Lactobacillus can be explained by the higher consumption of milk products and fermented food. Among the Malayali tribes from Tamil Nadu, the higher abundance of Bacteroidetes and Clostridiun could be explained by their daily intake of a moderate amount of pork meat, and non-intake of milk, and milk products due to their religious beliefs.17

### Comparison of Indian Gut Microbiota with Worldwide Data

It has now been consistently shown that the Indian gut microbiota differs significantly from that of other regions of the world. In our study,16 we observed two distinct clusters, the first involving the Hadza, Italian, and Americans individuals that abounded in Faecalibacterium. The rest of the tribal groups, including Indians, constituted the other group with a higher abundance of Prevotella. Interestingly, within this group there was close similarity of the Indian tribal microbiome to the Mongolian tribal microbiota. Of note, the origins of the Nepali and Tai-Phake tribes from India can be mapped to Mongolians.

In the study by Bhute et al.,13 comparison of gut microbiota of Western and North Indian cohorts with Americans revealed 76 OTUs, out of which six, including Prevotella, Lactobacillus, Lachnococcus, and Roseburia, specifically belonged to the Indians. In this study, it was also observed that Indians shared 25 OTUs with the Bangladeshi microbiota of Western and North Indian cohorts with Americans revealed 76 OTUs, out of which six, including Prevotella, Lactobacillus, Lachnococcus, and Roseburia, specifically belonged to the Indians. In this study, it was also observed that Indians shared 25 OTUs with the Bangladeshi cohort (majority belonging to families Lachnococcaceae, Ruminococcaceae, and Enterobacteriaceae, and genus Prevotella). Other than differences at the overall genera and species level OTUs, differences were also noticed between Indian and European cohorts even within the same genus.13

Finally, a metagenome wide meta-analyses (MGWAS) by Dhakan et al., which included datasets from India, China, USA, and Denmark demonstrated completely separate species level clustering of the Indian gut microbiome compared to the American, Danish, and Chinese microbiome.15 Prevotellaceae emerged as the most highly abundant bacterial family in the Indian individuals. In addition, the Indian gut microbiota was found to be enriched in functions that corroborate with a carbohydrate-rich diet.

### Conclusion

Results of gut microbiota studies can be influenced by several technical factors such as sample size, sample collection and storage, sequencing technique, reference database, and depth of statistical and bioinformatics analyses. Contd...
In this review, we discussed the gut microbiota in healthy Indians based on the individual studies that involved small to medium sample size and different techniques to evaluate the microbiome. The ideal way to evaluate the true core Indian gut microbiota would be to include a large homogeneous population across the entire country and use the same methods of sample processing, sequencing, and data analyses. The LogMPIE (Landscape of gut microbiome-Pan India Exploration) is such a study that was recently published. This study evaluated 1,004 individuals from 14 centers across India (4 from north, 3 from east, 4 from west, and 3 from south) and bacterial metagenomic sequencing was performed in the Ion oneTouch 2 system. There were 390 microorganisms that were common in all the geographic locations, while 36 were unique to north, 95 to west, and 62 to east India. The most predominant organisms emerged to be Prevotella copri and Faecalibacterium prausnitzii, thereby qualifying Prevotella and Faecalibacterium.

References

Abstract
Traditionally celiac disease (CeD) has been defined as a disease involving the proximal small intestine with a presentation with diarrhea, loose stools, malabsorption, weight loss, failure to thrive, and growth retardation in children. This presentation which has long been portrayed as “classical” for CeD, allows us to diagnose only the patients with most severe gastrointestinal involvement and thus miss out those with milder or no GI manifestations. However, it is being increasingly recognized that celiac disease is a multisystem disease with a myriad of presentation including asymptomatic. Even though studies have indicated around 1% population prevalence of celiac disease, most of these patients however remain undiagnosed and hence untreated. There is thus a need for increased awareness of these varied presentations of celiac disease so that the patients can be diagnosed and treated with gluten-free diet thus preventing complications. In this chapter we have discussed the indications for screening for celiac disease and the strategy for screening these individuals.

Introduction
Celiac disease (CeD) is a chronic immune-mediated enteropathy which is triggered on consumption of gluten protein present in cereals like wheat, barley, and rye in genetically predisposed individuals. Although initially believed to be an uncommon disease and limited to the western countries, CeD has now become a global disease and it is now reported from almost all the continents.

Global Burden of CeD
In a systematic review and meta-analysis, we have recently shown that the global pooled seroprevalence (proportion of people having a positive celiac specific serological test in a population) is 1.4% (that means, 1 in 70 people is seropositive for CeD) and the prevalence of biopsy-confirmed CeD (proportion of patients having a combination of positive serological tests and villous abnormalities on duodenal biopsies) is 0.7% (means 1 in 140 individuals globally has CeD). With a global population of 7.2 billion people, approximately 40–60 million people around the world are likely to have CeD.

Burden of CeD in India
Although reported since 1960s in India, an increase in number of patients with CeD in the last 2 decades has been reported from many states, predominantly Northern and Western States of India. Two population-based studies from Northern part of India have shown that the population prevalence of CeD is 1.04% (1 in 96) and 0.33% (1 in 330), respectively. Because of predominance of reporting of CeD from the Northern states, people believe that CeD is seen only in the Northern part of India. To explore the question “is there a regional variation in the prevalence of CeD in India,” we conducted a multi-site population-based study recruiting 23,331 healthy individuals from three different regions of India including Northern (Haryana),
Southern (Vellore), and Northeastern (Guwahati) regions of India. The combined pan-India prevalence of CeD is 0.67% (1 in 140). Indeed, there is a regional variation in the prevalence of CeD at this point of time, the highest being in Northern India (1.23%), lowest in Southern India (0.1%) and in between in the Northeastern region of India (0.87%). This difference is likely related to the different eating patterns, with rice being staple diet in Southern India and wheat in Northern India. However, with increase in the consumption of products made from wheat in rice eating regions, it is very likely that CeD will emerge in such populations also. With the Indian population of 120 crores, it is estimated that approximately 60–80 lakhs of Indians have CeD. Of this large estimated numbers of people having CeD, only a minority have been diagnosed and a large proportion of them (85–95%) exists in the population but currently remain undiagnosed.

Where are They?
If there are so many patients with CeD both worldwide and in India, then where are they? Why are we not able to pick them up? There are multiple reasons:

- The lack of awareness amongst physicians about changing epidemiology of this disease is the most important reason. We do not think about this diagnosis in appropriate clinical setting.
- It was believed that CeD affects only children, but now it is known that CeD can affect people of all age groups. Although not well established, it is however believed that the pathophysiological changes in CeD starts since early part of life. The clinical manifestations may appear at different ages of life depending upon the severity of the disease.
- While some patients have fully expressed disease with obvious symptoms and manifests in childhood or during adolescence, in others, the disease is expressed in milder form, and hence may not come to clinical attention till late. CeD is diagnosed nowadays more often in adulthood and even in the elderly.
- The classical manifestations, as portrayed in the older textbooks, draw our attention to mainly the more classical form of disease (emaciated child with diarrhea and anemia), which are present in those having a more advanced disease. In early stages of the disease, patients may not have any symptoms or have only mild symptoms.
- While CeD is thought to be mainly a disease of the intestine and recognized in those having gastrointestinal symptoms, only half of the patients however present with predominant gastrointestinal manifestations. The GI symptoms (Classical CeD) include chronic diarrhea, malabsorption, failure to thrive, abdominal distension, and weight loss (Fig. 1).
- Approximately half of all the patients with CeD present to a clinician with predominant non-GI symptoms such as short stature, liver abnormalities, infertility, endocrinopathies, etc. in the absence of or with minimal GI symptoms. The diagnosis of CeD is often not suspected in such patients, since most physicians believe that patients with CeD should have GI manifestations (Fig. 1).

Therefore, patients with CeD can present to an internist/gastroenterologists with symptoms of chronic diarrhea, anemia, fatigability, to a pediatrician with irritability, diarrhea, failure to thrive and anemia, to a hematologist with anemia refractory or unresponsive to iron supplementation, to an endocrinologist with type 1 diabetes, hypothyroidism, or growth failure, to a dermatologist with dermatitis herpetiformis, to a neurologist with ataxia, peripheral neuropathy, and to a gynecologist with menstrual abnormalities or infertility.

Thus, there is an increased need for increasing awareness amongst primary care physicians, internists, gastroenterologists, hematologists, endocrinologists, and neurologists about a wide and varied spectrum of manifestations of CeD so that these patients are diagnosed early. An early diagnosis and initiation of gluten-free diet in them can control and the symptoms, and prevent consequences of malabsorption and nutritional deficiencies and prevent adverse health consequences.  

Therefore, CeD should be suspected in the patients even in the absence of typical gastrointestinal manifestations. We have summarized below the diseases or symptoms where screening for CeD should be done.

Who should be Screened for CeD (Table 1)

Patients having Diseases and Symptoms Secondary to CeD

Chronic Diarrhea with Features of Malabsorption

Patients having intermittent or chronic diarrhea with features of malabsorption, such as anemia, growth
TABLE 1  Indications for screening for celiac disease

<table>
<thead>
<tr>
<th>Gastrointestinal manifestations</th>
<th>Extraintestinal manifestations</th>
<th>Associated conditions</th>
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</thead>
<tbody>
<tr>
<td>Chronic diarrhea</td>
<td>Cryptogenic hypertransaminasemia</td>
<td>First-degree relatives</td>
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<tr>
<td>Malabsorption</td>
<td>Cryptogenic cirrhosis</td>
<td>Type I diabetes</td>
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<tr>
<td>Growth retardation/Short stature</td>
<td>Infertility</td>
<td>Hypothyroidism</td>
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<tr>
<td>Failure to thrive</td>
<td>Idiopathic cerebellar ataxia</td>
<td>Other autoimmune diseases</td>
</tr>
<tr>
<td>Iron deficiency anemia</td>
<td>Dermatitis herpetiformis</td>
<td>Down's syndrome</td>
</tr>
<tr>
<td>IBS (IBS-D, IBS-M)</td>
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</tbody>
</table>

retardation, poor weight gain, easy fatigability, should be screened for CeD. CeD is now the most common cause of malabsorption syndrome, unlike tropical sprue being the most common cause some times back.

**Functional Gastrointestinal Disorders**

Some of the patients with CeD may have mild GI manifestations such as altered bowel activity, abdominal pain/discomfort, and bloating. With such a symptom complex, they are likely to be diagnosed as having functional gastrointestinal diseases including irritable bowel syndrome. In fact, in a meta-analysis of 7 studies including 3,383 patients with CeD, it was shown that 38% patients with CeD had IBS-like symptoms. In yet another meta-analysis of 22 eligible studies including 6,991 patients with irritable bowel syndrome, it was found that
3.3% of them had CeD more so in those having mainly IBS-diarrhea predominant and IBS-mixed subtypes.7

**Iron Deficiency Anemia**

Between 50–80% of patients with CeD have anemia and that occurs most commonly because of iron deficiency. Anemia secondary to B12 and folate deficiency in addition to iron deficiency has also been described.

On the other hand, it has been observed that 3.2% (95% CI 2.6–3.9%) of all patients with iron deficiency anemia, when screened for CeD, are found to have CeD.8 That would mean than 1 of every 31 patients with iron deficiency anemia has CeD. In a study from India, almost 1 in 10 with iron deficiency anemia had CeD. Thus, all patients with iron deficiency anemia should be screened for CeD.

**Short Stature/Growth Failure**

Almost one third of the adult patients and half of the adolescent patients with CeD have short stature. Since height can increase only till 18 years of age, it is really important to make a diagnosis of CeD much before that age. A timely treatment of CeD can lead to catch up growth and attainment of a normal height.

On that other hand, of the patients presenting for the evaluation of short stature, 6.6% (approximately 1 in 15) have been found to have CeD. The proportion of patients having CeD is still higher (13.4%; 1 in 8) in those having idiopathic short stature, when all known causes have been excluded. The prediction of having CeD in these patients is higher if they also have associated GI manifestations or anemia. Nevertheless, all patients with short stature at any age, with or even without associated GI manifestations, should be screened for CeD.

**Dermatitis Herpetiformis**

Dermatitis herpetiformis (DH) is characterized by clusters of papules and vesicles associated with intense pruritus. The typical sites for DH lesions include extensor surfaces of upper and lower extremities, elbows, knees, scalp, and buttocks. The extent of skin lesions may vary from small area to more diffuse involving multiple sites at one time. DH shows an excellent response to GFD with complete resolution of skin lesions. Thus, all patients with DH must be screened for CeD.

**Infertility**

Menstrual abnormalities including delayed menarche and secondary amenorrhea are quite frequent in patients with CeD. Furthermore, patients with CeD have been found to have a low rate of fertility. Patients with CeD are at three-times higher risk for infertility than the general population. On the other hand, 2.3% of patients with infertility have been found to have CeD.9 As CeD is one of the few treatable causes of infertility, all women patients with infertility should be screened for CeD.

**Liver Abnormalities**

Almost one-fourth patients with CeD have asymptomatic elevation of serum transaminases at the time of diagnosis which normalize within 1 year of GFD in majority. If this liver injury is not recognized and remains untreated, it can lead to cirrhosis of the liver. In fact, CeD has been found to be one of the causes of cryptogenic cirrhosis. Furthermore, approximately 7% of all those who have hypertransaminasemia and 5% of those having cryptogenic liver disease have been found to have CeD.10,11 Treatment of CeD in these patients has been shown to lead to an improvement in the liver disease. Therefore, all patients with cryptogenic hypertransaminasemia and cryptogenic cirrhosis of liver should be screened for CeD. As discussed below, as anti-tissue transglutaminase antibody may be falsely positive in those with cirrhosis; therefore, a more reliable screening test in this setting is anti-endomysial antibody.

**Neurological Disorders**

Some of the patients with cerebellar ataxia, especially those having idiopathic ataxia, have been found to have gluten-related disorders and CeD. The treatment of CeD has also been shown to lead to some improvement in ataxia. Therefore, patients with idiopathic ataxia should be screened for gluten-related disorders. In such patients both anti-gliadin antibody and anti-tissue transglutaminase antibodies should be used for screening.

**First-degree Relatives of Patients with CeD**

As we know, genes play a major role in the pathogenesis of CeD. The first-degree relatives of index patients with CeD are at much higher risk of developing CeD. A recent
meta-analysis including 10,252 FDRs of patients with CeD has shown that 7.5% of first-degree relatives of CeD have CeD. Furthermore, the sisters (1 in 7) and daughters (1 in 8) of the index patients with CeD are at the highest risks. Thus, all the first-degree relatives of index patients with CeD should be screened for CeD.

**Type I Diabetes**
CeD has been found to be strongly associated with type I diabetes and a recent meta-analysis has shown that 6% of all patients with type I diabetes have CeD. It means that of 16 patients with type I diabetes, one will have associated CeD. Many of them may have symptoms because of CeD, but these symptoms are often considered to be due to diabetes, and hence they are not specifically investigated for CeD. Therefore, all patients with type I diabetes should be screened for CeD.

**Autoimmune Thyroid Disease**
An association has been shown between CeD and autoimmune thyroid disorders. Between 10–15% patients with CeD have coexistent clinical hypo/hyperthyroidism. In fact, a recent study showed that of 6,024 patients with autoimmune thyroid disorders screened for CeD, 1.4% patients had CeD. Thus, all patients with autoimmune thyroid disorders should be screened for CeD.

**Down’s Syndrome**
Approximately 1%–19% patients with Down’s syndrome have been reported to have CeD. A recent meta-analysis of 31 studies and including 4,383 patients with Down’s syndrome has reported that 5.8% of them have CeD, which is much higher than that in the general population. Therefore, all patients with Down’s syndrome should be screened for CeD.

**Other Conditions**
A higher prevalence of CeD has also been observed in certain other conditions including patients having dental enamel defects, other autoimmune disorders like systemic lupus erythematosus, juvenile rheumatoid arthritis, and autoimmune liver diseases, etc.; however, there is a lack of robust data suggesting the utility of routine screening for CeD in these patients.

### How do we Screen for CeD?
Once we suspect a patient to have CeD, the first-line screening tests are the CeD specific serological tests. Immunoglobulin subclass A (IgA) anti-tissue transglutaminase, (IgA anti-tTG Ab), anti-endomysial antibody (IgA EMA), and deamidated glutamine dipeptide (IgA anti-DGP Ab) are the currently available assays for screening for CeD. Of these, IgA anti-tTG is the most commonly used test for the screening and diagnosis of CeD because of the ease of detection and a high accuracy with a sensitivity of 92.8% and specificity of 97.9% (Table 2). While IgA EMA testing has a high specificity of 99%, recent systematic review has reported a lower sensitivity of 73%. Detection of anti-EMA requires indirect immunofluorescence and it is not widely available. IgA anti-DGP assay have a pooled sensitivity of 87.8% (95% CI, 85.6–89.9%), and specificity 94.1% (95% CI, 92.5–95.3%) and thus have an inferior performance than anti-tTG Ab (Table 2). Since all these antibodies are IgA based, hence they may be falsely negative in patients having IgA deficiency. In such situations, IgG based tests such as IgG anti-DGP or IgG anti-tTG Ab should be done.

ELISA kits for anti-tTG antibody are manufactured by many companies and their performance varies significantly. Furthermore, there are differences in the cut-off values of the anti-tTG antibody amongst ethnically different population. Hence, a clinician should be aware about these limitations.

### Diagnosis of Celiac Disease (Flowchart 1)
If a patient screened for CeD is detected to have a positive celiac specific serological assays, the diagnosis needs to be confirmed by demonstration of villous abnormalities in the intestinal mucosa, which is still the gold standard.
for the diagnosis of CeD. Multiple biopsy specimens from the second part of duodenum and at least one biopsy specimen from the first part of the duodenum should be taken for adequate histopathological assessment. 19-21 Modified Marsh classification system is currently used to grade the severity of villous abnormalities based on identification of increased intraepithelial lymphocytes, crypt hyperplasia, and villous atrophy. A diagnosis of CeD is made in patients with villous abnormalities of modified Marsh grade II or more.

The gold standard diagnostic criteria of CeD is based on a combination of clinical manifestations, a positive celiac specific serology and demonstration of villous abnormalities of modified Marsh grade II or more. The
European Society of Gastroenterology, Hepatology and Nutrition (ESPGHAN 2019) has suggested a Non-Biopsy Approach for making of a diagnosis of CeD.20 This is based on the evidences that suggest a high degree of prediction of presence of villous abnormalities if anti-tTG Ab titers are more than tenfolds higher above the cut-off value. The ESPGHAN 2019 guidelines suggest that a non-biopsy approach may be considered in children if their anti-tTG Ab titer is more than tenfolds and there is a positive anti-endomysial antibody in a second blood samples. Otherwise, duodenal biopsies should be performed, if anti-tTG titer is less than tenfolds. For adults patients, most of the guidelines, including Indian, recommend a confirmation of diagnosis of CeD with small intestinal biopsy in patients having a positive serological test.19,21,22

More often around the world, the ESPGHAN guidelines are misinterpreted and the diagnosis of CeD is made even when anti-tTG Ab titer is less than tenfolds. A hurried diagnosis based on incomplete evidence leads to problems during follow-up. All efforts should be made for the confirmation of the diagnosis before advising GFD. One should realize that anti-tTG Ab, especially at low titer could be falsely positive and the enteropathic changes are not specific for CeD and they could be caused by many other conditions.

**Conclusion**

CeD has now become a global public health problem and it affects approximately 1% of the world’s population. The spectrum of clinical manifestations of CeD is wide include both gastrointestinal and extra-intestinal manifestations. Many patients with CeD do not have GI manifestations but present solely with non-gastrointestinal manifestations. All patients with high-risk of CeD should be screened using IgA anti-tTG antibody.

**References**

Abstract
Diagnosing intestinal tuberculosis (ITB) and Crohn’s disease (CD) has always been a challenge in countries like India where TB is endemic and incidence of inflammatory bowel disease (IBD) is increasing rapidly. Definitive diagnosis of tuberculosis requires demonstrating AFB in smear or culture, caseation necrosis in biopsy or necrotic lymph node in cross sectional imaging. But all these are limited by poor sensitivity. There are certain clinical (diarrhea, hematochezia, perianal disease common in CD; fever, night sweats common in ITB), endoscopic (longitudinal, aphthous ulcers common in CD; transverse ulcers/patulous ileocecal valve common in ITB), histologic (caseating confluent large granuloma common in ITB; microgranuloma common in CD) and radiologic (long segment involvement, comb sign, skip lesions common in CD; necrotic lymph node, contiguous ileocecal involvement common in ITB) differences between CD and ITB. Despite all these differentiating features, in more than 1/3rd of cases a definitive diagnosis cannot be made without a therapeutic ATT trial. Recent advances in this field like newer biomarkers (enumeration of peripheral blood T-regulatory cells) and CT based predictive models (quantification of visceral and subcutaneous fat) can help in difficult cases. As a clinician we need to assess all these clinical and investigational parameters meticulously to solve this diagnostic conundrum.

Introduction
Intestinal tuberculosis (ITB) and Crohn’s disease (CD), a sub-type of inflammatory bowel disease (IBD), are both chronic granulomatous disorders of the intestine with different etiologies, but similar presentations. Due to globalization and industrialization Southeast Asian countries like India, which are endemic for TB, are in a state of socio-epidemiologic transition with a rising incidence of CD and other non-communicable disorders (Crohn’s disease and the “white plague” hypothesis). Despite growing number of literature, conclusive diagnosis of ITB and CD still remains a clinical conundrum. There have been reports of misdiagnosing ITB as CD for as long as 7 years before the correct diagnosis was reached. Misdiagnosing these two clinical conditions can have disastrous implications like drug toxicity of anti-tubercular therapy (ATT), delay in CD-specific therapy leading to disease progression along with impaired quality-of-life, and flare up of TB on immunosuppressive therapy for CD. For definitive diagnosis of ITB, we need to demonstrate mycobacterium tuberculosis (MTB) in smear or culture, or caseating granuloma in biopsy or a complete symptomatic and endoscopic response to ATT; but all these methods have unsatisfactorily low sensitivity. So in clinical practice, most often we gather diagnostic clues from conglomerate of laboratory tests and investigations. In this review, we will discuss the overlapping and discriminative features of both the diseases and try to elucidate a proper approach to solve the diagnostic dilemma. Evaluation of any patient suspected of ITB or CD runs through the following steps (Flowchart 1):
Clinical Features

Both the diseases present with some common clinical features like abdominal pain, diarrhea, partial bowel obstruction, fever, weight loss and extra intestinal manifestation (EIM) like arthralgia, skin rash, or ocular symptoms. But some of the symptoms are more frequently seen in either of two diseases. Despite some heterogeneity most studies reported diarrhea, hematochezia, perianal disease, and EIMs as being more common in CD whereas partial bowel obstruction, night sweat, and ascites predominate in ITB (Table 1).\(^{10,13}\) Longer disease duration also supports the diagnosis of CD over ITB, but a specific cut off for duration is not available.\(^{12}\) A recent meta-analysis reported that diarrhea, hematochezia, perianal disease, and EIMs favored the diagnosis of CD, while fever, night sweats, lung involvement, and ascites favored the diagnosis of ITB.\(^{14}\)

Endoscopic Appearance

Endoscopic features in CD and ITB have been well described. Albeit some overlap, left colonic involvement, presence of longitudinal ulcers, aphthous ulcers, cobblestoning, and skip lesions are more common in CD whereas presence of transverse ulcers and patulous ileocecal valve are more common in ITB (Table 1 and Figs. 1A to D).\(^{10,11,13,14}\) Lee et al. described a predictive model based on four common endoscopic findings in CD (anorectal lesion, longitudinal ulcers, aphthous ulcers, and cobblestone appearance) and ITB (less than 4 segment involvement, patulous IC valve, transverse ulcers, and pseudopolyps). A score of +1 and -1 was assigned for each parameter of CD and ITB respectively. Total score >0 indicated the diagnosis of CD with a PPV of 94.9% and score <0 indicated diagnosis of ITB with a PPV of 88.9%.\(^{15}\)

Histopathology

Both these diseases are chronic granulomatous disease of the GI tract and share many histopathological features
like architectural abnormalities (crypt distortion, crypt branching, or crypt loss), chronic inflammation (chronic inflammatory infiltrate, increased IEL, basal plasmacytosis) and granulomas. But there are subtle differences which can be helpful to discriminate these two pathologies. As reported by Pulimood et al., granulomas are more common in tuberculosis than CD and tubercular granulomas are usually multiple (>5–10/HPF), large (>200 μm), confluent, located more in submucosa and with central caseation which is almost pathognomic for ITB while the granulomas in CD are sparse, small and poorly organized (microgranuloma). Apart from granuloma, ulcers lined by epitheloid histiocytes and disproportionate submucosal inflammation favors the diagnosis of ITB, on the other hand focally enhanced colitis is characteristic of CD. A recent meta-analysis also echoed similar findings.

One of the major limitations of HPE is that more often we do not find granuloma in biopsy specimens to characterize it. Minimum 6–8 biopsies must be taken from the ulcerated and inflamed area to mitigate this problem.

**Microbiology**

One of the major challenges of diagnosing ITB is the poor sensitivity of microbiological tests to detect the bacilli (Table 2). ITB is a paucibacillary disease, so demonstrating the organism is difficult. Acid fast bacillus (AFB) staining in a biopsy specimen has a sensitivity of 2.7–37.5% as reported in different studies. Although culture of intestinal biopsy in Lowenstein Jensen medium is the

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Figs. 1A to D: Endoscopic images. (A) Deep longitudinal jejunal ulcer in a patient with Crohn’s disease. (B) Cobblestoning in a patient with Crohn’s disease. (C) Ulcerated stricture in a patient with ITB. (D) Strictures IC valve with gaping in a patient with healed ITB
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Differentiating Crohn’s Disease from Intestinal Tuberculosis: A Diagnostic Challenge

Gold standard, it has been replaced largely by BACTEC culture which is less time consuming. Most of the studies have reported less than 50% culture positivity rate in biopsy from ITB patients. 8,21-23 Polymerase chain reaction targeted against IS6110 (TB-PCR) as a stand-alone test is not diagnostic for ITB but can help in diagnosis. Jin et al. in his meta-analysis reported a pooled sensitivity of 47% and specificity of 95% for TB-PCR in intestinal biopsy. 24 Gene-Xpert MTB/RIF in the intestinal biopsies has not been well studied in patients with ITB. In a study of 37 ITB patients it showed sensitivity of 8.1% and specificity of 100%.20 Another study by Bellam et al. reported sensitivity of 32% and specificity of 100%.25

**Radiology**

CT/MR enterography are the preferred imaging modalities for evaluating and differentiating between patients with ITB and CD. Along with access to whole of the GI tract, cross sectional imaging has additional advantage as it can detect other significant findings like peritoneal or omental involvement and mesenteric or intra-abdominal lymphadenopathy. CT findings commonly seen in patients with CD are left colonic involvement, multifocal (>3 segments) or long-segment involvement, comb sign, and pseudosacculation. On the other hand, involvement of ileocecal area, short segment involvement (<3 cm), and presence of lymph nodes larger than 1 cm are more common in ITB.26-27 A predictive model based on three characteristics [long segment (>3 cm) involvement, >1 cm lymph node, ileocecal involvement] had a specificity of 90% in differentiating CD from ITB.27 A meta-analysis involving six studies concluded that necrotic lymph nodes had the highest diagnostic accuracy (sensitivity 23%, specificity 100%) for ITB diagnosis, and comb sign (sensitivity 82%, specificity 81%) followed by skip lesions (sensitivity 86%, specificity 74%) had the highest diagnostic accuracy for CD diagnosis28 (Figs. 2A to D).

Patients with ITB may also have evidence of concomitant pulmonary involvement. 3–25% of ITB patients show evidence of healed or active pulmonary TB on chest X-ray.29 Data from our centre (not published) indicates addition of CT chest (in place of chest X-ray) with CT enterography can significantly increase the sensitivity of diagnosing ITB.

**Adjunct Tests**

Both interferon gamma release assays (IGRA) and Mantoux are predictive of latent TB rather than active TB; hence, a positive or a negative IGRA will neither rule in nor rule out the diagnosis of ITB. Positive Mantoux has been reported in 50–100% patients with ITB patients whereas meta-analysis on IGRA reported a pooled sensitivity of 74% and specificity of 87% in differentiating ITB from CD.30,31 Both these tests provide supporting evidence but are not diagnostic.

Another serological test, anti-saccharomyces cerevisiae antibody (ASCA), has been investigated for this purpose but one study from India and a recent meta-analysis denied any significant role.32,33

**Therapeutic ATT Trial**

As we have discussed above, all these investigations have limited diagnostic accuracies and despite all these tests, in some cases it is nearly impossible to conclusively diagnose ITB or CD. Treating with steroid in such cases can be disastrous if the patient has underlying ITB, so trial of ATT is almost imperative for further management of such a case. A recent retrospective study from Korea reported that 17.9% CD patients were misdiagnosed as ITB and 10.8% patients of ITB were misdiagnosed as CD before the correct diagnosis being made. Forty-eight percent of ITB patients required therapeutic ATT trial for the final diagnosis.34 Asia-Pacific consensus statements for CD have also advocated ATT trial in a patient with CD/ITB dilemma, and the diagnosis of CD should be considered in a patient who does not respond to ATT, and subsequently responds to CD-specific therapy.35 But the big question is the timeline of ATT trial, when to say a patient as non-responder and how to assess response. A recent study from our centre compared the response between two groups (CD patients who received ATT as therapeutic trial and ITB patients). By 3 months more than 90% of patients with

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<tr>
<th>TABLE 2</th>
<th>Sensitivity of different microbiological tests for ITB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnostic tests</strong></td>
<td><strong>Sensitivity</strong></td>
</tr>
<tr>
<td>AFB smear</td>
<td>(2.7–37.5)%</td>
</tr>
<tr>
<td>Culture (LJ/BACTEC)</td>
<td>(19–50)%</td>
</tr>
<tr>
<td>TB-PCR</td>
<td>47%</td>
</tr>
<tr>
<td>Gene-Xpert MTB/RIF</td>
<td>(8.1–32)%</td>
</tr>
</tbody>
</table>

Patients with ITB may also have evidence of concomitant pulmonary involvement. 3–25% of ITB patients show evidence of healed or active pulmonary TB on chest X-ray. Data from our centre (not published) indicates addition of CT chest (in place of chest X-ray) with CT enterography can significantly increase the sensitivity of diagnosing ITB.
ITB, and up to 1/3rd patients with CD responded to ATT but response was ill-sustained in patients with CD, and up to 80% of them worsened on follow-up. Moreover, repeat colonoscopy at 6 months of treatment showed mucosal healing in 100% patients with ITB, whereas less than 5% of patients with CD had an endoscopic response. Based on this study following algorithm has been proposed which is now a routine practice (Flowchart 2).

**Pitfalls of the Strategy**

One of the major concerns is that should we consider possibility of MDR-TB while designating a case as CD on the basis of non response to ATT trial. There is not much data on prevalence of MDR-TB in gastrointestinal tuberculosis. Lin et al. reported MDR-TB rate of 13% among patients with lower gastrointestinal TB. But an Indian study reported a prevalence of only 5.4% among patients with abdominal TB and another study from our center found no cases of MDR-TB among patients with ITB. Moreover ITB being a paucibacillary disease is expected to have a low rate of drug resistance.

Although most ITB patients respond well to ATT, study from our centre showed that only one-fourth of patients with ITB related stricture had resolution of stricture after ATT and majority had symptoms pertaining to stricture even after ATT. This observation should also be kept in mind during assessment of response to ATT.
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Flowchart 2: Algorithm for follow-up of a patient with CD/ITB dilemma who has been initiated on a therapeutic ATT trial

Predictive Models

Due to limitation in accuracy and sensitivity of any single characteristic, several multiparametric predictive models incorporating more than one feature across single or multiple diagnostic modalities have been described. A multicentre study from India described hematochezia, weight loss, sigmoid colon involvement, and focal enhanced colitis as independent predictors for diagnosis of CD/ITB, and a score based on these variables had an AUC of 0.91 in differentiating CD from ITB. Another Korean study included age, gender, diarrhea, transverse ulcer, longitudinal ulcer, sigmoid colon involvement, and suspicion of pulmonary TB in their predictive models. The AUC for differentiating CD and ITB was 0.98, and on validation in a separate cohort, the accuracy was similar with an AUC of 0.92. But most of these predictive models have their own limitations in terms of application in clinical practice and these have not been widely validated across other population.

Recent Advances in this Field

There have been many recent advances in the field regarding newer biomarker or other investigational parameters to differentiate these two diseases.

Mesenteric fat proliferation and creeping fat have long been associated with active CD. A Korean study described increased visceral fat (VF) in patients with CD and ratio of VF and subcutaneous fat (SF) can help in differentiating CD from ITB. Yadav et al. in his study established a cut off value for VF and SF ratio. At a cut off value of 0.63, VF/SF ratio was found to have a sensitivity of 82% and specificity of 81% in differentiating CD from ITB. It showed equally good diagnostic accuracy when applied to the validation cohort. Another study from our centre combined VF/SF ratio with other features on CT scan and showed that combination of VF/SF >0.63 and long segment involvement was almost exclusive for diagnosing CD.

T-regulatory cells (CD4+CD25+FOXP3+) are regulators of inflammation and these are increased in peripheral blood and at the site of infection in patients with pulmonary TB. In a preliminary study, it was shown that FOXP3 mRNA expression was upregulated in the colonic mucosa of patients with ITB as compared to CD. We further showed higher frequency of FOXP3+ T regulatory cells in peripheral blood of patients with ITB compared with CD. A value of more than 32.5% for FOXP3+ cells in peripheral blood could differentiate ITB and CD with 75% sensitivity and 90.6% specificity. This has also been validated in a separate cohort of 73 patients. VF/SF ratio and circulating FOXP3+ cells in peripheral blood are specially helpful where differentiation between CD and ITB is not possible on the basis of routine radiological, histological, and microbiological evidence.

One recent study reported that immune-histochemistry (IHC) for CD-73 in biopsies could differentiate granulomas of CD and ITB with high diagnostic specificity but it has not been replicated in other studies.

He et al. developed a nomogram based on seven parameters that were significant on regression analysis including age, transverse ulcer, rectum involvement,
skipped small bowel involvement, target sign, comb sign, and IGRA (for model 1) or Mantoux test (for model 2), respectively. Nomogram 1 showed a sensitivity of 86.8% and specificity of 90.9% while nomogram 2 showed 84.2% sensitivity and 100% specificity for differentiating CD from ITB in the validation cohort.48

One of the most significant findings was described recently from our centre. It described that patients who received ATT before an eventual diagnosis of CD have higher chance of progressing to stricturing or fistulizing disease compared to patients who are ATT naive (OR: 11.05; 95% CI 3.17–38.56, p < 0.001) and they also have higher risk of surgery than ATT naive patients (HR: 3.22; 95% CI, 1.46–7.12, p = 0.004) on long-term follow-up.49 This finding can challenge our practice of therapeutic ATT trial in cases with diagnostic dilemma. This also highlights the importance of accurate discrimination between these two diseases right at the outset and the importance of close follow-up and early assessment in suspected cases.

**TB on CD: The New Challenge**

As more and more patients of CD are now being treated with anti-TNF therapy in developing countries like India, a new challenge is setting in. Agarwal et al. reported that 11.6% IBD patients on infliximab therapy developed reactivation of tuberculosis despite that all these patients were screened for latent TB before the initiation of therapy and most of them developed it within 1st year of therapy.50 Similar findings have also been reported in other studies.51 A recent meta-analysis compiled 128 studies (130,114 IBD patients) and reported a pooled prevalence of 0.08% for developing TB on anti-TNF therapy. The risk increased with increasing TB burden, pooled prevalence being 0.02%, 0.21%, and 1.59% for low, intermediate, and high TB burden countries, respectively. Seventy-three percent of patients who developed TB had no evidence of latent TB on screening. Apart from therapeutic challenge, this tubercular reactivation poses a new set of diagnostic dilemma, as to decide whether it was ITB to start with or it is only tubercular reactivation on immunosuppression.52

**Conclusion**

Since time long the deceptive similarities between CD and ITB has been a matter of debate among clinical practitioners. With scientific advances and availability of newer radiological tools and biomarkers, we have made significant progress in solving the clinical dilemma. But it needs careful interpretation of all diagnostic evidence and clinical judgment on case to case basis. And with newer challenges like “TB on CD” or ATT complicating disease course of CD patients, we need to be more accurate, more precise, and more vigilant in diagnosing and managing patients with ITB and CD.

**References**

Differentiating Crohn’s Disease from Intestinal Tuberculosis: A Diagnostic Challenge

Acute liver failure (ALF) and acute-on-chronic-liver failure (ACLF) are severest forms of liver failure with high short-term mortality. Their definition and diagnosis depend upon the clinical phenotypic presentation and global consensus on each of these entities are lacking due to differences in regional etiologies of liver injury which is considered to be important determinants of the natural course and clinical manifestations of such liver failures. These differences have been discussed in the present chapter. While hepatitis virus(es) are the major causes of ALF and to some extent in ACLF India, etiologies of ALF in West is heterogenous with Paracetamol overdose as the major causes. Pregnant females in India are more prone to contact hepatitis virus(es), particularly hepatitis E virus and develop more severe hepatitis leading to more frequent ALF than similar patients in males and non-pregnant females. Such events in West is infrequent. Cerebral edema and infections are major complications in ALF leading to high mortality. Prognostic models in ALF are important to identify patients for liver transplant which is associated with significant improved survival in those who are likely to die with expectant therapy. The prognostic models in ALF described from West have been found to perform less efficiently than the recently described ALF-Early Dynamic model (ALF-ED) from India. The differences and controversies in definition of ACLF in Asia Pacific region including India and West (EASL-AASLD) have been discussed in the present chapter. At present Alcohol has emerged as a major cause of ACLF globally. Hepatitis virus(es), drugs, complementary alternative medicines induced acute hepatic insult over pre-existing chronic liver disease are other major causes of ACLF in India while infection, variceal bleed, and alcohol are the major causes of ACLF in West. Occurrence of severe systemic inflammatory response in such patients leading to multiorgan dysfunction results in high short-term mortality. Within 3–7 days of onset of ACLF the prognostic models described both from Asian Pacific region and west predicts mortality assisting in providing to liver transplant to such patients.
Acute precipitating event like acute hepatic insult (drugs, super infection of another hepatitis virus or reactivation of underlying etiology of existing chronic liver disease), or a sequel of cirrhosis like a variceal bleed, infection thus causing, rapid loss of hepatocyte reserve in an already compromised liver.

These later patients die quickly and a 28 days mortality of around 50% (high short-term mortality) have been documented in many reports. This is in contrast to those patients with cirrhosis who gradually decompensate over years in whom the annual mortality depending upon the decompensating event is much lower. Therefore, the former patients are identified as a distinct group with liver failure and named as “Acute-on-Chronic Liver Failure (ACLF),” albeit, there is no universally accepted consensus definition of this entity.

However, various hepatotoxic agents like drugs, hepatitis viruses, and ischemia may cause acute hepatitis in individuals with naïve liver. Patients with acute hepatitis may also have variable degree of liver injury with variable clinical manifestation and natural course such as: conventional acute hepatitis with high spontaneous recovery, severe acute liver injury (sALI), acute liver failure (ALF), or subacute hepatic failure (SHF). The later two forms are associated with high short-term mortality. So the presentations of liver failure in a naïve liver could be acute or subacute. Figure 1 depicts various forms of Liver Failure.

Patients with acute hepatitis having persistent or progressive jaundice for several weeks with coagulopathy (INR >1.5), but without encephalopathy, are recognized as sALI. Appearance of encephalopathy in such a patient with in few hours to days or weeks is termed as ALF (Fig. 2). Whereas, some with acute hepatitis, in whom the jaundice is prolonged or increases for over a month followed by appearance of ascites (as the manifestation...
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Acute Liver Failure and Acute-on-Chronic-Liver Failure in India: How They Are Different from West?

of liver failure), are identified as patients with SHF. These entities of ALF, SHF, and ACLF are associated with high short-term mortality but the former two occur over a naïve liver, whereas the later ensues over a pre-existing chronic liver diseases either known or diagnosed previously or unknown carrying a silent underlying chronic liver disease. Their diagnosis is based on their characteristic phenotypic presentation with absence of any evidence of presence of chronic liver disease in the former two and with direct or indirect evidence of clinical/endoscopic/imaging or histologic evidence of chronic liver disease in the later. The characteristic differences between these three forms of liver failure have been depicted in Table 1.

The present chapter is not intended to include the management of ALF and ACLF or any other form of liver failure and they need a complete chapter by themselves.

**Acute Liver Failure**

**Definition**
Trey and Davidson in 1969 first defined ALF “as appearance of encephalopathy within 8 weeks of the onset of acute hepatitic illness, in an individual without pre-existing liver disease.” However, over the ensuing time, regional difference in etiology, natural course, complication, and some demographic features in ALF were reported, resulting in variable definition of ALF. Each definition included encephalopathy as an essential criteria but some centers additionally included prolonged INR (>1.5) or prothrombin time (PT) prolongation by more than 15 seconds over control or prothrombin activity (<40%) as an additional criteria to define ALF. The essential difference in various definitions of ALF was “the interval between onset of acute hepatitis illness and subsequent encephalopathy and varied from 2 to 26 weeks.” In India, hepatitis virus(es) are the most frequent cause of ALF and encephalopathy occurred in all patients within 4 weeks of onset of jaundice. The American Association for the Study of Liver Diseases (AASLD), however defines ALF if encephalopathy ensues within 26 weeks of onset of acute hepatitis symptoms. Indian National Association for the Study of Liver (INASL) consensus statement on ALF published recently defines ALF “A clinical syndrome characterized by encephalopathy, jaundice, and prolonged PT (INR >1.5) developing in a patient without pre-existing liver disease within 4 weeks of the
### TABLE 1
Clinical differentiation between acute liver failure (ALF), subacute hepatic failure (SHF), and acute on chronic liver failure (ACLF)\(^7\)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>ALF</th>
<th>SHF</th>
<th>ACLF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Previous liver status</strong></td>
<td>Naïve – No h/o of previous liver disease</td>
<td>Naïve-No history of previous liver disease</td>
<td>Presence of underlying liver disease either in history or by evidences accrued at presentation</td>
</tr>
<tr>
<td><strong>Clinical Presentation:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Encephalopathy</td>
<td>Present (Definition)</td>
<td>Absent at presentation</td>
<td>Usually absent at presentation</td>
</tr>
<tr>
<td>• Jaundice</td>
<td>Usually present</td>
<td>Always present</td>
<td>Always present</td>
</tr>
<tr>
<td>• Overt features of Cerebral edema</td>
<td>In 50–80%</td>
<td>Usually absent</td>
<td>Usually absent—occurs as terminal event</td>
</tr>
<tr>
<td>• Ascites</td>
<td>Invariably absent</td>
<td>Always present</td>
<td>Always present</td>
</tr>
<tr>
<td>• Liver size</td>
<td>Small—not palpable—Liver span reduced markedly</td>
<td>Usually not small—Liver span normal or increased</td>
<td>Not small—may be palpable, span is not reduced in most</td>
</tr>
<tr>
<td>• Precipitating factors</td>
<td>Not identified—primary cause of liver damage causes liver failure</td>
<td>Not identified—Primary cause with impaired regeneration cause liver failure</td>
<td>Usually present—Sepsis, variceal bleed, super infection, Superadded DILI, alcoholic binge, flare of underlying cause of chronic liver disease, idiopathic</td>
</tr>
<tr>
<td><strong>Laboratory Parameter</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transaminases</td>
<td>Markedly raised 15–30 times ULN</td>
<td>Moderately raised—5–10 times ULN</td>
<td>Minimally or moderately raised depending upon Precipitating factors—3–5 times ULN</td>
</tr>
<tr>
<td>INR</td>
<td>&gt;1.5</td>
<td>Usually prolonged variably</td>
<td>Prolonged (&gt;1.5 as per APASL definition)</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>Markedly raised</td>
<td>Markedly raised</td>
<td>Moderately raised</td>
</tr>
<tr>
<td>Albumin</td>
<td>Usually normal—may be decreased in Pregnant females</td>
<td>Initially normal—reduces over time</td>
<td>Usually low than normal</td>
</tr>
<tr>
<td>Arterial Ammonia</td>
<td>Markedly raised (100 micromoles/L)</td>
<td>Not raised or moderately raised</td>
<td>Mildly raised—may be raised in flares or super added liver injury (usually less than 100 micromoles)</td>
</tr>
<tr>
<td><strong>Natural Course</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of disease course</td>
<td>Usually 2–7 days</td>
<td>Months—4 week to 6 months</td>
<td>4 weeks to 1 year</td>
</tr>
<tr>
<td>Imaging</td>
<td>Naïve small liver</td>
<td>Regenerating nodules—resulting in humps on liver surface</td>
<td>Evidence of chronic liver disease with or without porto-systemic collaterals</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>No varices (but not usually done)</td>
<td>In 30% small varices may present</td>
<td>More than half usually have varices</td>
</tr>
<tr>
<td>Histology</td>
<td>Features of acute hepatitis with sub massive necrosis of liver</td>
<td>Acute hepatitis with bridging necrosis</td>
<td>Features of Chronic liver disease with or without super added acute liver damage</td>
</tr>
<tr>
<td>Etiology</td>
<td>Mostly hepatitis viruses, ATT drug</td>
<td>Hepatitis viruses, drugs</td>
<td>Alcohol, hepatitis virus, NAFLD, other cause of CLD, Precipitating factors in preexisting CLD</td>
</tr>
</tbody>
</table>

APASL, Asian Pacific Association for the Study of Liver; CLD, chronic liver disease; INR, international normalized ratio; NAFLD, non-alcoholic fatty liver disease; ULN, upper limit of normal
onset of symptoms. A few patients presenting with sALI mostly due to DILI may develop encephalopathy later than 4 weeks up to 8 weeks. Further, because the etiology of ALF is heterogenous in the West, all patients clinically do not have similar natural course and subclassification of ALF depending upon the interval between onset of acute hepatitis illness and encephalopathy has been suggested by British and French. The French subclassification categorizes ALF in to:
- Fulminant Liver failure (encephalopathy occurring within 2 weeks of onset of jaundice) and
- Subfulminant (encephalopathy occurring between 2 and 12 weeks of jaundice).

The British subcategorizes them to three groups:
- Hyperacute liver failure (encephalopathy within 7 days of onset of jaundice)
- ALF (encephalopathy between 7 days and 4 week)
- Subacute hepatic failure (SHF) (encephalopathy within 5–24 weeks of onset of jaundice).

These regions noticed that those presenting with hyperacute or fulminant liver failure had better survival than the other ones and therefore subcategorized them and such events do influence on deciding high risk patients for liver transplantation. However, in India, large series have reported that rapidity of onset of encephalopathy (hyperacute) and the others had similar outcome probably due to homogeneous etiology. Therefore, in India, most patients are either hyperacute or acute without any difference in outcome and practically do not need any subcategorization.

### Etiology

The differences in etiology of ALF among the adults across the world are striking (Tables 2 and 3). In India, viral etiology predominates, which is responsible for

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Etiological profile in ALF across various centers in India</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Center/Year</strong></td>
<td><strong>Number</strong></td>
</tr>
<tr>
<td>Delhi, 1986–2015 (AIIMS)</td>
<td>1462</td>
</tr>
<tr>
<td>Delhi (ILBS), 2011–2016 Pediatric Population</td>
<td>109</td>
</tr>
<tr>
<td>Assam, 2207–15</td>
<td>255</td>
</tr>
<tr>
<td>Bangalore, 1997–2017 Only drug induced ALF</td>
<td>128</td>
</tr>
<tr>
<td>Kashmir, 1989–1996</td>
<td>180</td>
</tr>
<tr>
<td>Kolkata, 2005–2007</td>
<td>45</td>
</tr>
<tr>
<td>Lucknow, 2003–2010</td>
<td>52</td>
</tr>
<tr>
<td>New Delhi (ILBS) 2011–2018</td>
<td>61</td>
</tr>
<tr>
<td>Chandigarh, 1998</td>
<td>204</td>
</tr>
<tr>
<td>Country</td>
<td>Cases</td>
</tr>
<tr>
<td>--------------</td>
<td>-------</td>
</tr>
<tr>
<td>UK (1999–2008)</td>
<td>422</td>
</tr>
<tr>
<td>USA</td>
<td>1696</td>
</tr>
<tr>
<td>France (1986–2006)</td>
<td>363</td>
</tr>
<tr>
<td>Germany (2008–2009)</td>
<td>109</td>
</tr>
<tr>
<td>Australia (1988–2001)</td>
<td>80</td>
</tr>
<tr>
<td>Japan (1998–2006)</td>
<td>856</td>
</tr>
</tbody>
</table>

90% of ALF cases. The various viral etiologies in order of frequencies those reported in published studies include, non-A to non-E in about 40%, HEV in approximately one third, whereas HBV and HAV causing ALF is less frequent. Among other causes of ALF, drugs—especially antituberculosis drugs—account for 6% of the cases of ALF. Whereas in the West, where safe drinking water is available, feco-orally transmitted viruses (HEV and HAV) are not seen; drugs and toxins are major causes of ALF and acetaminophen overdose is the most common factor responsible. Tables 2 and 3 highlight the different etiologies of ALF across the world.

### Complications of ALF

Patients with ALF may develop various life-threatening complications but their magnitude varies regionally.

- **Renal failure:** In the western reports renal failure in ALF was documented in 40–80% of ALF. NSAIDs and acetaminophen are the dominant cause of ALF in the West and these agents are well-known nephrotoxic agents. In contrast, hepatitis virus(es) being the most common cause of ALF in India do not cause direct nephrotoxicity and therefore renal failure have been reported in about 10% of the patients. The other causes associated with increased incidence of renal failure include amanita poisoning and trimethoprim-sulfamethoxazole toxicity.

- **GI bleed:** Gastrointestinal bleed has been reported more frequently as the encephalopathy grade worsens. Intracranial pressure estimation assesses the intracranial hypertension subsequent to cerebral edema. With the wide availability of such
methods, presence of intracranial hypertension due to cerebral edema has been documented in all patients with ALF irrespective of the grades of encephalopathy.9 However, in the West, over the years, improvement in awareness about ALF, early referral to tertiary care center and improved intensive unit care, frequency of cerebral edema in the West is being reported to be less frequent than in former years.9

- **Sepsis**: Infection in ALF is frequent and reported from both West and India.9 ALF is a condition associated with innate immune system compromise occurring rapidly.7 Therefore infection in them occur very early in the course of the disease.9,12 The incidence of infection in the authors’ experience, from a single center in India is around 55%, the most common site of infection is respiratory tract and the commonest organisms are Gram-negative bacilli.9,11 Quarter of the patient in the series reported by the author had also fungal infections.11 From the UK, the report on ALF in early series, identified that about 90% of their patients develop infection, which included bacterial sepsis in 80% and 32% had fungal infection.9 In more recent reports the predominant organisms reported from the West are Gram-negative but the initial reports from the UK the gram positive organisms were isolated more frequently.13

### Key points: Complications
- Renal failure in ALF is frequent in the West, because the bulk of the patients are due to drugs (Acetaminophen is associated with direct nephrotoxicity)
- Renal failure in ALF is infrequent in India because of predominant viral etiology
- Sepsis is frequent in ALF. In the West and the bacterial species are mixed between Gram-positive and Gram-negative whereas Gram-negative organisms are common in India. In about quarter of Indian patients’ fungal infection has also been documented

### Gender, Pregnancy, and Acute Liver Failure
All over the globe, in ALF females predominates except in Japan where the sex distribution is even between the two genders. Despite the fact that the etiology across the region are distinct, the predilection of female sex to develop ALF remains unclear. In India as described earlier, hepatitis virus(es) are the major etiological agent particularly HEV. Various epidemiological as well as sporadic studies reveal that pregnant females are more prone than nonpregnant females and males to contact HEV infection and also develop severe liver diseases than similar male and nonpregnant females patients.7,9 Further, it is believed that pregnant women with ALF than the ALF in nonpregnant women and males are more sick with higher complication rates and mortality. However, the later conjecture was not evidence based and a large study on pregnant ALF due to viral hepatitis from India disproved this conjecture indicating that in India pregnant females with ALF (except in Acute Fatty Liver of Pregnancy or severe pre-eclamptic toxemia induce ALF) do not benefit from the termination of pregnancy.14 A summary of studies reporting pregnancy and ALF is shown in *Table 4*.7,8

The number of pregnant patients developing ALF is relatively small in the West and therefore do not constitute a major problem in management. In India, about 60% of the females with ALF in the child bearing age are pregnant whereas, the fertility rate among similar population in general is 2.9%.9,14 It is believed that pregnancy is an immunocompromised state with predilection to contact various infections and manifest usually in more severe form. Multiple epidemics of HEV infection have been documented in India.7 During such epidemics, pregnant females had more frequent infection (12–20%) than the men and nonpregnant women (2–4%) for unclear reasons.9,15 The frequency of ALF among the pregnant females was also higher (10–22%) than similar men and nonpregnant women (1–2%).9,15 This observation indicate that pregnant females are more prone as well develop more severe liver disease subsequent to HEV infection, which is the major cause of viral hepatitis as well as ALF in India. Therefore, the mortality was significantly higher among pregnant women with epidemic hepatitis (10–39%) than in the general population affected with similar hepatitis (0.06–12%).9,11 In the sporadic setting, HEV is one of the most important etiology of ALF in India accounting for about 30–45% of patients hospitalized with ALF (*Table 2*). However, the mortality in pregnant females has been found to be similar to that of nonpregnant females and males and is independent of the cause or trimester.14 The reason for predilection of pregnant females to contact HEV and severe liver disease remains unclear. To elucidate this, viral and host factors in HEV-ALF were evaluated in one study.15 The study reported more frequent progesterone receptor (PR) gene mutations (PROGINS) associated with reduced expression of PR and progesterone induced blocking factor (PIBF), a
higher IL-12/IL-10 ratio, and a high viral load. The author associated these changes to the poor outcome in HEV-ALF in pregnant females. Pregnancy as a predisposition to ALF in India could be due to: (1) large number of pregnant population (3%); (2) unavailability of clean drinking water; (3) predilection of pregnant females to contact HEV infection. Hepatitis E virus has been identified as a very important cause of severe liver disease in areas of the world where more than 70% of the global population resides. The Global Disease Burden study by World Health Organization identified that, approximately 3.7 million people are infected by HEV annually and 70,000 of them die due to HEV induced severe liver disease of whom a large proportion are pregnant.16

Acute fatty liver of pregnancy (AFLP) on the other hand is more frequent in the West than in India.7 Termination of pregnancy is required for improving prognosis in AFLP. However, termination of pregnancy may not be appropriate in pregnant females with HEV-ALF because:
- ALF-HEV, in comparison to other causes of ALF, has lowest mortality,17
- the mortality in ALF-HEV with pregnancy, ALF-HEV in females without pregnancy and males with ALF-HEV are similar and not higher, indicating that in the pregnancy once ALF develops does not influence the natural course.14

Genotypes 1 and 2 of hepatitis E virus are prevalent in hyperendemic regions where the reservoir for HEV seems to be human, and cause outbreaks, sporadic acute hepatitis, ALF, and ACLF.18 Genotypes 3 and 4 are more prevalent in the USA, Europe, and Japan, where the reservoir seems to be represented by pigs, and the zoonotic transmission is considered to be the cause of infection of human beings, leading to autochthonous acute HEV. Genotypes 3 and 4 have not been reported to be associated with severe liver disease and the majority of cases appear to represent subclinical infection.19

### Key Points: ALF in Pregnancy
- West and Europe: Pregnant females account for 1–3% of cases
- India: 40–60% of females of child-bearing age with ALF are pregnant and HEV is the most frequent cause in them
- Mortality is not increased in pregnant ALF than the others
- Termination of pregnancy not indicated in such patients
- AFLP: Genetic predisposition, termination of pregnancy improves prognosis

### Outcome
The etiology of ALF, which is regionally varied, influences outcome, particularly in the West where the etiology is heterogeneous. Paracetamol is the major cause of ALF in the West. Paracetamol induced ALF presents rapidly (hyperacute) with a spontaneous survival rate of 64% which is significantly higher than similar outcome due to other causes such as ALF due to idiosyncratic drug toxicity (spontaneous survival in 20% cases).9,11 However, paracetamol induced ALF may progress very rapidly in some. The paracetamol being the frequent etiology in the West constitutes the bulk of all ALF patients in these regions and therefore the total number of deaths due to paracetamol toxicity exceeds all other diagnoses. Nearly one third of these patients who develop encephalopathy die. Paracetamol overdose whether suicidal or unintentional presenting with ALF has similar outcomes.20

### Table 4
<table>
<thead>
<tr>
<th>Country</th>
<th>No. of cases (N)</th>
<th>Number of females overall (%)</th>
<th>Pregnancy</th>
<th>Percentage of female patients with pregnancy associated liver failure</th>
<th>Etiology of ALF</th>
<th>Overall mortality (pregnant females)</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>1696</td>
<td>1173 (69%)</td>
<td>16</td>
<td>1.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>422</td>
<td>257 (61%)</td>
<td></td>
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</tr>
<tr>
<td>Germany</td>
<td>109</td>
<td>69 (63%)</td>
<td>3</td>
<td></td>
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<td>33%</td>
</tr>
<tr>
<td>Australia</td>
<td>80</td>
<td>64 (80%)</td>
<td></td>
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</tr>
<tr>
<td>India</td>
<td>1015</td>
<td>590 (58%)</td>
<td>249</td>
<td>38.5%</td>
<td>59.4% (HEV)</td>
<td>54%</td>
</tr>
<tr>
<td>India</td>
<td>180</td>
<td>111 (62%)</td>
<td>49/83</td>
<td>59%</td>
<td>96% (HEV)</td>
<td>66%</td>
</tr>
<tr>
<td>France</td>
<td>363</td>
<td></td>
<td>2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>856</td>
<td>423 (49%)</td>
<td></td>
<td></td>
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</tbody>
</table>
In the India, acetaminophen overdose induced ALF is infrequent. The drug induced ALF are due to antituberculosis therapy (ATT).21 The mortality in ATT-ALF has been reported to be 70%.21 In India, about 90–95% of ALF are due to hepatitis viruses (homogeneous etiology).7,9,11,12 ATT induced ALF constitutes about 6–7% of all ALFs.21 Therefore, etiology could not be identified as an independent predictor of mortality.9,12,21 However, when HEV as a separate group was compared with each individual other etiologies, such as ATT induced ALF and non-A non-E–ALF, etc. the survival frequency among HEV was reported to be significantly superior to other etiologies.18,21 These survival frequencies reported are transplant-free survivals. Liver transplantation is established therapy in all end stage liver disease and with transplantation, overall survival exceeds 75%.7,9

Key points: Outcome
- **West:** Etiology affects the outcome, because etiology is heterogeneous
- **India:** Etiology in general does not influence the outcome, because etiology is almost due to hepatitis virus(es)
- Among hepatitis virus induced ALF, HEV has a better prognosis
- Commonest cause of drug induced ALF in India is antitubercular drugs and have high mortality

Prognostic Models7,9,12

Liver transplantation has been well established as a curative option in ALF.7,11 Prognostic models are therefore necessary to identify patients who will need transplantation or should continue on medical therapy. Many prognostic models from all around the globe have been described.22 Each of the prognostic models in summary have highlighted the following important facts. Age and etiology in most reports are important variables influencing survival. HAV, HEV, acetaminophen toxicity, and acute fatty liver of pregnancy induced ALF, survive more frequently.7,9,12 Patients with drug induced, autoimmune, HBV, and cryptogenic ALF all have spontaneous survival of less than 30%.7,9,18,21,22 Wilson’s disease with ALF survive rarely.7 Among the dynamic variables, the degree of encephalopathy was documented to influence survival—Patients with encephalopathy grade of III or more in comparison to less advanced encephalopathy (I & II) die more frequently.7,9,21,22

Among the prognostic models, King’s College Hospital Criteria (KCC) for liver transplantation were proposed by O’Grady, and have been widely used.22 Although these criteria are specific, they are not very sensitive in predicting cases that will need transplantation. Unfortunately, none of the currently available models have consistently demonstrated reliable accuracy in predicting outcome.23

Multiple prognostic models have been reported from India.7,9,12 A report from North India, the following variables present at admission were identified as independent predictors for poor outcome:
- age 40 years or more;
- bilirubin 15 mg/dL or more;
- PT prolongation 25 seconds or more; and
- clinical features of overt cerebral edema.21 With increasing number of above risk factors, mortality increased; with three or more factors it was 93%.11,12,24

In another study from India, clinical prognostic indicators (CPI) included age 50 years or more, jaundice encephalopathy interval (JEI) more than 7 days, grade 3 or 4 encephalopathy, presence of cerebral edema, PT ≥35 seconds, and creatinine ≥1.5 mg/dL. Presence of any 3 of 6 CPIs was superior to model for end stage liver disease (MELD) or King’s College hospital (KCH) criteria in identifying survivors and nonsurvivors.9

ALF is a dynamic process in which variables determining prognosis at admission change over time, and thus the clinical course varies accordingly. A new prognostic model, ALF early dynamic (ALFED) model was reported which included four variables: arterial ammonia, serum bilirubin, INR, and hepatic encephalopathy more than grade II, which were identified as the independent predictor of outcome at admission.7,24 This model evaluated the dynamicity of these four variables over 3 days and documented that the prediction of outcome using these variables on day 3 was markedly superior to the prediction based on admission parameters. Recently, the INASL recommended the ALFED prognostic model to be more appropriate for the Indian subcontinent because it was derived from the cohort of Indian patients who had predominantly viral etiology unlike in the West where viral etiology as a cause of ALF is infrequent.7

This is one of the first dynamic models to assess and stratify ALF patients dynamically over a period of 3 days rather than considering variables at baseline. ALFED model study identified four prognostically significant variables: arterial ammonia, serum bilirubin, INR, and hepatic encephalopathy more than grade II. This ALFED
model had an AUROC of 0.91 in the derivation cohort and of 0.92 in the validation cohort. The model showed similar increase in mortality with increasing risk scores from 0 to 6 (Table 5). The performance of the ALFED model was found to be superior to the KCH and the MELD score, even when their 3-day serial values were considered. An ALFED score of ≥4 had a high PPV (85%) and NPV (87%) in the validation cohort. Further, in each patient the model could stratify the risk of dying or surviving on day 3 (score 1 through 6) of hospitalization. Those with score of 1–3 had a survival frequency of about 80% or more and those with ≥4 had a mortality risk of more than 80%. These parameters at baseline were also independent predictors of mortality. On day 3 a score of 4 is associated with 90% mortality whereas score 1 is associated with about 5% mortality. With increasing score mortality increases.

Summary
- ALF in India and the West have different etiology and natural course, and therefore the prognostic models are different. In India, the etiology is homogenous in contrast to the West where it is heterogeneous.
- In the West: Drug induced ALF and in the East: Viral etiology is the most common.
- Outcome of viral (HAV, HEV) and Drug (paracetamol) are better than other etiologies, but antitubercular drug-ALF has high mortality.
- In India, pregnant females are more prone for ALF but not so in the West.
- Prognostic models described across the world; dynamic models have been described recently from India and are appropriate for Indian patients.
- Management: conservative, organ support and liver transplantation in select group.

Acute-on-Chronic-Liver Failure

Introduction
In the early sections of the present chapter the concept of liver failure in general and ALF, ACLF, and chronic liver
failure as well as SHF in particular has been highlighted. Table 1 depicts the essential phenotypic difference between ALF, SHF, and ACLF.

Patients with decompensated cirrhosis clinically presents with heterogeneity with variable prognosis. AD in cirrhosis usually denotes appearance of ascites, encephalopathy, variceal bleeding or combination of any later three.\textsuperscript{4,5} Since liver transplantation in such patients is probably is the only curative option, there short-term survival prediction (usually in 2 years) has been used at many centers.\textsuperscript{5} Three states with increasing risk of death have been proposed for decompensated cirrhosis defined by the occurrence of a first variceal bleeding alone (without other decompensating events—mortality 20%), any first non-bleeding decompensating event alone (80% ascites—mortality 24%), or any second decompensating event (mortality—50–78%).\textsuperscript{25} However, recent reports indicate that a more advanced rapid AD state do occur with a very high short-term 28 days mortality of around 20–90% depending upon degree and extent of associated extrahepatic organ failure.\textsuperscript{25} These are patients, who developed systemic inflammatory response through proinflammatory precipitating factors (sepsis, excessive alcohol consumption, sudden reactivation of previous chronic liver disease inducing further acute hepatic necrosis) who are usually jaundiced with prolonged INR and develop various organ failures (OF) probably because of cytokine storm effecting extrahepatic organs resulting from the proinflammatory precipitating events. These are patients with ACLF.

**Definitions and Concept**

The term ACLF was first introduced to identify the above mentioned often observed but not categorized entity in 2002.\textsuperscript{26} The first consensus definition on ACLF was provided by APASL (Asian Pacific Association for the Study of Liver) as “an acute hepatic insult manifesting as jaundice (total bilirubin ≥5 mg/dL) and coagulopathy (INR ≥1.5), complicated within 4 weeks by ascites and/or encephalopathy in a patient with chronic liver disease.”\textsuperscript{22} However, it was slightly modified in 2014 in which chronic liver disease was modified to “with previously diagnosed or undiagnosed chronic liver disease/cirrhosis” and a “high 28 days mortality” was added.\textsuperscript{27} With this APASL criteria, 28 days mortality was reported by the APASL between 25–34%.\textsuperscript{27} However, certain patients with AD having above criteria with OF had markedly higher mortality than those without. Therefore, the EASL-AASLD (European Association for the Study of Liver-American Association for the Study of Liver) defined ACLF as “Acute deterioration of pre-existing, chronic liver disease, usually related to a precipitating event and associated with increased mortality at 28 days due to multisystem organ failure.” Some report suggested and documented that severity of OF assessed by sequential organ failure assessment (SOFA) scores could differentiate patients with various prognosis (58% with OF vs. 8% without OF).\textsuperscript{31}

The first prospective, observational, multicentric European study known as CANONIC study documented the distinction between AD without OF and AD with OF (which according to Western concept was ACLF). Among patients with known cirrhosis admitted with AD (ascites, variceal bleed, encephalopathy, infection; n=1,343), the 28 days and 90 days mortality in those with OF versus those without OF were 34% and 51% versus 5% and 14%, respectively. Thus, this study provided the documentation that patients with AD who were hospitalized with or developed OF after hospitalization were distinct and were named as—ACLF and justified their definition (EASL-CLIF—European Association for the Study of Liver-Chronic Liver Failure definition).\textsuperscript{28} North American Consortium for the Study of End-Stage Liver Disease (NACSELD) defined ACLF by the presence of at least two very severe extrahepatic OFs (shock, grade III/IV HE, renal replacement therapy, or mechanical ventilation), which are much more stringent criteria than those of the EASL-CLIF consortium or the APASL. The NACSELD-defined ACLF is associated with a 30-day mortality rate of 41% compared to 7% for patients without ACLF. Accordingly, by definition, the main difference between traditional AD and ACLF is the short- and medium-term prognosis. To unify the definition on ACLF the WGO (World Gastroenterology Association) suggested that “ACLF is a syndrome in patients with chronic liver disease with or without previously diagnosed cirrhosis, which is characterized by acute hepatic decompensation resulting in liver failure (jaundice and prolongation of the INR) and one or more extrahepatic organ failures that is associated with increased mortality within a period of 28 days and up to 3 months from onset” (Fig. 3).\textsuperscript{4}

**Components of ACLF**

All the above definitions and concept irrespective in their disagreement and region of origin elucidated that there should be five components in ACLF:
There should be pre-existing chronic liver disease (APASL excluded known decompensated liver disease and emphasized that only non-cirrhotics or compensated cirrhosis of any etiology should be included as underlying silent liver disease, which may have been diagnosed or undiagnosed previously; however, the EASL-CANONIC study as described earlier did not exclude patients with chronic liver disease with previous history of decompensation and WGO in an effort to unify these categorized underlying Chronic liver Disease to A-CLD without cirrhosis, B-compensated Cirrhosis and C-Cirrhosis with previous history of decompensation—Fig. 3).

There should be a precipitating factor causing acute hepatic insult with systemic inflammatory response which were different regionally (described below) which should result in overt acute deterioration of hepatic function as well as reserve, resulting in features overt liver failure (CANONIC study defined them as AD and included both hepatic and extrahepatic insult but APASL excluded extrahepatic insults like variceal bleed and sepsis and emphasized on only acute hepatic insult to be further qualified by presence of conjugated hyperbilirubinemia of more than 5 mg/dL with INR more than 1.5 accompanied with development AD in the form of ascites and/or encephalopathy; there by quantifying the severity of the hepatic insult resulting in AD).

The above-mentioned acute deteriorations should occur within a short period of time (APASL defined it to be within 4 weeks).

The presence or development of hepatic failure should be associated with extrahepatic organ failure like encephalopathy, respiratory failure, renal failure, coagulation abnormality, circulatory compromise in form of hemodynamic instability as per the EASL-AASLD and NASCLED definition but APASL did not include it and suggested that only with liver failure the mortality exceeded 30% and should be enough to define ACLF and extrahepatic organ failures are the sequels of ACLF. However, the INASL consortium experiences documented that indeed occurrence of the extrahepatic organ failure imparts high short-term mortality.29-31

As has been elucidated earlier, these patients with CLD are distinct from AD and should be categorized as another form of liver failure and to be termed as ACLF. By now both APASL and Western group agree that they have high 28 days mortality (various reports from different region describe it to a tune of around 50%).1,5 The mortality, however, linearly increases with increases in number of extrahepatic OF (20% with one OF to 90% with >4 extrahepatic OF) (Table 7).29-31

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**Fig. 3: World Gastroenterology Definition of ACLF**

AD, acute decompensation; ACLF, acute on chronic liver failure; CLD-A, chronic liver disease (non-cirrhotics); CLD-B (cirrhosis compensated); CLD-C (cirrhosis with previous history of decompensation).
Acute Liver Failure and Acute-on-Chronic-Liver Failure in India: How They Are Different from West?

### TABLE 7

<table>
<thead>
<tr>
<th>Parameter for organs</th>
<th>Panel A</th>
<th>Panel B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Score 1</td>
<td>Score 2</td>
</tr>
<tr>
<td>Liver—Serum Bilirubin (mg/dL)</td>
<td>&lt; 6</td>
<td>6-11.9</td>
</tr>
<tr>
<td>Kidney—Serum Creatinine (mg/dL)</td>
<td>&lt;2</td>
<td>2-3.4</td>
</tr>
<tr>
<td>Brain—Encephalopathy (West-Haven Criteria)</td>
<td>Grade 0</td>
<td>Grade 1-2</td>
</tr>
<tr>
<td>Coagulation (INR)</td>
<td>&lt;2</td>
<td>2-2.4</td>
</tr>
<tr>
<td>Circulation (MAP in mm Hg)</td>
<td>≥70</td>
<td>&lt;70</td>
</tr>
<tr>
<td>Respiration</td>
<td>PaO(_2)/FiO(_2)</td>
<td>&gt;300</td>
</tr>
<tr>
<td></td>
<td>SPO(_2)/FiO(_2)</td>
<td>&gt;357</td>
</tr>
</tbody>
</table>

**Score 1:** Absence of OD or OF. **Score 2:** Organ Dysfunction (OD). **Score 3:** Organ Failure (OF)

INR: International Normalized Ratio; MAP: mean arterial pressure

### TABLE 8

<table>
<thead>
<tr>
<th>Precipitating factors causing ACLF(^{27-32})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute hepatic Insult</td>
</tr>
<tr>
<td><strong>Environmental</strong></td>
</tr>
<tr>
<td>HBV Reactivation</td>
</tr>
<tr>
<td>HAV super infection</td>
</tr>
<tr>
<td>HEV Super infection</td>
</tr>
<tr>
<td>Hepatotoxic drug injury</td>
</tr>
<tr>
<td>Autoimmune hepatitis flare</td>
</tr>
</tbody>
</table>
| Precipitating Factors Causing ACLF

Varieties of acute insults causing rapid deterioration in liver functions (clinical, biochemical, coagulation parameters) needing hospitalization have been documented and they vary regionally. In brief they can be categorized as follows in **Table 8**.\(^{4,5,26,28-32}\)

Acute hepatic insult as mentioned in the above table are more often documented as the cause of ACLF in Asian Countries whereas they are less frequent in Europe and America. The hepatitis virus(es) are endemic in Asia as well as antitubercular therapy.\(^{30,31}\) In the West the common causes were variceal bleed, infection, and idiopathic.\(^{31}\) However, in recent time Asian region as well as in India the major cause of ACLF has been reported because of continuous excess alcohol consumption, which causes chronic liver disease as well as acute insult on the liver resulting in rapid AD (severe alcoholic hepatitis) and ACLF.\(^{29,30}\)

### Categorization/Types of ACLF and Prediction/Prognostic Models in ACLF

Depending upon the pre-existing hepatic reserve due to underlying CLD and further loss of hepatic functional capacity due to acute hepatic insult and its regenerative capacity, severity of the systemic inflammatory response due to the cytokine storm and their effect on extrahepatic...
organs, the course in ACLF is dynamic and usually unfolds over subsequent few days usually between 3–7 days.\(^{33,34}\)

**Types/Categorization of ACLF**

The canonic study first tried to identify and qualify the extrahepatic organ failure by quantifying the change in the sequential organ failure assessment (SOFA).\(^{26,31}\) The study included six organs to be evaluated for SOFA score (Liver, Kidney, Brain, Coagulation, Circulation, and Respiration) and graded their dysfunction based on values of serum bilirubin, creatinine, INR, mean arterial pressure (MAP), and ratio between \(\text{PaO}_2/\text{FiO}_2\) or \(\text{SpO}_2/\text{FiO}_2\), respectively and allocated 1–3 point scores to these values. Patients with score 2 for each parameter were considered as organ dysfunction (OD) like liver dysfunction (LD), kidney dysfunction (KD), brain dysfunction (BD), circulatory dysfunction (CD), coagulation dysfunction or respiratory dysfunction (RD) and patients with score 3 were defined as individual organ failure. This score was named as EASL, CLIF, SOFA score and depending on these scores as mentioned above. No OD and OF were defined for each of the six organs and then the ACLF in patients with AD were graded as No ACLF, ACLF grade 1–3 depending upon presence or subsequent development of number of OD/OF. With increasing grade, the 28 days mortality increased (Table 7). Since OF were not included in APASL definition, the ACLF was not categorized or typed in APASL cohorts collated subsequently. However, in APASL cohort and many other reports on ACLF which included large cohorts of patients with ACLF reported that occurrence of OF was major determinant of outcome and prognosis.\(^{32}\) Further the admission grading or status of organs were dynamic and the outcome prediction based on the OF on day 3–7 were more accurate predictors of outcome. Both EASL-CLIF (CLIF-C-ACLF) score and APASL groups have defined their dynamic prognostic scores, which simply reflect the dynamic changes of variable organ parameters.\(^{3,33}\)

**Pathogenesis (Flowchart 1)\(^{26,31}\)**

Pathogenesis in ACLF is unclear. However, the severe cytokine storm in ACLF has been documented to be more pronounced (documented by enhanced C-reactive protein response, neutrophilic leukocytosis, tumor necrosis \(\alpha, \text{IL}18\)) than in patient with AD as well as in patients with compensated cirrhosis without AD.\(^{31}\) The ammonia levels also have been recently identified to be markedly increased in such patients than in the other groups.\(^{32}\) The Cause of Cytokine Storm has been briefly explained in the Flowchart 1. The DAMP (damage associated molecular pathogen) due to liver cell damage in diseases causing

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**Flowchart 1: Pathogenesis in ACLF**

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BD, brain dysfunction; BF, brain failure; DAMP, damage associated molecular pattern; KD, kidney dysfunction; KF, kidney failure; NLRs, nod like receptors; NO, nitric oxide; PAMP, pathogen associated molecular pattern; RLRs, rig like receptors; TLR, toll like receptors
super added injury to liver or sepsis or bleeding causing ischemia to liver are recognized by the innate immune systems presence in liver cells such as TLRs and other Innate immune PRR (pathogen recognizing receptors) sensors and produce various cytokines which cause neutrophilic recruitment and also attracts the immune cells of adaptive immune system resulting in release of various proinflammatory cytokines which may spill over to systemic circulation effecting various extrahepatic organs. Perpetuating the events by the transmigration of gut microbes due to a leaky gut documented in such patients further enhance such response and also induces endothelial nitric oxide by upregulating the nitric oxide synthase enzyme. These events result in various organ dysfunction or OF depending upon the severity of the cytokine storm and the degree of liver injury resulting in ACLF.

Management
The management principles comprise of:
- Treating the precipitating factors
- Support to the failing organ
- Continuous assessment and by day 3–7 decision for liver transplant.

The Model for End Stage Liver Disease (MELD) score and addition of sodium value (MELD-Na) score in addition to the scores of failing organs have been the principles to prognosticate and transplant such patients to improve survival. The Table 9 briefly provides the components of management in ACLF.

Conclusion
ACLF is a syndromic condition that occurs in patients with underlying chronic liver disease (CLD) irrespective of the cause of CLD. These patients develop intense systemic inflammation, organ failure, and high short-term mortality and ensue in close temporal relationship with a precipitating event, which is regionally variable. Whether extrahepatic organ failure is an integral part of the syndrome or consequence is the difference in defining the syndrome in the West and Asia. Bacterial infection is frequent in these patients and in the West it is considered as a precipitating event, but in Asia it is considered as a frequent association in ACLF. However, irrespective the differences between the West and Asia the syndrome is seen across the world and about half of them need liver transplant.

References
10. Tandon BN, Bernauau J, O’Grady J, et al. Recommendations of the international association for the study of the liver subcommittee on
Abstract
Proton Pump Inhibitors (PPIs) have been an important part of the physicians’ arsenal in the fight against acid peptic disorders. PPIs are among the drugs which are most frequently prescribed both to outpatients and those admitted in the hospital including critically ill patients. The approved indications for PPI therapy include erosive esophagitis, peptic ulcer, NSAID-induced ulcer, Gastroesophageal Reflux Disease, Helicobacter pylori infection and management of pathologic hypersecretory conditions like Zollinger-Ellison syndrome. However, long-term use of PPIs has also been associated with multiple side effects including small intestinal bacterial overgrowth, pneumonia, increased bone fractures, Vit B12 deficiency among others. A sensible strategy for PPI prescription should be as per indications, avoiding broad off-label use and following deprescription strategies.

Introduction
The pharmacologic use of Proton Pump Inhibitors (PPIs) started in the late 1980s and since then they have been an important part of the armamentarium of physicians and gastroenterologists for treating acid peptic disorders. PPIs are substituted benzimidazoles, which are similar to the H2 receptor antagonists (H2RAs) in structure but have a different mechanism of action. PPIs are given as prodrugs. Oral formulations are prepared as acid resistant delayed release enteric coated capsules or tablets so that they do not undergo destruction due to the acid in the stomach. PPIs easily diffuse across lipid membranes into acidified compartments like parietal cell canaliculus where the protonation of the prodrug takes place and gets converted to its active form, a thiophilic sulfenamide cation.1 This cation irreversibly inactivates the H/K-ATPase (Figure 1) by forming a covalent disulfide bond with it.1,2

PPIs should be taken empty stomach because food decreases the bioavailability of all agents by around 50%. They are taken around 1 hour before a meal, so that the maximal activity of proton pump secretion is at the same time as the peak serum concentration of the PPI. They have a short half-life of approximately one and a half hour, but since they irreversibly inhibit the proton pump the secretion of acid remains inhibited up to 24 hours. In optimal doses PPIs inhibit around 90–98% of 24-hour acid secretion. When intravenous preparations are used, only the actively secreting pumps are inactivated. Therefore, during the first 24–48 hours of treatment, the intravenous formulations must be given as infusion or as repeated bolus injections.1

PPIs are the cornerstone of treatment regimens of a number of acid peptic disorders and other related conditions. The various definitions of long-term use of PPI that have been used in different studies vary from one repeated prescription over 12 months to continuous therapy for periods ranging from 4 to >12 months.3 Prolonged use of PPI, however, is a two-edged sword and has been related with an excess of systemic adverse effects,
which lead to the subject that whether long-term use of PPI is a boon or a bane?

**Long-term PPI Use: Is It a Boon?**

PPIs have statistically proven benefit over placebo/H2RAs in management of diseases associated with increased acid production. The indications for PPI therapy, which are approved by FDA include Gastroesophageal Reflux Disease (GERD), erosive esophagitis, peptic ulcer, NSAID-induced ulcer (treatment and prophylaxis), *Helicobacter pylori* infection (along with antibiotics) and management of pathologic hypersecretory conditions (including Zollinger-Ellison syndrome). 4

However apart from the above-mentioned indications, the existing evidence suggests overuse of PPIs with almost 25–70% of prescriptions lacking appropriate indication. 5 In fact, the “off-label” use of PPIs is among the highest (55% prevalence) in intensive care units. 6

In patients of GERD, who present with reflux symptoms after meals, long-term inhibition of acid secretion is achieved by use of PPIs. 5-10 Since the effect of acid suppression remains for almost 24 hours, a single dose of PPI empty stomach in the morning is effective. There is evidence that PPIs can be used in prevention of recurrent reflux symptoms as well as esophageal erosions/ulcers. 7-9 The regular use of PPIs as maintenance therapy of GERD decreases the recurrence rates to less than 15% for 1 year compared to recurrence rates of more than 50% for patients without any maintenance therapy. 11,12 Long-term administration of PPIs may also prevent transformation of Barrett’s esophagus to a neoplastic lesion. 13 Common indications of long-term PPI use along with the studies establishing their role have been summarized in Table 1.

The other common indication of long-term PPI use is for prevention of NSAID-induced gastroduodenal ulcers recurrence by decreasing it to approximately one-tenth on comparison with patients treated with placebo. 10 Thus, they are the drug of choice for the prevention of aspirin/NSAID induced ulcers.

**Long-term Use of PPI: Is It a Bane?**

Increased usage of PPI for past many years now has led to the conundrum of their long-term effects. Prolonged PPI use has been implicated in adverse effect of several body functions and has been associated with increased incidence of various diseases. Common adverse effects of long-term PPI usage along with the studies establishing their role have been summarized in Table 2.
These side effects can be separated either as per the mechanism or as per the involved site.

**As Per the Mechanism**

Adverse effects of PPIs occur either due to the fact that they cause acid inhibition or else they are unrelated to their property of acid inhibition. These adverse effects have been shown in Table 3.

**As Per the Site Involved**

**Gastrointestinal System**

Increased risk of gastrointestinal infection—Use of PPIs has an association with increased risk of *Clostridium difficile* (*C. difficile*) infection. Possible mechanism is that long-term PPI use alters the colonic microbiome and hampers the normal barriers against *C. difficile*, which proliferates using the available amino acids.

Gastric neuroendocrine tumor—Prolonged PPI use leads to increased intra-gastric pH thereby causing increased plasma gastrin concentration, thus stimulating enterochromaffin like (ECL) cells proliferation. There are only isolated case reports of PPI administration-related gastric neuroendocrine tumors in humans and presently to ascertain a pathogenic role, the data is scarce. Therefore, at present there is insignificant clinical relevance of the risk of carcinoid tumor after long-term PPI use. Although periodic endoscopic screening may be considered during the period of use.

Gut microbiome changes and Small Intestinal Bacterial Overgrowth (SIBO)—The resultant decrease in the acid secretion and the bactericidal effect of the gastric juice due to PPIs leads to an increase in the microbial density of the gut especially with *Streptococcus* which colonize the oral cavity. Lo et al. in a meta-analysis done in 2013 found that as compared to non-users, there was 7.5 times increased risk of SIBO in PPI users. Therefore, prolonged PPI administration is considered a risk factor for SIBO (Defined as presence of 100,000 bacterial colonies/mL in small intestinal contents). However, the clinical importance of this altered microbiome in patients treated with PPIs is elusive at present.

Spontaneous bacterial peritonitis (SBP)—PPI administration is useful in few cases of cirrhosis as they reduce the risk of variceal rupture and ulcer occurrence. Long-term PPI use leads to hypochlorhydria promoting bacterial translocation, colonic transmigration and may lead to Gram-negative organisms related SBP in cirrhotics. Although, the available evidence at present does not recommend withholding PPIs whenever indicated in patients with liver disease; the evidence does suggest that PPI use is associated with augmented risk of SBP in cirrhotics.

Gastric cancer—In patients with *H. pylori* infection, long-term PPI usage increases mucosal inflammation, hastens mucosal atrophy, which might be a potential risk factor for gastric malignancy. However, more data is required to establish causality between long-term PPI use and gastric malignancy in *H. pylori* patients.

Gall bladder dysfunction—Cahan et al. in 2006 found that PPI therapy reduces gallbladder motility in healthy volunteers. Chronic PPI therapy may pose a risk for long-term gallbladder dysfunction and biliary complications.

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**TABLE 2** Adverse effects of long-term use of PPIs

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Study</th>
<th>Inference</th>
</tr>
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<tbody>
<tr>
<td>SIBO</td>
<td>Lo WK et al., 2013</td>
<td>Increased risk</td>
</tr>
<tr>
<td>Gall bladder dysfunction</td>
<td>Cahan et al., 2006</td>
<td>Increased risk</td>
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<tr>
<td>Pneumonia</td>
<td>Wongtrakul et al., 2020</td>
<td>Increased risk</td>
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<tr>
<td>Acute interstitial nephritis</td>
<td>Xie et al., 2016</td>
<td>Increased risk</td>
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<td>Chronic kidney disease</td>
<td>Wijampreecha et al., 2017</td>
<td>Increased risk</td>
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<tr>
<td>Hypomagnesemia</td>
<td>Park CH et al., 2014</td>
<td>Decreased magnesiu levels</td>
</tr>
<tr>
<td>Dementia</td>
<td>M A Khan et al., 2020</td>
<td>No definite risk</td>
</tr>
<tr>
<td>Bone fracture</td>
<td>Nassar et al., 2018</td>
<td>Increased risk of bone fracture</td>
</tr>
</tbody>
</table>

**TABLE 3** Adverse effects of PPI based on their property of acid inhibition or unrelated to it

<table>
<thead>
<tr>
<th>Due to acid inhibition</th>
<th>Pneumonia, GI infection, Carcinoid tumor, GI mucosal hypertrophy, Fractures, SIBO, Vit B12 deficiency, Gastric cancer, SBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrelated to acid inhibition</td>
<td>Collagenous colitis, Acute interstitial nephritis, Dementia</td>
</tr>
</tbody>
</table>

---
Atrophic gastritis—PPIs can alter the gastric mucosal architecture and Li et al. found in a meta-analysis in 2017 that there was a higher presence of gastric atrophy in PPI group compared to the control group.27

Respiratory
Pneumonia—PPIs increase gastric pH by suppressing gastric acid release, promoting bacterial overgrowth which in turn leads to colonization of trachea and pneumonia. There is evidence to suggest that immune cell function may also be impaired by PPIs, thereby augmenting the risk of infectious complications.28 Wongtrakul et al. in their recent meta-analysis concluded a significantly higher risk of development of pneumonia in cirrhotic patients with a history of PPI use than those without. Thus, prudent use of PPIs in patients with definite indication may be suggested.29

Renal
Acute interstitial nephritis—In patients on PPI treatment, an allergic reaction to the drug may cause interstitial nephritis.30 As many as 70% of acute interstitial nephritis was reportedly related to drugs, of which 14% were caused by PPIs in biopsy-proven cases.31

Chronic kidney disease—The mechanism by which PPI use can lead to CKD is not well understood. One of the mechanisms proposed is the acute interstitial nephritis caused by PPI. Other postulated mechanisms include lysosomal acidification hydrogen/potassium adenosine triphosphatase enzyme system abnormalities, reduced renal tubular cells regeneration, altered gene expression, and elevated oxidative stress.32 Although, there is a need of more data to ascertain this association, it is suggested that the indication of initiation as well as continuation of PPIs should be carefully assessed in patients with pre-existing risk factors for CKD development.

Nutrient Absorption
Hypomagnesemia—One of the postulated mechanism for hypomagnesemia related to PPI use is a reduction in the affinity of magnesium to its transport receptors caused by the pH change thereby decreasing the active transport of magnesium across the intestinal lumen. Park et al., in their meta-analysis, showed an increased incidence of hypomagnesemia in PPI users.33

Vitamin B12—The acidic environment of the stomach assists in the release of Vit. B12 bound with food and subsequently helps its binding to intrinsic factor. Lam et al. in 2013 found a 65% increased risk of B12 deficiency in PPI users more than 2 years.34

Neurological
Dementia—Long-term PPI use inhibits beta and gamma secretase, which may lead to an increase in the amyloid beta peptide levels in the brain. Khan et al. in their systematic review found lack of evidence pertaining to the proposed suggestion of PPI use and an increased risk of dementia.35 They recommended that PPI use should not be curtailed because of concerns about dementia risk.

Drug Interactions
Anti-platelets—There is competitive inhibition of CYP2C19 to variable grades by PPIs, thus affecting the metabolism of clopidogrel. Omeprazole is the most noteworthy inhibitor of CYP2C19. The two meta-analyses done in this regard found an increased rate of adverse cardiovascular events in patients on simultaneous PPI-clopidogrel therapy.36 While the pharmacological interaction between these two drugs is established beyond doubt, more data is required to ascertain the clinical significance of this interaction.

Endocrine
Alteration in bone density—The bone health and increased fracture susceptibility due to PPIs may be linked to impaired calcium absorption (acid suppression leads to decreased release of ionized calcium from insoluble calcium salts) and hypergastrinemia. In a meta-analysis conducted by Nassar et al. published in JBM in 2018 it was found that long-term PPI use might increase the fracture risk but has no significant alteration of bone mineral density (BMD).37 Presently there is insufficient evidence to recommend regular BMD monitoring of patients on PPIs.

Hematological
PPIs have their anti-inflammatory properties as they can bind to neutrophils and can inhibit neutrophil accumulation and release of ROS. However, long-term use can also lead to neutropenia and thrombocytopenia.38 In general, the recognized theories are the immune-
mediated and the toxic mechanism. Drug-induced antibodies against circulating hemocytes form the basis of immune mediated mechanism whereas the toxic mechanism is due to direct toxicity of the drug to hematopoietic cells.

**All-cause Mortality**
Xie et al., in their cohort study, demonstrated an increased risk of all-cause mortality in association with PPI use.\(^3^9\) The speculated mechanism for this association was the probable role of oxidative stress, heme oxygenase-1 and accelerated senescence of human endothelial cells.

**The Road Ahead**
Presently, PPIs are among the most frequently prescribed class of drugs and are often continued for duration way beyond the indication. In view of this and with many recent studies suggestive of systemic adverse effects of long-term PPI use, a lot of research is going on to formulate a well-structured model to deprescribe PPIs.

**Deprescribing PPIs**
Patients on PPIs should be monitored for symptom recurrence and symptoms should gradually be managed with on-demand PPIs, stepping down to H2RA therapy, other over-the-counter agents (e.g., calcium carbonate) or nonpharmacologic approaches (weight loss, avoid meals 2–3 hours before bed time, head end elevation, avoid dietary triggers). Stepping down to H2RA involves discontinuation or tapering of the PPI followed by prescription of an H2RA. Any H2RA at any approved dose and dosing interval can be used.\(^4^0\) Implementation of deprescription guidelines (Flowchart 1) will encourage clinicians to carefully evaluate the ongoing use of medications and potentially reduce the negative effects of polypharmacy.
Conclusion

PPIs have a robust helpful impact when used correctly for the standard indications. However, PPIs have also been incriminated with multiple systemic side effects. Although the evidence is limited for causality at present and this is an area of active research, there is enough evidence to indicate a tendency to develop adverse effects with long-term use of PPIs. Optimal strategy at this time for PPI prescription is to advise it to patients with clear indications, following of clear deprescription strategies and avoidance of broad off-label usage.

References

Abstract

Eosinophilic oesophagitis (EOE) is a locally immune mediated chronic oesophageal disease occurring as a consequence of allergen exposure. It is a male predominant widely prevalent but less well recognized disease with genetic preponderance and often associated with atopy. EoE has a progressive course from mucosal disease to subepithelial disease over decades resulting in fibro stenotic oesophageal disease. The diagnosis is based on the constellation of symptoms, endoscopic and histological findings with >15 eosinophils/HPF confirming the diagnosis. The new genetic, molecular, cellular, animal, and translational studies show the cascade of coordinated type 2 inflammatory response. The newer classification based on histologic, endoscopic, and molecular features defines three endotypes each with distinct genetic, clinical, endoscopic, and histological features. Treatment principles include elimination of possible food allergen, mast cell stabilizer, proton pump inhibitor which has a cause and effect relationship, steroids, and biologicals. Earlier diagnosis with newer tools and biopsy help to diagnose EoE early in disease thus preventing progression to fibro stenotic disease thereby reducing morbidity. (Eosinophilic oesophagitis; Food allergens; esophageal eosinophilia; proton pump inhibitors; Allergy)

Introduction

Eosinophilic esophagitis (EoE) is a part of spectrum of eosinophilic disorders of the gastrointestinal tract histologically characterized by eosinophilic infiltration and inflammation consequent to exposure to an allergen, often food, resulting in esophageal dysfunction and progressive serious complications, though a definite cause eludes. This diagnosis from esophageal eosinophilia (1968) has progressed from initial association with reflux disorders to EoE in 1993. A male predominant disease, is associated with various allergic disorders including atopy and seen to increase progressively over these two decades. Etiopathobiology includes genetic and IgG 4 association and as a cause with familial susceptibility. Care of these patients involves primary care providers to multi-specialty departments.

Definition

EoE is defined as locally immune mediated chronic esophageal disease with clinical symptoms of esophageal dysfunction and histological eosinophil predominant inflammation with a progressive natural course. It is IgG 4 mediated disease associated with atopy (20–80%), urticaria and anaphylaxis; positive family history (50%), asthma (30–50%) and allergic rhinitis (50–75%) in children.

Natural History

- Epidemiology: It is a disease with global presence including America, Europe, Australia, and Asia, male predominant [3:1], ethnically variable (more common in Caucasians) with overall pooled prevalence of 22.7/100,000, 0.5–1 per thousand, 2–7% of gastroscopy,
12–23% of gastroscopy for dysphagia, and is seen to be increasing over time.7

- **Course:** EoE is a chronic and progressive disease. Earlier symptoms in children are due to inflammation and later in life to subepithelial collagen deposition resulting in fibro stenotic EoE. Presence of strictures was observed in 17% and 71% with less than 2 years and 20 years of symptoms thus emphasizing the need for early diagnosis.

- **Temporal trends:** From 9 to 12.8/100,000 over 3 years in Ohio, USA, 0.35 to 9.5/100,000 in Minnesota, USA, over 15 years, 1.2 to 7.4/100,000 in Switzerland over 20 years indicating that there is an increasing incidence. The reasons for increase will be discussed in etiopathobiology in addition to awareness and increasing mucosal biopsies.

**Etiopathobiology (Fig. 1)**

- **Allergen and Hygiene Hypothesis:** The strength of evidence stems from increased prevalence and incidence in developed countries which have better hygiene and association with most of the allergic disorders in a significant proportion. Aero-allergen exposure gains support by the increased incidence in summer or fall. Increased prevalence is noted in arid region, cold weather lacking vegetation, rural low density populated regions. This requires further research. Food elimination results in improvement of EOE, and hence is considered a risk. Various reasons mentioned stay unproven. Allergen/infection in an unprimed host living in virtual hygienic environment initiate Th2 response over Th1 which is mild and protective.

- **Helicobacter pylori (H. pylori)/Proton Pump Inhibitor (PPI) Hypothesis—Harmful or protective:** Presence of *H. pylori* polarizes the immune system toward a Th1 response and the lack of it leads to Th2 response. EoE has a strong inverse relationship with *H. pylori* and atopic disorders.9
  - PPI is hypothesized to increase upper gastrointestinal tract (GIT) permeability facilitating new route of antigen entry;
  - use of PPI is associated with food specific IgE antibodies.
  - PPI has shown anti-inflammatory/anti-eosinophilic effects.

  Use of PPI has resulted in histological resolution of inflammation and eosinophils in 30–40% making use of PPI as a candidate trial drug. PPI thus can cause EoE indirectly by removing the protective barrier and eliminating *H. pylori*; paradoxically PPI heals EoE by its anti-inflammatory and anti-eosinophilic activity; conclusive evidence is required to say if PPI is causative or curative.10–17

- **Early Life Exposure Hypothesis/Environmental Factor:** EoE is associated with use of antibiotics in children delivered by caesarean, less than 1 year of age, premature babies, non-exclusively breast fed babies. Establishment of esophageal microbiome would help in understanding microbial dysbiosis as the cause.
**Familial/Genetic Susceptibility:** EoE is associated with connective tissue and auto-immune disorders.\(^{24,25}\) EoE has racial and gender bias, predominance in white ancestry, inherited in non-Mendelian manner, a sibling risk ratio of 80%; parents had history of esophageal stricture and eosinophilic infiltrate in 10% and 8% respectively.

The new genetic, molecular, cellular, animal, and translational studies help to postulate a detailed pathway. This shows how, exposure to allergens results in a complex and coordinated type 2 inflammatory cascade. Delayed intervention can result in odynophagia, esophageal strictures, and food impaction.\(^{26}\)

The genetics, epigenetics, and transcriptional analysis, the role of cytokines, chemokines, and other molecules, pathological and protective cells including commensal bacteria are vividly described.\(^{26-28}\)

**Diagnosis**

The diagnosis of EoE is made on the constellation of clinical manifestations, endoscopic and histological findings.

- **Clinical:** There is a distinct phenotypic variability in symptomatology amongst people in early and advanced disease. Esophageal dysfunction symptoms include esophageal dysphagia in 60–100%, food impaction in 25%, heart burn in 30–60%, atypical chest pain in 8–44% and 1–8% of those with refractory reflux symptoms.\(^{29}\) Dysphagia, refractory heart burn, and mucosal disruption on intubation are the predominant symptom/sign in advanced disease. Vomiting, food rejection and growth retardation are also observed.\(^{30}\)

- **Endoscopic:** Endoscopic Reference Scoring (EREFS)\(^{31,32}\) classification as given by Hirano et al. has scoring for visually observed endoscopy findings like edema, rings, exudates, furrows, and strictures graded separately at upper, middle, and lower third of esophagus. The inflammatory signs edema, exudates, and furrows had a sensitivity of 89%, 96%, 89%, and specificity of 88%, 76%, and 90%, respectively and correlated with eosinophilia. Composite inflammatory score, the sum of maximum of inflammatory variables namely edema, rings, and exudate excluding furrows and stricture showed a superior correlation amongst the diagnostic and post-treatment cohorts.\(^{31,32}\) Schatzki’s ring is one of the endoscopic manifestations of EoE.

- **Histologic:** Biopsy is mandatory in patients clinically suspected to have EoE even if the esophageal mucosa looks normal. Endosonography guided deeper biopsies would provide more information. A meta-analysis of EoE endoscopic findings in isolation have poor sensitivity, specificity, and predictive value\(^{33}\) and the sensitivity increases to 100% when 6–9 esophageal mucosal biopsies are taken.\(^{34,35}\) Presence of \(\geq 15\) eosinophils/hpf confirms the diagnosis of EoE.

**Newer principles**\(^{36}\) (Fig. 2):

- Removal of age cut-off
- Removing PPI from list of diagnostic criteria
- Evaluate for condition causing esophageal eosinophilia rather than excluding them
- Criteria should be clinically operational
- Should be utilizable in patients in whom diagnosis was made using earlier criteria, applicable clinically widely and for future research

**Newer tools:**

- Tetsuo Shoda et al.\(^{37}\) using EoE diagnostic panel (EDP) and Consortium of Eosinophilic Disease Researchers (CEGIR), Endoscopic Reference Scoring (EREFS) and histologic scoring system (HSS) analyzed the

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Endoscopic reference scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
<td><strong>Grade 0</strong></td>
</tr>
<tr>
<td>Edema</td>
<td>Distinct Vascularity</td>
</tr>
<tr>
<td>Rings</td>
<td>None</td>
</tr>
<tr>
<td>Exudate</td>
<td>None</td>
</tr>
<tr>
<td>Furrows</td>
<td>None</td>
</tr>
<tr>
<td>Stricture</td>
<td>Absent</td>
</tr>
</tbody>
</table>
association of histologic, endoscopic, and molecular features. This study characterized three endotypes namely EoEe1, EoEe2, and EoEe3 each with distinct genetic, clinical, endoscopic and histological features providing effective therapeutic intervention (Table 2).

**Diagnostic criteria:**
- Symptoms suggestive of esophageal dysfunction
- Presence of eosinophilic infiltrate (>15 e/hpf) on esophageal biopsy
- Exclusion of other disease like Gastro Esophageal Reflux Disease (GERD) and Proton Pump Inhibitor Responsive Esophageal Eosinophilia (PPI-REE) after 8 weeks PPI trial.

AGREE Conference 2018 includes the following:
- Symptoms of esophageal dysfunction.
- Esophageal mucosal biopsies with eosinophils ≥15/hpf (60 eosinophils/smm).
- Presence of exudates, grooves, rings, stenosis, luminal narrowing, and crepe’ mucosa.
- Concomitant atopic conditions.
- Esophageal eosinophilic infiltration in isolation.
- Evaluation of potential contributors of esophageal eosinophilia.

**Updated diagnostic algorithm**

**Emerging diagnostic tools:** Transnasal endoscopy, Endoscopic functional lumen imaging probe (FLIP), Cytosponge to obtain biopsy have sensitivity and specificity of 75% and 86%, respectively, esophageal string test and real time mucosal impedance measurements. Absolute eosinophil count (AEC) is the single biomarker of relevance as on this date.

**Treatment**

Treatment principles include elimination of potential antigen, attenuation or elimination of antigen induced allergic/immunogenic pathway induced inflammation early in the disease using PPI and steroids and to treat fibrostenotic complications of like strictures endoscopically in advanced disease. 3D acronym for Diet, Drugs, and Dilatation forms the basis of treatment of EoE.

**Diet:** Elimination diet: Elemental diet still is the most effective strategy but associated with poor compliance. A meta-analysis by Arias et al. observed efficacy of elemental diet in 90.8%, six food elimination diet (SFED—cow milk, wheat, egg, soy, peanut, and seafood) in 72.1% and allergy testing directed elimination diet in 45.5% of cases. A novel 2-4-6 step up elimination diet strategy with each elimination diet step lasting for 6 weeks observed 43% remission in Two Food Elimination Diet (TFED Milk and gluten containing diet), 60% in those receiving TFED and four food elimination with addition of eggs and legumes (FFED) and 79% with six food elimination diet by additionally excluding nuts and seafood. This method helped to identify possible food antigen and avoided unnecessary food elimination.

**Drugs:**
- **Steroids:** Dampening of EoE associated inflammation, improving mucosal barrier function and histologic
TABLE 2  EoE Endotypes

<table>
<thead>
<tr>
<th>Variable</th>
<th>EoEe1</th>
<th>EoEe2</th>
<th>EoEe3</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of subjects</td>
<td>35%</td>
<td>29%</td>
<td>36%</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Pauci-Inflammatory Near normal esophagus</td>
<td>High type 2 immune mechanism with steroid refractoriness Inflammatory</td>
<td>Higher frequency of narrow caliber esophagus Fibrostenotic</td>
</tr>
<tr>
<td>Epithelial differentiation genes</td>
<td>Small changes</td>
<td></td>
<td>Low expression</td>
</tr>
<tr>
<td>Onset</td>
<td>Pediatric</td>
<td>Adult</td>
<td>Adult</td>
</tr>
<tr>
<td>Allergy</td>
<td>Atopic</td>
<td>Atopic</td>
<td>Non-Atopic</td>
</tr>
<tr>
<td>Steroid sensitivity</td>
<td>Sensitive</td>
<td>Refractory</td>
<td>Refractory</td>
</tr>
<tr>
<td>Genetic</td>
<td>Low expression of ALOX 15 Mild phenotype</td>
<td>Inflammatory cytokines IL-4, TSLP are expressed Expression in ACTG2 gene</td>
<td>Enriched for epithelial genes that lose expression, of ACP9, CITED2, CTNNAL1, EML1, FLG, GRPEL2, MT1MPNLIPPR3, TSPAN12</td>
</tr>
<tr>
<td>Treatment response</td>
<td>Anti-Type 2 immune therapy (anti IL-4 Ralpha) Anti TSLP Biologicals</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Learning                  | • Adult and pediatric EoE have comparable pathogenesis  
• Adult and pediatric EoE are amenable to similar therapeutic interventions  
• Eosinophils levels may not indicate severity or help to subtype EoE  
• Endotyping offers useful subtyping of EoE  
• Biomarkers need to be developed  
• EoE exists in three disease endotypes with characteristic/unique clinical, endoscopic and molecular features  
• Endotyping could transcend eosinophil levels as gold standard | • Removal of age cutoff  
• Removing PPI from list of diagnostic criteria  
• Evaluate for condition causing esophageal eosinophils rather than excluding them  
• Criteria should be clinically operational  
• Utilization in patients in whom diagnosis was made using earlier criteria, applicable clinically widely and for future research |
remodeling; improved esophageal diameter and dispensability.\textsuperscript{41-44} Induction regimen of oral 1 mg budesonide twice daily for 2–4 weeks to reach clinical response followed by maintenance regimen of 0.25 mg twice daily for not less than 6 months after which steroid can be discontinued if remission is maintained. Deep remission was achieved at 89 weeks in 9.4% of adult EoE patients with corticosteroid discontinuation at 104.7 weeks and relapse at 22.4 weeks. Relapse is managed with induction regimen for 1–2 weeks. Esophageal candidiasis in 20% and herpetic infection, adrenal insufficiency were reported following steroid use. Oral and aerosolized fluticasone is also used.

- **PPI:** The ability of PPI to reduce inflammation—PPI responsive esophageal eosinophilia (PPI-REE) has made it a first-line therapeutic modality. Use of PPI (8 weeks) by a meta-analysis showed clinical response in 60.8%, histological remission in 50.5%, sustained remission in 73–86%.\textsuperscript{45,46}

- **Leukotriene B\textsubscript{4} inhibitor:** Use of Montelukast a leukotriene B\textsubscript{4} inhibitor results in mast cell inhibition thereby reducing cytokine release retarding or preventing inflammatory cascade.

- **Biologics:** These include monoclonal antibodies against IL-13, IL-5, IL-4, anti-tumor necrosis factor alpha (TNF alpha) and antibodies against immunoglobin E. Studies indicate a promise for dupilumab, monoclonal antibody acting on IL-4 receptor by a negative regulation of Th2 response causing inhibition of IL-4/IL-13 signaling.\textsuperscript{47}

**Dilatation therapy:** Advanced disease with fibro-stenotic manifestation need endoscopic dilatation, incising of Schatzki’s ring.

Reduction in esophageal subepithelial activity (ESEA) could evolve as a relevant objective endpoint of treatment. ESEA can be known by deeper biopsies guided by endosonography. Presently available instruments—biomarkers and clinical techniques—are limited or not fully utilized. This remains as a need to meet.\textsuperscript{48,49}

**Treatment Response and Monitoring:** spectrum includes non-response, response, and complete remission (Table 3). All biomarkers now on use are investigational and include IL-3, IL-5, IL-6, IL-13, transforming growth factor alpha, and beta, TNF alpha, eotaxin 1, 2, and 3 thymic stromal lymphoprotein (TSLP) and major basic protein and neurotoxin derived from eosinophils.

**Future Directions**

Aimed at identifying the antigens responsible for the inflammatory cascade, early detection of EoE, noninvasive biomarkers for detection and monitoring, target directed therapies and prevention of relapse after achieving remission.

**Conclusion**

EoE is a chronic antigen induced immune mediated progressive disease of the esophagus characterized by eosinophilic infiltration. This progresses from inflammation to fibrostenotic disease. Earlier diagnosis by liberal biopsies in symptomatic but with normal esophageal mucosa can identify more patients. Endosonography guided deeper biopsies will give more information on subepithelial activity, which results in fibrostenotic disease. Earlier intervention improve the quality and quantity of life with less morbidity and mortality indices. Increasing awareness amongst family physicians and patients with allergic disorders coupled with esophageal biopsies is desirable.

**TABLE 3**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-response</th>
<th>Response</th>
<th>Complete remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom</td>
<td>Less than 30% symptom persistence in a symptom metric</td>
<td>90% decrease in symptom metric, Eosinophilia decrease by 30%</td>
<td>Greater than 90 % response in symptom metric EEsAI score &lt; 20</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>Persistent endoscopic finding &lt; 30% decrease in EREFS</td>
<td>Improved endoscopic findings EREFS ≥ 2 but less than baseline</td>
<td>Normal esophagus EREFS &lt; 2</td>
</tr>
<tr>
<td>Histology</td>
<td>Persistent eosinophilia ≥15 eos/HPF</td>
<td>Reduced eosinophilia 7–14 eos/HPF to 1–6 eos/HPF</td>
<td>Normal biopsy &lt; 1 eos/HPF</td>
</tr>
</tbody>
</table>

EEsAI, eosinophilic esophagitis symptom activity index; eos/hpf, eosinophils/high power field; EREFS, eosinophilic esophagitis endoscopic reference score
References

Eosinophilic Esophagitis—An Underdiagnosed Entity

Non-cirrhotic portal hypertension is an entity with a normal hepatic venous pressure gradient (HVPG) but significant portal hypertension. It could be due to pre-hepatic, hepatic, or post-hepatic causes. The most notable etiologies are extrahepatic portal vein obstruction (EHPVO) and non-cirrhotic portal fibrosis (NCPF) while other causes include schistosomiasis, congenital hepatic fibrosis, and regenerative nodular hyperplasia. The pathogenesis for NCPF and EHPVO is multifactorial and not very clear. However, there is evidence to suggest the role of a prothrombotic state and infection. EHPVO presents 10–20 years before NCPF and they both predominantly present with gastrointestinal bleed without other decompensations. In severe cases, they may have ascites and encephalopathy as well. They differ in their association of portal biliopathy, associated autoimmune conditions, histology, and diagnostic modalities needed. Diagnosis is established easily for EHPVO by Doppler ultrasonography; however, NCPF requires exclusion of cirrhosis and may necessitate a liver biopsy. Treatment options include variceal ligation and beta-blocker for secondary prophylaxis of bleeding. A major complication of EHPVO is portal biliopathy which needs endoscopic therapy if cholangitis occurs. Shunt surgeries remain important in the long term; however, their role for bleeding has reduced due to better endotherapy and availability of newer modalities like TIPSS. With advent of better therapy, the prognosis of these conditions has improved and most patients live a healthy life.

Abstract

Non-cirrhotic portal hypertension is an entity with a normal hepatic venous pressure gradient (HVPG) but significant portal hypertension. It could be due to pre-hepatic, hepatic, or post-hepatic causes. The most notable etiologies are extrahepatic portal vein obstruction (EHPVO) and non-cirrhotic portal fibrosis (NCPF) while other causes include schistosomiasis, congenital hepatic fibrosis, and regenerative nodular hyperplasia. The pathogenesis for NCPF and EHPVO is multifactorial and not very clear. However, there is evidence to suggest the role of a prothrombotic state and infection. EHPVO presents 10–20 years before NCPF and they both predominantly present with gastrointestinal bleed without other decompensations. In severe cases, they may have ascites and encephalopathy as well. They differ in their association of portal biliopathy, associated autoimmune conditions, histology, and diagnostic modalities needed. Diagnosis is established easily for EHPVO by Doppler ultrasonography; however, NCPF requires exclusion of cirrhosis and may necessitate a liver biopsy. Treatment options include variceal ligation and beta-blocker for secondary prophylaxis of bleeding. A major complication of EHPVO is portal biliopathy which needs endoscopic therapy if cholangitis occurs. Shunt surgeries remain important in the long term; however, their role for bleeding has reduced due to better endotherapy and availability of newer modalities like TIPSS. With advent of better therapy, the prognosis of these conditions has improved and most patients live a healthy life.
incriminated most commonly. Although data is limited, better obstetric hygiene and neonatal care are likely the reason behind to bring down the incidence of NCPF. This has been shown in Western countries and supports the role of hygiene in pathogenesis of disease. India is more predisposed as populations have lack of clean drinking water, inadequate sewage facilities, and continuous gut inflammation due to antigenic exposure. Autopsy series from western countries showing high prevalence of PV thrombosis lend support to the role of prothrombotic factors. An imbalance of low ADAMTS13 and von Willebrand factor levels could be linked to promotion of PV radicals. This was first established from relation between therapeutic arsenic exposure (Fowler’s solution) and NCPF in Europe. It has been shown to be associated with autoimmune diseases like inflammatory bowel disease (IBD) and celiac disease. Patients with HIV have shown a higher prevalence of NCPF. Possible contributory factors could include opportunistic gastrointestinal (GI) infections, antiretroviral therapy or the effect of the viral by itself.

**Etiopathogenesis**

Perinatal history is important as sepsis and manipulation of the umbilical vein have been implicated as inciting factors. At the time of diagnosis, most of the times a cavernoma is seen as the initial thrombosis is often missed as it is asymptomatic and there is formation of collaterals within 1–2 weeks followed by cavernoma in another week. These collaterals are able to compensate partially and overcome the prehepatic obstruction, but their insufficiency leads to formation of varices.

**Diagnosis**

The typical scenario when one should suspect NCPF and EHPVO is presentation with GI bleed with relatively well preserved liver function tests. Ultrasound of the abdomen provides a further clue since massive splenomegaly is seen in both conditions, which is larger than cirrhosis. Doppler shows a thrombosed PV with surrounding collaterals (cavernoma) in case of EHPVO and normal flow in NCPF.

**Clinical Features**

EHPVO presents in the first decade with peaks at 3 and 8 years of age. NCPF on the other hand is seen more in young and middle aged adults median age of onset in Indian series being 30–32 years. Patients often give a history of long standing dull aching pain in the left upper abdomen due to massive splenomegaly; however, it requires medical attention infrequently. Unlike cirrhosis, the episodes of variceal bleed are often not life threatening and well tolerated. Being a childhood chronic disorder affecting the
liver blood supply, EHPVO is often complicated by anemia and growth retardation (Table 2).

Incidences of variceal bleed are frequently precipitated by infections and recurrences tend to decrease after puberty. Hypersplenism is present in both the disorders. Although liver cell failure is rare, ascites may occur in up to one third of the patients. This usually occurs after a bleed and is related to low serum albumin levels or in cases of secondary biliary cirrhosis. The left upper abdomen pain may be exacerbated and acute at times of perisplenitis or splenic infarction.

On clinical examination, liver span is normal or slightly reduced. Peripheral clinical stigmata of cirrhosis are absent. Icterus may be seen in EHPVO in those with portal biliopathy.

**Laboratory Parameters**

Hypersplenism with anemia is the commonest finding. Liver function tests are usually normal; however, albumin levels in serum may be reduced at the time of bleed further creating a diagnostic dilemma with cirrhosis. Elevated conjugated bilirubin and cholestatic pattern (raised alkaline phosphatase) may be a harbinger of portal biliopathy in long standing cases. Prolonged prothrombin time, reduced fibrinogen is seen in most patients. The shunted blood flow leads to impaired production of coagulation factors and lead to a low grade of disseminated intravascular coagulopathy. Hyperdynamic circulation is seen in both conditions and along with raised nitric oxide has been proposed to lead to autonomic dysfunction. Cell mediated immunity may be hampered.

**Findings on Esophagogastroduodenoscopy**

Esophageal varices are seen in more than 80% of patients. Compared to cirrhotics, esophageal varices are larger and gastroesophageal varices are commoner. Ectopic varices in the rectum and colon may lead to lower GI bleed in EHPVO.

**Radiological Features**

At clinical suspicion, ultrasound of the abdomen with Doppler for splenoportal axis is the initial investigation of choice. In NCPF, liver is normal in size and spleen is enlarged with a dilated and patent splenoportal axis. PV is thickened (>3 mm) and intrahepatic branches show a withered tree appearance. The etiological workup for cirrhosis is negative. NCPF may mimic early stage cirrhosis very often and only HVPG can reliably differentiate between them. The diagnosis of EHPVO in children is usually much simpler as the finding of a portal cavernoma replacing the PV has a very high sensitivity and specificity. In adults, with cirrhosis, it becomes difficult as cirrhosis may also lead to bland PV thrombosis. There is cavernomatous transformation of PV. CT and MR venography have better sensitivity and also provide a roadmap to surgery.

<table>
<thead>
<tr>
<th>Nature of precipitating event</th>
<th>NCPF</th>
<th>EHPVO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associated autoimmune diseases</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Portal biliopathy</td>
<td>Not seen</td>
<td>Seen</td>
</tr>
<tr>
<td>HVPG</td>
<td>Normal or elevated</td>
<td>Normal</td>
</tr>
<tr>
<td>Investigation of choice for diagnosis</td>
<td>Liver biopsy</td>
<td>Ultrasound Doppler</td>
</tr>
<tr>
<td>Hallmark on liver biopsy</td>
<td>Obliterative portal venopathy</td>
<td>Normal liver architecture unless secondary biliary cirrhosis occurs</td>
</tr>
</tbody>
</table>

**TABLE 2** Differences between NCPF and EHPVO

EHPVO, extrahepatic portal vein obstruction; HVPG, hepatic venous pressure gradient; NCPF, non-cirrhotic portal fibrosis.
Pathology
EHPVO can be reliably diagnosed by USG; however, a liver biopsy may be needed to differentiate early cirrhosis and NCPF. The characteristic pathological findings for NCPF by phlebosclerosis, periportal, and perisinusoidal fibrosis, aberrant vessels in portal tract, preserved lobular architecture, and “obliterative portal venopathy.” In cases of EHPVO, the PV is replaced by cluster of varying sized vessels more so around the hilum. Nodular arrangement and fibrosis, which are characteristic of cirrhosis are absent.

Natural History
The natural course of NCPF is usually much more predictable as compared to the complexity seen in EHPVO sometimes. A likely reason for this is the early insult in life, which leads to a long time available for the disease to progress insidiously. It may lead to short stature, parenchymal destruction, poor quality of life, hepatic encephalopathy, and portal biliopathy. Once GI bleed is controlled after variceal eradication, long-term prognosis in NCPF is excellent. Liver cell failure and decompensation is usually absent but may occur at times of GI bleed or in nodular NCPF. Uncontrolled upper GI bleeding from varices may lead to mortality.

While the general outcome of EHPVO is good, certain complications need to be monitored and treated carefully. Growth retardation occurs in up to half of the children. The postulated mechanism behind this is deprivation of hepatotropic factors and malabsorption due to portal hypertensive enteropathy. They also have a poor health-related quality of life.

Portal biliopathy is defined as cholangiographic abnormalities, which occur in patients with portal cavernoma. This may be intrahepatic or extrahepatic. Long standing portal cavernoma in the biliary region causes compressive and ischemic changes on the biliary tree. Portal biliopathy usually remains asymptomatic may lead to jaundice, biliary colic, abdominal pain, and recurrent cholangitis. Another dreaded complication is minimal hepatic encephalopathy (MHE). It is understandably more after shunt surgery but it may occur even prior to surgery. Usage of lactulose improves MHE. Prolonged portal biliopathy leads to extinction of liver parenchyma gradually and may mimic cirrhosis later. It may manifest as poor synthetic function, jaundice, and decompensation in the form of ascites.

Treatment
The event that can change the natural history of a patient with NCPF is massive upper GI bleed. Control of the index bleed and prevention of further bleed is the focus in most cases. Another aspect of the treatment is symptomatic splenomegaly and hypersplenism. Rest of the treatment revolves around complications like MHE, portal biliopathy, and growth failure.

Control and Prophylaxis of Variceal Bleed
Variceal bleed is an important complication in NCPF. In view of limited data as compared to variceal bleed, guidelines recommend the principles of management to remain same. The patient should be resuscitated with fluids and be taken up for endoscopy within 24 hours. Endotherapy in the form of endovascular ligation is the mainstay of therapy in terms of intervention. Older studies used more of sclerotherapy. These techniques are successful in more than 80% patients. Vasoactive agents should be started prior to endotherapy to reduce the severity of bleed and possibly control it. The goal should be variceal eradication as role of beta blockers is not very clear although they are widely used. Non-selective beta blockers should be used for secondary prophylaxis.

Transjugular Intrahepatic Portosystemic Shunt (TIPS)
TIPS is an option for treatment for complicated NCPF, especially those with recurrent or refractory bleed. However, it is best avoided in cases of renal dysfunction, malignancy, or prothrombotic conditions.

Surgery
The most common indication for surgical management is recurrent bleed or bleed refractory to endotherapy. Other indications are symptomatic hypersplenism, hepatopulmonary syndrome, or portopulmonary hypertension. Surgery has now mainly been replaced by TIPS. The types of surgeries performed are:
- Shunt procedures: They bypass blood from the portal system to systemic circulation removing the cavernoma from the pathway. Shunts may be
physiological or non-physiological depending on whether they preserve the hepatic portal blood flow or not (maintained in physiological). As is expected, surgery reduces complications of PHT like varix size and spleen size; however, adverse effects from portosystemic shunting include risk of MHE and shunt nephropathy. Selective shunts like distal splenorenal shunt are associated with less complication than proximal, non-selective shunts. Shunt surgery is undertaken only after a particular age (generally 8 years) and with a favorable anatomy (adequate shuntable vein diameter).

- **Ablative procedures**: These surgeries are very morbid and include visceral devascularization with or without splenectomy. It has gone out of vogue due to advances in endotherapy and is reserved for emergency scenarios.

### Salvage Emergency Therapy

In spite of newer endoscopic modalities, in 10% of the cases endotherapy fails. Options then include ablative procedures, TIPS, or balloon occluded retrograde transvenous obliteration. Routine anticoagulation is not recommended in EHPVO or NCPF according to the current available data. The management for portal biliopathy is generally supportive and not curative. Biliary stenting is done using ERCP for biliary strictures.

### Miscellaneous Causes of NCPH

Although infrequently seen in clinical practice, a few important causes of NCPH that merit discussion have been described here.

#### Schistosomiasis

Schistosomiasis is one of the most common causes of NCPH in the world but rarely seen in India. *Schistosoma mansoni* and *Schistosoma japonicum* are the two main species of Schistosoma that are known to cause liver disease. *S. japonicum* is distributed throughout the world and *S. mansoni* is endemic to Africa and Middle East. Both are however not found in India. The eggs are stuck in the portal venules and lead to granulomatous inflammation. Over a period, fibrosis occurs and portal pressures increase. Chronic hepatic schistosomiasis is characterized by hepatomegaly with features of PHT. Diagnosis is based on detection of eggs in stool or rectal biopsy or ELISA test for antigen. On ultrasound, PV radicles show echogenic thickening giving the appearance of a mesh of fish scales. There may be complete reversal of periportal thickening with use of antihelminthic like praziquantel.

#### Congenital Hepatic Fibrosis

Congenital hepatic fibrosis (CHF) is a developmental disorder of the portobiliary system characterized histologically by defective remodeling of the ductal plate and progressive fibrosis of the portal tracts. It is usually autosomal recessive in inheritance and presents in the first or second decade of life. Autosomal recessive polycystic kidney disease and ciliopathies are commonly associated disorders. Clinical findings include an enlarged, abnormally shaped liver and splenomegaly with preserved liver functions. Biliary complications include cholangitis and an increased predisposition to cholangiocarcinoma. Imaging reveals dilatation of biliary system and enlarged caudate lobe and splenomegaly. Since no specific therapies are available, treatment of complications and eventually liver transplant may be needed.

#### Nodular Regenerative Hyperplasia

Nodular regenerative hyperplasia (NRH) is a characterized by widespread benign transformation of hepatic parenchyma into small regenerative nodules. It is common in Europe and Japan with preponderance amongst octogenarians. There is a limitation of population based studies on NRH. It can be caused by various drugs (commonly chemotherapeutic agents and immunosuppressants), hematological, autoimmune, inflammatory, and neoplastic disorders. Pathogenesis appears to be related to adaptive hyperplastic reaction of hepatocytes in response to mechanical or functional abnormalities of portal hepatic blood flow. Pathologically, it is differentiated from cirrhosis by absence of perinuclear collagen and fibrous septa. Most patients remain asymptomatic, but some present with NCPH. Treatment is aimed at removal of inciting factor and management of primary disease.
Conclusion

NCPH are important causes of PHT in developing countries like India. The most important disorders are NCPF in adults and EHPVO in children. The complications if managed well, patients can have a good prognosis and leave a healthy life.

References

CHAPTER
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Drug-induced Liver Injury

Harshad Devarbhavi

Abstract
Drug-induced liver injury is an under-diagnosed cause of liver disease. It mimics all forms of liver disease. The three patterns of DILI are hepatocellular, cholestatic, and mixed. Presence of hepatocellular jaundice in DILI is associated with a mortality of >10%; this is also known as “Hy’s law”. Combination anti-TB drugs, i.e., isoniazid, rifampicin, and pyrazinamide are the most common cause of DILI and drug-induced acute liver failure (ALF) in India followed by traditional and complementary medicines. Prompt recognition and cessation of the “culprit” drug is the key to managing patients with DILI followed by supportive therapy. Few antidotes include N-acetyl cysteine for paracetamol toxicity and drug-induced ALF, cholestyramine for leflunomide DILI, and steroids for drugs associated with hypersensitivity features or drugs causing autoimmune like hepatitis.

Introduction
Drug-induced liver injury (DILI) is underdiagnosed and underappreciated as a cause or contributor to liver injury. Drugs and toxins should be considered in the differential diagnosis of all types of liver injury across all ages, although the risks are higher in older individuals and in women. It is not clear why older individuals or women have an increased risk; this may be due to increased intrinsic risk or because older people take more drugs and therefore have more opportunities to experience adverse drug reactions (ADRs). This review will focus on recent concepts on DILI with particular emphasis on DILI from India.

DILI is a diagnosis of exclusion. A high degree of suspicion and consequently a careful history of prescription medication and over the counter drugs (pain killers) exposure as well as exposure to herbal and traditional medicines or dietary supplements (often overlooked by the physician) should be obtained. While most patients experience DILI within the first 2–3 months of therapy, in some instances (e.g. amoxicillin-clavulanate related DILI) symptoms can present with up to a month delay after treatment cessation or arise after months of exposure to a drug such as nitrofurantoin, minocycline, and alpha methyldopa.

Causality Assessment
Since DILI is a diagnosis of exclusion there are no established diagnostic markers. Causality assessment methods are used to determine likelihood of a drug causing liver injury and the best known is the Roussel Uclaf causality assessment method (RUCAM). Information on time to onset (latency), course of reaction upon medication discontinuation, time to resolution, risk factors, concomitant drugs exclusion of other causes, prior knowledge on DILI potential, and response to readministration are variables required to establish a compatible relationship with the suspected
causative agent. The degree of causality is assessed as definite (highly probable), probable, possible, and unlikely in descending order of strength.  

**Case Definitions and Severity**

Transient asymptomatic minor elevation of aspartate transaminase (AST) or alanine transaminase (ALT) is common during routine evaluation. In one study incidence of baseline liver chemistry abnormalities in a population of over 18,000 patients (without underlying liver disease), the baseline prevalence of any ALT elevation above the upper limit of normal (ULN) was 6% while the overall prevalence of ALT values of more than 3 × ULN was 0.076% (<1 in 1,000).  

Transient elevation of AST or ALT may occur following exposure to medication and may resolve on its own or with continuation of drugs or following decrease in dose. This phenomenon (called adaptation) is characteristic of antituberculosis (anti-TB) drug or statin therapy and depends on the frequency of liver biochemistry estimation. Awareness of this condition will prevent inappropriate withdrawal of medications such as in the treatment of tuberculosis where even a temporary cessation of treatment may have adverse disease outcome including risk of drug resistance.  

DILI is defined as an adverse hepatic reaction that is unexpected on the basis of the pharmacological action of the drug administered. International expert panel recommended DILI to be considered when any one of the following thresholds are met even in the absence of symptoms:

- ALT or AST ≥ 5 × ULN
- ALP ≥ 2 × ULN in the absence of extrahepatic source driving the rise in ALP level
- Total bilirubin concentration exceeding 2 × ULN associated with any elevation of the aminotransferases or alkaline phosphatase.

**Hy’s Law**  
Hyman Zimmerman observed the presence jaundice in the setting of DILI suggested severe hepatocellular functional impairment with potential for liver failure and 10–50% mortality. Thus, “Hy’s law” is used clinically and during drug evaluation to indicate highly significant and severe hepatotoxic potential of a drug when patients fulfill the following criteria, that is, AST or ALT more than 3 × ULN + bilirubin >2 × ULN (in absence of biliary tract disease). Presence of jaundice during anti-TB therapy results in a mortality of 16–26% in India. Patients with anti-TB DILI who fulfill Hy’s law criteria have a mortality of 17%. Furthermore, development of acute liver failure during treatment of anti-TB drugs results in a mortality in two-thirds of patients. Paradoxically in the Indian setting a substantial proportion of individuals who develop anti-TB DILI, never required the drugs in the first place, having received anti-TB drugs empirically on a presumptive basis. Therefore, great caution should be exercised while administering anti-TB drugs empirically, especially in women, the elderly, and those with comorbidities.

**Patterns of Liver Injury**

Most patients with DILI in clinical practice are characterized based on their liver biochemistry, these are categorized as hepatocellular, cholestatic, or mixed pattern of DILI. Pattern of liver disease is based on Ratio (R value) of ALT (or AST) activity expressed as fold elevation over its ULN laboratory range to ALP activity. Pattern of DILI is hepatocellular when R is ≥5, cholestatic when R is ≤2 and mixed when R is 2–5. The pattern of liver injury has implications for prioritizing immediate including any of the following: fever, nausea, vomiting, jaundice, dark urine, right upper quadrant pain, skin rashes, and itching.  

The level of elevation of liver enzymes alone does not reflect liver function severity. Liver enzyme elevation is a reflection of liver injury not function, whereas bilirubin elevation (liver excretory function), or increased INR or decreased albumin (liver synthetic function) are more accurate indices of liver function. The presence of jaundice, or development of ascites, coagulopathy, and/or encephalopathy indicates severe disease and connotes poor prognosis.
investigations essential to exclude alternative causes of the event as well as prognosticate outcome.

Examples of drugs associated with above patterns and other additional patterns are listed below: 13

- **Hepatocellular**: Isoniazid, rifampicin, pyrazinamide, diclofenac, lamotrigine, minocycline, nitrofurantoin, nevirapine, efavirenz, sulfonamides, disulfiram.
- **Cholestatic**: Chlorpromazine, erythromycin, penicillins, amoxicillin-clavulanate, sulfonamide, terbinafine, androgens, oral contraceptives.
- **Mixed pattern**: Phenytoin, carbamazepine, lamotrigine, sulfonamides.
- **Drug reaction with eosinophilia and systemic symptoms (DRESS)**: Carbamazepine, phenytoin, phenobarbitone, allopurinol, lamotrigine, cephalosporins, dapsone, sulfonamide, nevirapine.
- **Autoimmune like hepatitis**: Nitrofurantoin, α-methyldopa, minocycline, diclofenac, statins, adalimumab, infliximab, herbs and complimentary medicines.
- **Nonalcoholic fatty liver disease (NAFLD)**: Amiodarone, methotrexate, tamoxifen, 5-fluorouracil, amiodarone, didanosine, stavudine.
- **Vanishing bile duct (ductopenic) syndrome**: Azathioprine, amoxicillin-clavulanate, carbamazepine, chlorpromazine, erythromycin, phenytoin, terbinafine and cotrimoxazole.

**Causes**

Antibiotics are the most common cause of idiosyncratic DILI and drug-induced acute liver failure worldwide and also in India. 7,9,13-16 In India, first-line combination anti-TB drugs, isoniazid, rifampicin, and pyrazinamide are the commonest agents causing DILI accounting for 46% of all cases followed by complementary and alternative medicines at 14%. 7 Combination anti-TB drugs accounts for 67–72% of cases of drug-induced acute liver failure followed by anti-epileptic drugs (10%), and dapsone (5.5%) in a single center series. 9,17,18 DILI from anti-TB drugs appears disproportionately more severe than other drugs causing liver injury. 7 Almost three-fourths of anti-TB DILI occur within the first 2 months of administration of drugs although the risk of DILI persists throughout the course of treatment. 19 Paradoxically paracetamol-induced DILI and liver failure is very uncommon in India and accounts for less than 1% of DILI or drug-induced ALE. 9,18 This is in stark contrast to the high incidence of paracetamol hepatotoxicity in western countries. In a prospective India nationwide study, 9 drugs causing DILI in the descending order of frequency were as follows:

- Combination anti-TB drugs (46.4%)
- Complementary and alternative medicines (13.9%)
- Antiepileptic drugs (AED) (8.1%)
- Non-anti-TB antimicrobials (6.5%)
- Antimetabolites (3.8%)
- Antiretroviral drugs (3.5%)
- NSAIDs (2.6%)
- Hormones (2.5%)
- Statins (1.4%)
- Others (11.3%)

Although patients with pre-existing liver disease are not more likely than others to experience hepatic injury on exposure to drug, recovery from DILI in patients with chronic liver disease is generally poor. 20 Complementary and alternative medicines (73%) and anti-TB drugs (22%) are responsible for 99% of cases of drug-induced acute on chronic liver failure (ACLF) in India and Asia and is associated with 46% mortality, much more than other causes of ACLF. 21

**Mechanism of Liver Injury**

Simplistically, the mechanism of DILI may be divided into two broad groups, that is, direct hepatotoxicity as exemplified by paracetamol overdose or idiosyncratic injury wherein the characteristics of the individual patient/subject plays a major role in causing DILI. 20 In idiosyncratic reaction, the dose of a drug does not play a role although most DILIs are encountered following exposure to drugs used in daily dose of 50 gm or higher. 21 **Table 1** summarizes the characteristics of mechanism of injury. A recently described third category is the indirect hepatotoxicity, wherein hepatotoxicity is secondary to the indirect action of agent on liver or immune system (Table 1). 23

**Management**

The first consideration in the management of DILI is to harbor a high index of suspicion regarding the role of medications in causing liver injury. The drugs implicated should be stopped immediately and alternate causes including viral hepatitis especially hepatitis E (which is common in Northern India) 24 and biliary causes...
(by ultrasonography) should be excluded. Most episodes of DILI resolve with discontinuance of the culprit drug and with supportive treatment. There are very few antidotes for specific drugs producing DILI. These include N-acetylcysteine for paracetamol toxicity,25 desferrioxamine for ferrous sulfate toxicity, L-carnitine for valproate DILI, and cholestyramine for leflunomide DILI. Patients who develop hypersensitivity skin rashes and eosinophilia or DRESS should be considered for steroid treatment, which should be continued for 4–8 weeks, although steroids have not been evaluated in a randomized fashion.26

Reintroduction of anti-TB drugs after an episode of anti-TB DILI needs special mention. The American Thoracic Society guidelines are the most up to date and elaborate.27,28 Ethambutol has no hepatotoxic potential and needs to be continued during and after DILI. Rifampicin is the least hepatotoxic drug and needs to be considered first followed by isoniazid and pyrazinamide. These drugs may be administered sequentially with staggered doses. In case of a severe DILI at index presentation, pyrazinamide should be omitted during rechallenge.27

**Conclusion**

Anti-tuberculosis drugs are the most common cause of DILI and drug-induced acute liver failure in India. DILI is a diagnosis of exclusion. Awareness of the fact that drugs can mimic all forms of liver disease is crucial in diagnosing DILI. Occurrence of hepatocellular jaundice entails a mortality of >10%, and hence the implicated drug should be stopped immediately. There is emerging evidence of the increasing role of traditional and complimentary medicines in causing DILI all over the world including India.

**References**

Achalasia cardia is a primary esophageal motility disorder due to autoimmune neurodegeneration of esophageal myenteric plexus resulting in impaired relaxation of lower esophageal sphincter (LES) on swallowing and failure of peristalsis in distal smooth muscle segment of the esophagus. High resolution manometry (HRM) has greatly improved the sensitivity of diagnosing achalasia in the early stages of disease when endoscopy and barium esophagogram can be normal or equivocal. Manometrically achalasia cardia can be divided into three subtypes, which help in deciding treatment, and hence have prognostic significance. The primary distinction from other motility disorders (e.g., Jackhammer esophagus and distal esophageal spasm) is failure of LES relaxation in achalasia. So, most of the therapies are directed toward reduction in LES pressures. Treatment modalities in AC acts by causing either mechanical disruption of LES by per oral endoscopic myotomy (POEM), laparoscopic Heller’s myotomy (LHM) and pneumatic dilatation (PD) or biochemical reduction in LES pressure (pharmacological therapy, e.g., nitrates and botulinum toxin). There is renewed interest in this motility disorder in the past few years as with the advent of third space endoscopy (i.e., POEM), the endoscopic management of achalasia has been revolutionized.

Introduction

Achalasia cardia (AC) is rare yet most common and best characterized esophageal motility disorder. It is equally common in both sexes and most frequently observed in 40–60 years age. AC is characterized by progressive degeneration of ganglion cells in the esophageal myenteric plexus resulting in impaired relaxation of lower esophageal sphincter (LES) on swallowing and failure of peristalsis in distal smooth muscle segment of the esophagus. Presenting symptoms are dysphagia to both liquids and solids, regurgitation of undigested food, retrosternal chest pain, heartburn, weight loss, and symptoms due to aspiration pneumonia. Upper GI endoscopy and timed barium esophagogram are the initial investigations and high resolution manometry (HRM) is diagnostic. Therapy in AC is directed toward reduction in LES pressures either by biochemical reduction or mechanical disruption of LES. Mainstay of management of AC is by pneumatic dilatation (PD), per oral endoscopic myotomy (POEM) and laparoscopic Heller’s myotomy (LHM) in surgical fit candidates. Biochemical reduction of LES by botulinum toxin (BT)/pharmacotherapy (nitrates, calcium channel blockers) are reserved for surgical unfit patients or patients with limited life expectancy due to short lasting efficacy. Esophagectomy is reserved for surgically fit patients with long standing symptoms who failed multiple therapies repeatedly. In this chapter we shall focus on diagnosis and endoscopic treatment (BT, POEM, and PD) of AC.

Diagnosis

History and Clinical Examination

Dysphagia to both solids and liquids (85–91%), regurgitation of undigested food (75–91%), substernal chest pain and
heartburn (40–60%), weight loss and aspiration pneumonia (8–10%) are the various symptoms of achalasia. Appropriate history taking help to differentiate esophageal motility disorders from mechanical dysphagia (Table 1). Liquids require better neuromuscular coordination than solids for esophageal emptying so dysphagia to both solids and liquids are present from the onset. Compression of the esophagus between spine and manubrium sterni in specific postures like raising arms in erect position increase the intraesophageal pressure and propel food in aperistaltic esophagus.

Achalasia is often misdiagnosed as gastroesophageal reflux disease (GERD) as retrosternal chest pain and heartburn are common. Reflux or lactate production by fermentation of undigested carbohydrates lead to heartburn. Chest pain is least responsive to treatment compared to other symptoms but can spontaneously disappear over time. Weight loss is not as profound as in mechanical dysphagia. Aspiration pneumonia can occur due to regurgitation into bronchopulmonary tree can lead to cough and fever. Impaired belching due to compression of membranous trachea by dilated esophagus and inadequate relaxation of upper esophageal sphincter is a rare but noteworthy symptom in achalasia. Eckardt score is a system for evaluation of achalasia symptoms and treatment efficacy which is based on degree of dysphagia, regurgitation, chest pain, and weight loss (Table 2). Clinical examination is usually unremarkable except emaciation and oral cavity ulcerations in some patients. Examination of the respiratory system may show diminished breath sounds, dull note on percussion, and crepitations over area of consolidation due to aspiration pneumonia.

### Diagnostic Tools

#### Primary Diagnostic Tools

Upper GI endoscopy and timed barium esophagogram are the initial investigations in any case of dysphagia. Once, mechanical obstruction is ruled out on endoscopy/barium swallow, HRM is diagnostic and helps subclassification.

#### Upper GI Endoscopy

Normal upper GI endoscopy rules out mechanical causes of dysphagia. Upper GI endoscopy in AC shows dilated and often tortuous esophagus with food/liquid residue.
The contracted LES in AC does not open spontaneously and is usually traversed with a gentle pressure with the endoscope unlike neoplastic/fibrotic strictures. The esophageal mucosa is usually normal in AC but can develop erythema and ulceration due to food stasis (stasis esophagitis). Stasis predisposes to esophageal candidiasis. Tertiary contractions may be noticed during endoscopy due to spontaneous, simultaneous contractions of esophageal smooth muscles. An esophageal epiphrenic diverticulum (EED) (pulsion type pseudodiverticulum) can be associated with AC, which makes endoscopic therapy challenging but yet feasible.

**Laboratory Work Up**

Complete blood count, serum creatinine, serum electrolytes, liver function tests, and thyroid profile can be done as a part of work up for endoscopic/surgical myotomy, which requires general anesthesia.

**Imaging**

*Timed barium esophagogram:* Timed barium esophagogram is the imaging of choice in AC. 100–250 mL of barium (45% weight/volume) is swallowed by the patient over 15–20 seconds and X-ray done at 1, 2, and 5 minutes. The height and width of the barium column in esophagus is measured at 1, 2, and 5 minutes which denotes the esophageal emptying. In AC, there is delayed emptying of barium from the esophagus, tertiary contractions and bird-beak appearance (Figs. 1A and B). It is done in both pre- and post-treatment states in AC to evaluate response to therapy. Hugely dilated esophagus or megaesophagus (>7 cm) can be seen in late/long standing cases of AC. Dilated, tortuous esophagus in late stage AC is termed as sigmoid esophagus. Both mega-esophagus and sigmoid esophagus denote decompensated disease, which implies poor response to therapy. Esophageal epiphanic diverticulum (EED) can rarely be found in association with AC.

*Other imaging:* Chest X-ray may be required in AC to evaluate for aspiration pneumonia. Computed tomography (CT) of chest could be helpful to rule out pseudoachalasia. Endoscopic ultrasound (EUS) findings of marked (>10 mm)/asymmetric lower esophageal wall thickening suggest underlying malignancy.

*High resolution manometry (HRM)* *(Table 3):* HRM is superior to conventional esophageal manometry for diagnosis and classification of AC with higher sensitivity and reproducibility. AC can be classified into three subtypes according to Chicago classification 3.0 *(Table 3)* *(Fig. 2A).*

Type I AC represents later stage disease leading to dilated astatic esophagus due to minimal esophageal muscle activity. Type II AC is characterized by panesophageal pressurization indicating simultaneous contraction of esophageal muscles between upper and LES due to disorganized neuromuscular activity of esophagus.

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**Figs. 1A and B:** Timed barium esophagogram (TBE) in achalasia cardia. (A) Preprocedure TBE after 1 minute showing tertiary contractions and dilated esophagus and no esophageal emptying. (B) Preprocedure TBE after 2 minutes showing dilated esophagus with minimal esophageal emptying.
**TABLE 3** High resolution manometry diagnostic criteria of achalasia cardia\(^2\)

**Integrated relaxation pressure (IRP) > upper limit of normal with 100% failed peristalsis**

- Type I: No contractility, no esophageal pressurization, IRP > 10 mm Hg
- Type II: Panesophageal pressurization in ≥20% swallows, IRP > 15 mm Hg
- Type III: Premature contractions (distal latency < 4.5 s) in ≥20% swallows, Segmental esophageal pressurization, IRP > 15 mm Hg

**Management**

The goal of management of AC is symptomatic relief of dysphagia and associated complications. Treatment directed at underlying pathology is not available as pathophysiology is poorly understood. Treatment of AC is directed by AC subtypes and surgical risk of the patient.\(^2\) Mechanical disruptions of LES by PD, LHM, or POEM contraction of the distal esophagus (Fig. 2C). Type III AC is least common and least responsive to both endoscopic and surgical therapy.\(^2\)

**Differential Diagnosis (Table 4)**

The differential diagnoses of AC are GERD, pseudo-achalasia, esophageal motility disorders, and mechanical dysphagia.

**(Fig. 2B)** Panesophageal pressurization indicates that esophageal smooth muscle tone is still intact, and hence type II AC represents early stage of disease. Type II AC is the most common subtype of AC and most responsive to PD. Type III AC is characterized by premature, spastic contraction of the distal esophagus (Fig. 2C). Type III AC is least common and least responsive to both endoscopic and surgical therapy.\(^2\)

**Figs. 2A to C:** (A) High resolution manometry picture of Type I achalasia showing absent esophageal body contractility and integrated relaxation pressure of 17 mm Hg (more than upper limit of normal). (B) High resolution manometry picture of Type II achalasia showing panesophageal pressurisation and high integrated relaxation pressure (>15 mm Hg). (C) High resolution manometry picture of Type III achalasia showing premature contractions (distal latency < 4.5 sec), segmental distal esophageal pressurization and high integrated relaxation pressure (>15 mm Hg).
are the mainstays of AC treatment. However, in patients with high surgical risk and/or limited life expectancy, biochemical reduction of LES pressure can be attempted (botulinum toxin ± pharmacotherapy). In this review we shall discuss endoscopic treatment of AC (botulinum toxin, PD, and POEM).

**Botulinum Toxin**

BT blocks release of acetylcholine (ACh) from the presynaptic cholinergic nerve terminals. Selective loss of inhibitory nitrinergic (NO producing) ganglion cells with partial preservation of cholinergic neurons is responsible for such therapeutic benefit.\(^\text{14}\) Hundred units of vacuum dried BT powder is dissolved in sterile saline solution (4 mL) and 1 mL (25 U) each is then injected into all four quadrants via sclerotherapy needle under endoscopic guidance at 1 cm above the Z line (squamocolumnar junction). Doses >100 U do not have increased efficacy. BT decreases LES pressure in one third of patients and improves dysphagia in two-thirds of patients of AC for up to 6 months. Up to 50% patients require re-injection by 612 months.\(^\text{15}\) The short lasting effect is due to growth of new cholinergic neurons leading to loss of efficacy. Side effects like esophageal perforation, mediastinitis, and heartburn/chest pain can occur post BT, but BT is usually safe.\(^\text{16}\) Repeat injections can be done for patients in whom surgical risk remains high even on follow-up but it can lead to fibrosis precluding continued BT injections/other endoscopic therapy. Hence, repeated BT injections should be used in patients with high surgical risk and poor life expectancy.\(^\text{17}\)

**Pneumatic Dilatation**

PD is a recommended initial treatment for AC.\(^\text{2}\) PD is done with Rigiflex balloon dilator (Microvasive, Milliford, MA, USA) available in three sizes (outer diameter: 30 mm, 35 mm, and 40 mm). Initially 30 mm balloon is used followed by progressively larger size balloon (graded approach) except in case of young male in whom 35 mm can be used initially due to poor response rate with 30 mm.\(^\text{18,19}\) Graded dilatation is performed for index dilatation. Repeated dilatation on follow-up when required for recurrent symptoms is known as “on demand approach.” Patient is kept on overnight fast. Conventionally the procedure is done under fluoroscopic guidance with conscious sedation although a novel technique without fluoroscopy under endoscopic guidance has been described.\(^\text{20}\) Initially a guide wire (preferably 0.038 inch diameter) is passed into the stomach under endoscopic guidance and scope is withdrawn to the GE junction (GEJ). The length between

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### TABLE 4  Differential diagnosis of achalasia cardia

<table>
<thead>
<tr>
<th>Suspected diagnosis</th>
<th>Clinical clues</th>
<th>Diagnostic testing</th>
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<tr>
<td>GERD</td>
<td>Normal clinical examination</td>
<td>History of reflux, regurgitation and heartburn</td>
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<td>Endoscopic findings of esophagitis, Lax LES, or hiatus hernia</td>
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<td>24 Hour pH monitoring</td>
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<td>Pseudoachalasia</td>
<td>Hepatomegaly (may suggest liver metastasis) and</td>
<td>Symptoms of dysphagia</td>
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<td></td>
<td>supraclavicular lymph nodes</td>
<td>Endoscopic finding of mechanical resistance at GE junction and may show GE junction tumor</td>
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<td></td>
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<td>EUS may show asymmetric, thickening of GEJ (&gt;10 mm)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT chest may show extrinsic compression by tumor or lung malignancy</td>
</tr>
<tr>
<td>Other motility disorders (Distal esophageal spasm, Jackhammer esophagus)</td>
<td>Hot and cold food sensitivity and disproportionate chest pain relative to dysphagia could be a diagnostic clue</td>
<td>On high resolution manometry</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal IRP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Distal esophageal spasm (DES) (&gt;20% premature contractions: distal latency &lt;4.5 sec)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Jackhammer esophagus (&gt;20% swallows with distal contractile integral -DCI &gt;8000 mm Hg.s.cm)</td>
</tr>
<tr>
<td>Mechanical dysphagia</td>
<td>Duration and course of dysphagia, relation to food/posture and associated symptoms can differentiate (See Table 1)</td>
<td>Endoscopy usually shows mechanical obstruction (malignancy, web, strictures, etc.)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Biopsy can be taken if any growth is noted in endoscopy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Barium swallow findings show asymmetric, long segment strictures with shoulder</td>
</tr>
</tbody>
</table>

*Chicago Classification v.3.0\(^\text{27}\)*
the incisors and GEJ is noted along length of endoscope. Endoscope is then withdrawn maintaining position of the catheter. Rigiflex balloon is passed over the guide wire into the stomach marking a tape in the dilating ballon catheter corresponding to distance from incisors to GEJ (balloon catheter working length 90 cm and diameter is 14 Fr). Alternatively small amount of radiographic contrast can be injected at the GEJ prior to placing catheter to mark the GEJ. Balloon (length 10 cm) is then placed across the GEJ under fluoroscopic guidance (by help of radiopaque marks in the balloon catheter). Small volume of dilute contrast can be used for radiographic visualization of balloon. As the placement of balloon waist is confirmed across GEJ, the balloon is gradually inflated with air to 10–15 psi until the balloon waist disappears and maintained for 1 minute (Fig. 3). Adequacy of dilatation confirmed by waist obliteration, blood smearing of the balloon, chest pain, and mucosal tear/widening of GEJ. Adverse events are esophageal perforation (3–5%), hematoma formation, diverticula formation. Incidence of GERD post PD is around 2–4%. Tachycardia, persistent chest pain more than 4 hours should alert the endoscopist for possible perforation. Contrast esophagogram should be done if perforation is suspected based. Small perforations can be managed conservatively with antibiotics and parenteral nutrition whereas large perforations with free flow of barium into mediastinum warrant urgent thoracotomy and repair. Hence, patients with high surgical risk should not be subjected to PD. Age less than 40 years, chest pain, type III achalasia, and pretreatment esophageal diameter less than 4 cm are poor predictors of treatment success with PD. Response rate for chest pain is around 50%. Based on available evidence (meta-analysis of three RCTs and one large RCT), clinical efficacy of PD is comparable with LHM although long-term durability (especially in young males) was higher in LHM compared to PD as higher proportion (24%) of patients had recurrent symptoms after PD requiring redilatation compared to LHM (14%). PD was compared with POEM in a recent RCT which showed significantly higher success rate at 2 years follow-up with POEM compared to PD (92% vs. 54%). This low response rate in PD could be due to dilatation with only 30–35 mm balloon and inclusion of 40 mm balloon would increase response rate to 76% (Table 5).

**Per Oral Endoscopic Myotomy**

POEM is a form of natural orifice transluminal endoscopic surgery (NOTES), which uses submucosal endoscopy to perform myotomy and is efficacious for both treatment naive and treatment failure cases. The procedure is done under general anesthesia with endotracheal intubation and carbon dioxide insufflation. There are four steps of POEM: mucosal incision, creation of submucosal tunnel, myotomy, and closure of mucosal incision (Fig. 4). Normal saline (10 mL) mixed with 0.3% indigocarmine is injected approximately 13 cm proximal to GEJ and 2-cm longitudinal incision is made anteriorly or posteriorly with the use of triangular tip (TT knife) (Fig. 4A). Endoscope with transparent cap inserted into submucosal tunnel and tunnel is extended by injection and cautery (Fig. 4B). Attention should be given not to injure the mucosal layer by keeping the scope close to circular muscle layer. The tunnel should be one third of the esophageal circumference and should extend 3 cm distal to the GEJ. GEJ is identified by palisade vessel visualization/narrowing of tunnel/visualization of aberrant longitudinal muscle bundle/ by transillumination of ultra-slim gastroscope in the submucosal tunnel. Myotomy should begin at 2–3 cm distal to mucosal entry and initially circular muscle is cut with TT knife until longitudinal muscles are visible (Fig. 4C). Then myotomy should continue in the plane between circular and longitudinal muscle fibers. Prior to closure, 20 mL saline with 80 mg gentamicin is injected into the tunnel.
and then mouse incision is closed by application of 5–10 clips at a distance of 5 mm applying first clip at the distal end of the longitudinal incision (Fig. 4D). A water soluble contrast esophagogram is done at postoperative day 1 (POD1) to exclude leak and ascertain smooth passage of contrast into stomach. Routine CT most procedure is not warranted. Patients, who tolerate oral diet and timed barium esophagogram has shown no leak, can be started on liquid diet on POD1, pureed diet on POD2 and regular diet from POD4. Initial clinical success with POEM is 82–100% and intermediate term efficacy at 2 years is 78–91% at 2 years follow-up.27–29 The choice of anterior (1 o’clock) or posterior myotomy (5–6 o’clock) is operator dependent and based on clinical scenario as there is equal efficacy of both the approaches with shorter procedure time in posterior approach.30,31 Adverse events can be insufflation related (pneumoperitoneum: 16–30%, 8% require decompression, pneumomediastinum: 8.7–11%, 2.7% require decompression, mediastinal emphysema: 4.9%, and subcutaneous emphysema: 21–36%), bleeding (early or delayed) an mucosal perforation (2.6%).32 Low/extra low flow CO₂ can reduce the incidence of pneumoperitoneum (up to 10%). Tense capnoperitoneum manifested by high end tidal CO₂ can be treated with Veress needle.33 Minor bleeding during dissection can be controlled with coagrasper or electrocautery knife. Significant delayed bleeding is rare (0.7%) and can be tackled by reentering the tunnel and coagulating the culprit vessel.34 Mucosal perforation can be closed with clips ± endoloops, fibrin glue, suturing by overstitch device or fully covered metal stent. The prevalence of increased esophageal acid exposure, reflux esophagitis, and GERD symptoms after POEM ranges from 13% to 58%, 18% to 65%, and 17% to 40%, respectively.35 Novel modifications of POEM by addition of fundoplication (POEM-F) like in LHM have been shown to reduce reflux in pilot studies.36 Anterior gastric wall is retracted at GEJ to form endoscopic fundoplication wrap. Increased procedure time, cost, and uncertain durability are the drawbacks of this novel procedure. Preservation of sling fibers by identifying two penetrating vessels at distal end of myotomy can reduce degree of esophagitis.37 A short course of proton pump inhibitor (PPI) for 1 month is recommended for all patients and further continuation of therapy should be based on pH metry, symptoms, and endoscopic finding of esophagitis.2

POEM has been shown to be superior to PD and non-inferior to LHM in two recent RCTs. It is emerging as one of the first-line options to treat AC (Table 5).25,38 Results of POEM are better than LHM, especially in type III achalasia due to ability to perform long myotomy based on length of spastic distal segment of esophagus.2 POEM is also better than LHM in case of sigmoid esophagus and other spastic motility disorders.39

### TABLE 5
Landmark randomized controlled trials comparing outcome of various treatment modalities for achalasia cardia

<table>
<thead>
<tr>
<th>Name/year</th>
<th>Comparison</th>
<th>n</th>
<th>Success</th>
<th>Follow-up</th>
<th>Adverse events</th>
<th>GERD</th>
<th>Drawbacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moonen et al., 2016</td>
<td>PD vs. LHM + Dor Fundoplication</td>
<td>n-96</td>
<td>82%</td>
<td>5 years</td>
<td>5% 11%</td>
<td>12% 34%</td>
<td>Re-dilatation required in 25% of PD patients—considered as treatment success</td>
</tr>
<tr>
<td>Boeckxstaens et al., 2016</td>
<td>PD vs. LHM + Dor Fundoplication</td>
<td>n-96</td>
<td>86% (2 years)</td>
<td>43 months</td>
<td>4% 12%</td>
<td>15% 23%</td>
<td>Follow-up short as effect may decrease over time</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n-105</td>
<td>90% (2 years)</td>
<td>p=0.46</td>
<td></td>
<td></td>
<td>Rigorous PD protocol over 2 years—only 3rd series of PD within 2 years of 2nd series considered as failure</td>
</tr>
<tr>
<td>Ponds et al., 2019</td>
<td>POEM vs. PD</td>
<td>n-67</td>
<td>92%</td>
<td>2 years</td>
<td>0% 3.03 %</td>
<td>41% 7%</td>
<td>Only allowed PD up to 35 mm Considered re-dilatation as treatment failure</td>
</tr>
<tr>
<td>Werner et al., 2019</td>
<td>POEM vs. LHM + Dor fundoplication</td>
<td>n-112</td>
<td>83%</td>
<td>2 years</td>
<td>2.7% 7.3%</td>
<td>44% 29%</td>
<td>Length of myotomy was not standardized</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n-109</td>
<td>81.7%</td>
<td>p=0.007 non-inferiority</td>
<td></td>
<td></td>
<td>POEM was not accompanied by any anti-reflux procedure where LHM was done with for fundoplication</td>
</tr>
</tbody>
</table>

(continues)
**TABLE 6** Comparison of treatment efficacy of various treatment modalities in achalasia cardia

<table>
<thead>
<tr>
<th></th>
<th>PD</th>
<th>LHM</th>
<th>POEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I AC</td>
<td>63.3–85%</td>
<td>81%</td>
<td>91.3%</td>
</tr>
<tr>
<td>Type II AC</td>
<td>90–93%</td>
<td>93–100%</td>
<td>96.3%</td>
</tr>
<tr>
<td>Type III AC</td>
<td>33.3–40%</td>
<td>80–86%</td>
<td>87.5–98%</td>
</tr>
<tr>
<td>Overall efficacy</td>
<td>44–84%</td>
<td>57–89.3%</td>
<td>75–97%</td>
</tr>
<tr>
<td>Follow-up (yrs)</td>
<td>≥5 years</td>
<td>≥5 years</td>
<td>1–3 years</td>
</tr>
<tr>
<td>GERD</td>
<td>2–4%</td>
<td>2–33%</td>
<td>20–54%</td>
</tr>
</tbody>
</table>

AC, achalasia Cardia; GERD, gastroesophageal reflux disease; LHM, laparoscopic Heller's myotomy; POEM, per oral endoscopic myotomy; PD, pneumatic dilatation

**Figs. 4A to D:** Steps of per oral endoscopic myotomy. (A) Mucosal incision, (B) Submucosal tunneling, (C) Myotomy, (D) Closure of mucosal incision
Flowchart 1: Diagnosis and management algorithm for achalasia cardia

Conclusion

Diagnosis of achalasia is based on clinical history and investigations like endoscopy, timed barium esophagogram, and HRM. Treatment of achalasia should be individualized (Table 6) (Flowchart 1). Patients with high surgical risk should undergo BT/pharmacotherapy. For patients with low surgical risk options are PD, LHM with fundoplication, and POEM. In young (<40 years), type I achalasia POEM/LHM should be the first option of treatment as response rates to PD is low. In type II AC, PD can be used as initial option along with POEM/LHM as results to PD is best in type II AC. For type III AC, POEM with extended myotomy is recommended. On failure of therapy, any of the three modalities can be used as salvage therapy but POEM is preferred in both prior endoscopic failure. Esophagectomy should be reserved for end stage AC that is surgically fit with leg standing symptoms after repeated failure of different therapies.

References


Abstract
Non-variceal upper GI bleed could be caused by peptic ulcer disease, Mallory Weiss tear, erosive gastritis/duodenitis, esophagitis, and malignancy. The resuscitation and management go hand in hand. The hematocrit may be initially high due to adjustments in the vascular spaces and the physician should not be misled by it. Gastrointestinal endoscopy has revolutionized both the diagnosis and treatment of non-variceal upper GI bleed. Risk stratification tools enable physicians to assess the risks of mortality and rebleeding.

Introduction
Upper gastrointestinal (GI) bleed with source of bleeding in esophagus, stomach, or proximal duodenum comprises the major cases of non-variceal upper GI bleed of which peptic ulcer disease (related to Helicobacter pylori infection, use of NSAIDs, low dose aspirin) happens to be the most common cause. Despite great advances in the field of medical gastroenterology, the annual incidence remains at around 50–150 per 100,000 population with a mortality of around 10–35%.

The common causes of non-variceal upper GI bleed are peptic ulcer (20–50%), Mallory Weiss tear (15–20%), erosive gastritis/duodenitis (10–15%), esophagitis/esophageal ulcer (5–10%), malignancy (1–2%), angiodysplasias/vascular malformations (5%). Severe GI bleeding is described as GI bleeding that is associated with shock or orthostatic hypotension, decrease in hematocrit by 6% or decrease in hemoglobin by 2 g/dL or transfusion requirement of at least two units of PRBCs. Occult GI bleed describes subacute bleeding that is not clinically visible. Obscure GI bleed refers to a type of bleeding wherein the site of bleed could not be determined after routine upper GI endoscopy, colonoscopy, and even a small bowel radiography.

Initial Assessment
History and Physical Examination: Simultaneous to resuscitation, history taking and initial assessment of the vital signs is done. It is important to ask for history of nasopharyngeal malignancy, hemoptysis, heartburn, alcohol use, use of medicines (NSAIDs, aspirin), dysphagia, excessive vomiting, liver disease, chronic kidney disease. Regarding physical examination, special attention should be paid to signs of hypovolemia like tachycardia, hypotension, orthostatic hypotension along with a close examination of the skin, lips, and buccal mucosa. The abdomen should be examined for tenderness, scar or any lump along with a rectal examination. Signs of chronic liver disease should be specifically looked for as they can help us differentiate variceal from non-variceal bleed.

Laboratory Studies
In addition to routine tests, it is important to do the blood grouping and cross matching of the patient as PRBC transfusion may be needed. The hematocrit of the patient may not reflect the actual amount of blood loss in the immediate period as the vascular space needs time to
adjust to the blood loss and administration of crystalloid intravenous fluid. Special attention should be paid to the mean corpuscular volume (MCV), serum ferritin, total iron binding capacity (TIBC), total leukocyte count (TLC), platelet count, prothrombin time (INR). The blood urea nitrogen (BUN) is usually higher than the serum creatinine in upper GI bleed cases due to intestinal bacteria acting on the blood proteins and increasing absorption of urea. Elderly patients, especially those who are known cases of cardiac ailment, need to have an ECG done.

Management

A case of upper GI bleed necessitates hospital admission, but those patients having mild bleed, being hemodynamically stable, near normal blood tests, with easy access to hospital care may be treated on outpatient basis. On the other hand, those patients who are hemodynamically unstable, have lost a large amount of blood, are having serious associated comorbidities need ICU admission.

Treatment of an upper GI bleed patient should start along with the examination and history taking. Once intravenous access has been established, crystalloids like normal saline are the fluid of choice and attempt should be made to keep the pulse below 100/min and the systolic blood pressure above 100 mm Hg. Blood transfusion with PRBC may be needed to keep Hb >7 g/dL. The hematocrit level should be monitored every 4–8 hours. In cases of severe acute upper GI bleed or in patients with altered mental status, endotracheal intubation may be needed.

The advent of proton pump inhibitors (PPIs) has revolutionized the management of non-variceal upper GI bleed along with availability of endoscopic therapy. But then there are cons of PPIs like no change in blood transfusion requirements and no change in rebleeding rates (except in cases of PUD).3

Role of Endoscopy

GI endoscopy has brought in major advantages in the management of upper GI bleed, be it variceal or non-variceal. Important points to note are:

- Patient must be hemodynamically stable with heart rate of less than 100/min and systolic blood pressure greater than 100 mm Hg.
- There must be no respiratory difficulty, altered sensorium or ongoing hematemesis as these cases might needs endotracheal intubation first.

- Correction of coagulopathy and decreased platelet count is paramount.
- Emergency versus urgent endoscopy—those patients who have active high volume bleed need to undergo emergency endoscopy (within 6 hours) after medical resuscitation and preferably after having access to an ICU bed. Urgent endoscopy (within 12 hours) is suitable for patients who do not have ongoing hemorrhage and are hemodynamically stable.
- Role of gastric lavage in upper GI bleed cases is controversial as some societies do not approve of it. However, in cases with large volume bleeding, careful gastric lavage and prokinetic agents like metoclopramide or erythromycin can help in endoscopic visualization.
- Around 1% of patients may experience complications like aspiration pneumonia, inadvertent bleeding, perforation, hypotension, hypoxia.

Endoscopic techniques of hemostasis have revolutionized the management of upper GI bleed. Amongst these techniques are the contact probes of which the multipolar electrocoagulation probe is the most commonly used. It enables to tamponade a bleeding vessel and then thermal energy is used to seal off the offending vessel. Risks include perforation, coagulation injury. Another useful technique is the use of endoscopic injection therapy mostly done with epinephrine, diluted to a concentration of 1:10,000 or 1:20,000 into or around the site of bleeding. It is easily available, cheap, safe in patients with coagulopathy, less chances of perforation or thermal burns. Then there are the endoscopic hemoclips that apply mechanical pressure to the bleeding site. Hemostatic spray is a kind of inorganic powder with clotting abilities.

Risk Stratification

There are several stratification tools to help patients with non-variceal upper GI bleed. These scores help identify patients with higher risk of mortality and rebleeding.5,6 It enables physicians to assess patients who need higher medical care or urgent endoscopy. Amongst these scores, the pre-endoscopy scores are:

- BLATCHFORD SCORE—includes blood pressure, BUN, hemoglobin, heart rate, syncope, melena, liver disease, heart failure
- CLINICAL ROCKALL SCORE—includes patient’s age, presence of shock, coexisting illnesses
ARTIFICIAL NEURAL NETWORK SCORE—includes 21 variables to predict the presence of stigmata of recent hemorrhage and the need for endoscopic therapy.
- AIMS65—aggregate of five variables like albumin <3 g/dL, INR >1.5, altered mental status, systolic BP ≤90 mm Hg, age >65 years. Amongst the post-endoscopy scores, COMPLETE ROCKALL SCORE is most popularly used. It includes the Clinical Rockall Score and the endoscopic findings. This scoring system correlates well with mortality but not with risk of rebleeding.

**Role of Surgery**

There are some situations where surgery plays an important role in non-variceal upper GI bleed cases:
- Cases of severe and ongoing hemorrhage wherein endoscopy and colonoscopy procedures fail to localize the bleeding site and control it.
- Cases of massive hemorrhage who are hemodynamically unstable need either an urgent angiography or urgent surgical exploration.
- Cases of severe, recurrent obscure GI bleed may benefit from surgical exploration.

**Individual Etiologies**

We shall now address some special issues pertaining to non-variceal upper GI bleed.

**Peptic ulcer:** With the advent of PPIs, it has been observed that worldwide, incidence of bleeding peptic ulcers has decreased whereas, bleeding from ulcers due to intake of NSAIDs, aspirin have gradually increased. However, in the developing countries it has been seen that the prevalence of *H. pylori* infection is nearly 80% whereas, in the developed countries it ranges between 20–50%. Amongst the patients taking NSAIDs gastric ulcers tend to be more common than duodenal ulcers. The Forrest classification is used in cases of bleeding peptic ulcers to categorize the endoscopic findings:
- Forrest 1A—active spurting bleed
- Forrest 1B—oozing bleed
- Forrest 2A—non bleeding visible vessel (NBVV)
- Forrest 2B—adherent clot
- Forrest 2C—flat pigmented spot
- Forrest 3—clean based ulcer

Patients with active arterial, NBVV, adherent clot are at high risk for rebleeding and would benefit from endoscopic therapies. Adherent clot is defined as a blood clot overlying an ulcer that is resistant to several minutes of vigorous jet water irrigation. When a clean based ulcer is found at the time of endoscopy, the chances of rebleeding are less than 5%. However, if it is a clean-based ulcer in the stomach, it is suggested that a biopsy of the ulcer edge and the gastric mucosa should be taken to rule out malignancy. In cases of gastric and duodenal ulcer suspected to be due to *H. pylori* infection, endoscopic mucosal biopsies of the normal looking antrum and greater curvature (midbody) should be taken. The role of PPIs in reducing rebleeding in peptic ulcer cases is more pronounced in people of Asian origin than others. Luminal gastric pH needs to be higher than 6.8 is needed for normal clotting function. H2 receptor antagonists can do this job but tolerance to this drug is the major hindrance. In case of PPIs this problem does not occur, thereby ensuring mortality benefit especially in Asian patients.

Routine second look endoscopy in bleeding peptic ulcers is not always recommended unless the first examination was inadequate due to poor visualization, technical issues with hemostasis or clinically significant rebleeding has occurred. Repeat upper GI endoscopy is advisable in cases of gastric ulcer after 6–10 weeks of acid suppression therapy. Those patients who continue bleeding despite two sessions of endoscopic hemostasis are suitable for angiographic embolization or surgery. Urgent surgery is advisable for those patients who have massive hemorrhage, who cannot be resuscitated. Also, if the endoscopic expertise is not available for treatment of a large or pulsating visible vessel and if on endoscopy, a bleeding malignant ulcerated mass is found, surgery is a more suitable option.

Following endoscopic hemostasis of patients with high-risk endoscopic stigmata (active arterial bleeding/ NBVV/adherent clot), patient should be put on high dose intravenous PPI in a hospital setting. Drugs like NSAIDs, warfarin should be withheld. Those patients who need aspirin for cardiovascular illnesses may be started on the drug by day 7.

It is recommended to test all cases of bleeding due to peptic ulcer disease for *H. pylori* infection. Bleeding can however cause false negative result of *H. pylori*. Antibiotic therapy should be initiated for those found to be positive.
for *H. pylori* infection. It is important to confirm the eradication of *H. pylori* once treatment is completed. In cases of bleeding due to aspirin use, concomitant therapy with a PPI in future can reduce the rebleeding rates significantly. On the other hand, those patients who need to continue NSAIDs long-term, need to opt for selective COX2 inhibitors.

**Esophagitis:** Esophagitis may be caused due to gastroesophageal reflux disease (GERD), infections like Candida, Herpes simplex virus, Cytomegalovirus and also pill induced esophagitis, ultimately leading to upper GI bleed. GERD causing esophagitis and upper GI bleed is treated with a PPI for a period of at least 8–12 weeks along with lifestyle modifications. It is essential that these cases need to undergo a repeat endoscopy and biopsy to rule out Barrett’s esophagus. For all the rest etiologies, endoscopic biopsy/brushing is taken and treatment is done according to etiology.

**Ulcer hemorrhage in hospitalised patients:** There are two types of conditions usually seen in cases presenting with ulcer hemorrhage within the hospital—Stress Related Mucosal Injury/Stress Ulcer (SRMI) and Inpatient Ulcers. SRMI is characterized by diffuse bleeding from erosions and superficial ulcers, usually due to decreased mucosal protection and mucosal ischemia. It is most commonly seen in the stomach, and the most common risk factors are severe coagulopathy and mechanical ventilation for more than 48 hours. Prophylactic treatment with an H2 receptor antagonist or PPI can prevent bleeding in cases who are at high risk for SRMI. In those cases who present with UGI bleed, whether it is due to SRMI or inpatient ulcers, good medical treatment can help heal the lesions. Endoscopic therapy is feasible only in focal inpatient ulcer hemorrhage.

**Dieulafoy’s lesion:** This lesion comprises of a large submucosal artery that protrudes through the mucosa and can cause massive bleeding. Most commonly, such lesions occur in the gastric fundus, within 6 cm of the gastroesophageal junction. Whenever such a lesion is identified and treated endoscopically, it is suggested to mark the site with submucosal injection of ink for future need of easy identification and retreatment.

**Mallory-Weiss tears:** This is characterized by mucosal or submucosal lacerations that start at the gastroesophageal junction and extend to a hiatus hernia sac distally. Usually the patients with Mallory-Weiss tear, present with non-bloody vomiting that is followed by hematemesis, probably due to raised intra-abdominal pressure. This lesion usually self-heals but in cases with severe bleeding, endoscopic hemostasis may be attempted with hemoclips or multipolar electrocoagulation.

**Cameron’s lesion:** This lesion is described as linear erosions or ulcerations in the proximal stomach at the end of a hiatus hernia sac, near the diaphragmatic pinch due to mechanical trauma and local ischemia. It is a common cause of obscure GI bleed. Medical management is done with PPI and iron supplements if needed.

**Neoplastic etiology:** Tumors of the upper GI tract, mostly esophagus, stomach, or duodenum that are large, ulceroproliferative masses can present with upper GI bleed. Endoscopic hemostases is a temporary measure till the definitive management can be initiated. Those tumors that continue to bleed despite endoscopic hemostases need to undergo angiography with embolization. Wherever possible, GIST tumors should undergo resection.

**Gastric antral vascular ectasia (GAVE):** This type of lesion is characterized by rows of ecstatic mucosal blood vessels that start from around the pylorus and extend proximally to the antrum. Also called “Watermelon Stomach,” the exact cause of this lesion is not known, but may be due to mucosal trauma from contraction waves in the antrum. It has been found to be associated with cirrhosis, scleroderma, end stage renal disease. GAVE is targeted with endoscopic hemostatic methods like laser, MPEC, argon plasma coagulation. Besides these, medical management of anemia like iron supplements, blood transfusion may be needed.

**Portal hypertensive gastropathy:** This comprises of ectatic blood vessels in the proximal gastric body, cardia due to increased portal venous pressure and severe mucosal hyperemia. Management options are with beta-blockers, TIPS, liver transplantation. Endoscopic management does not have much role.

**Hemobilia:** Patients of hemobilia present with upper GI bleed and deranged liver function tests. It may occur as a complication in cases of liver biopsy, ERCP, TIPS or those who are suffering from hepatocellular carcinoma or parasitic infection of the hepatobiliary system. Side viewing endoscopy (SVE) is needed for diagnosis and
arterial embolization with arteriography may be used for treatment.

**Hemosuccus pancreaticus:** This kind of lesion is associated with pancreatic pathology or as a complication of ERCP or due to rupture of splenic artery aneurysm into the pancreatic duct. SVE is needed for diagnosis while angiographic embolization or surgery is needed for treatment purposes.

**Aortoenteric fistula:** This is a condition wherein patient presents with acute and massive hemorrhage with very high mortality rates. In some cases, there might be a herald bleed that may precede. Primary aortoenteric fistula is the communication between native abdominal aorta and third part of duodenum. Secondary aortoenteric fistula is a communication between the small intestine (most commonly, third part of duodenum) and an infected abdominal aortic surgical graft. In both the cases, surgery plays the more important role in management, and endoscopic hemostasis has no role.

**Conclusion**

The resuscitation and management of non-variceal upper GI bleed goes hand in hand. Prompt action on the part of the treating physicians as well as timely use of endoscopy for diagnosis and management can help save valuable lives.

**References**

Abstract
Irritable bowel syndrome is a symptom complex resulting from an interplay of various gastrointestinal and extraintestinal factors. Previously thought to have been resulted as a pathology in the gut brain axis, the pathophysiology and management of IBS has been reconditioned recently. The introduction of new diagnostic criteria and concept of multidimensional clinical profile has changed the management of IBS completely. In this chapter we have concised the most updated knowledge on the diagnosis and management of IBS and its various subtypes.

Introduction and Epidemiology
Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder characterized by chronic abdominal pain and altered bowel habits, which are unexplained by any organic cause during routine workup. It is not a disease, but a complex of symptoms arising out of pathologies of diverse clinical significance. IBS is a global problem with prevalence ranging anywhere from 1% to 45% of the general population having symptom complex satisfying the diagnostic criteria of IBS.

More than one third of patients in GI practice have functional GI disorders (FGID) and of all the FGIDs, IBS accounts for the most common diagnosis. The documented prevalence of IBS in Asians ranges from 4% to 9% depending on the criteria used. IBS is twice as prevalent in women as compared to men globally. However, there is no sex predilection in South Asia, South America, and Africa. IBS significantly affects the quality of life and imposes a large burden to the patient and the health-care system.

Rome IV Criteria for Diagnosis of IBS: Something New Something Borrowed
Manning and Thompson in 1978 introduced the concept of making positive diagnosis of IBS using a set of criteria, which led to an exemplar shift in the diagnostic approach in patients with IBS.

This was followed by Rome I, Rome II, and Rome III criteria pertaining to the origin of newer scientific evidences.

The Asian consensus was published in 2010 considering the differences in dietary habits and stool frequency patterns in Asians, which was different from the criteria used to define stool frequency and stool form as they were based on the Western studies.

Rome IV criteria were published in 2016, a decade after Rome III was introduced. Rome IV criteria emphasized on the gut brain interaction rather than the older concept of psychogenic predominant pathogenesis of IBS.

As per the Rome IV criteria IBS is defined as—Recurrent abdominal pain on average at least 1 day/week in the last 2 years associated with two or more of the following: alteration of defecation, abdominal bloating, and discomfort (pain or distention) in the absence of other organic disease.
Recent Updates in Management of IBS

In context to Asian population, a Chinese study compared the diagnosis of IBS using the Rome III criteria as well as Rome IV criteria and showed lower sensitivity of Rome IV as compared to Rome III in Asian population and concluded that Rome IV positive patients were subgroup of Rome III with more severe manifestations of the disease.15

Rome IV also recognizes overlap syndrome amongst various FGIDs as observed in various studies.16-18 This is an important step based on scientific evidence as it will help the clinicians to diagnose and manage such patients.

In 2019, Second Asian consensus on IBS19 was published representing the current knowledge and management protocols in context to Asian population. The consensus emphasized that IBS is a disorder of Gut brain interaction rather than predominantly the psychopathological phenomenon. The consensus also encouraged the treatment based on micro-organic pathology.

Subtyping and Assessing the Severity of IBS: The Concept of Multidimensional Clinical Profile

The concept of multidimensional clinical profile was introduced to categorize patients on the basis of the severity of their symptoms along with psychological evaluation and physiological dysfunction (Table 1). This helps the physicians to address other issues apart from only the categorical diagnosis.

Severity assessment helps physicians to rationally approach any patient, and necessitate the aggressive management of patients with severe symptoms. Various scales have been used to assess the severity of IBS, but none have been accepted till date.

Multidimensional clinical profile also emphasizes on the micro-organic basis of IBS such as abnormal gut transit, post-infectious IBS, low-grade inflammation, gut dysbiosis, dietary intolerance, abnormal intestinal permeability, and central as well as peripheral nervous dysregulation (Flowchart 1).

Subtyping of IBS is essential as it helps in defining the targeted therapy and those with mixed type and unclassified types need modifications of the pathophysiological process such as alteration of Gut microbiota or neurohumoral regulation.
### TABLE 1
Severity assessment of IBS patients on the MDCP model

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychometric correlate</td>
<td>FBDSI, &lt;36 IBS-SSS, 75–175</td>
<td>FBDSI, 36–109 IBS-SSS, 175–300</td>
<td>FBDSI, &gt;110 IBS-SSS, &gt;300</td>
</tr>
<tr>
<td>Physiological factors</td>
<td>Primarily bowel dysfunction</td>
<td>Bowel dysfunction and CNS pain dysregulation</td>
<td>Primarily CNS pain dysregulation</td>
</tr>
<tr>
<td>Psychosocial difficulties</td>
<td>None or mild psychosocial distress</td>
<td>Moderate psychosocial distress</td>
<td>High psychosocial distress, catastrophizing, abuse history</td>
</tr>
<tr>
<td>Sex</td>
<td>Men = women</td>
<td>Women &gt; men</td>
<td>Women &gt;&gt;&gt; men</td>
</tr>
<tr>
<td>Age</td>
<td>Older &gt; younger</td>
<td>Older = younger</td>
<td>Younger &gt; older</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Mild/intermittent</td>
<td>Moderate, frequent</td>
<td>Severe/very frequent or constant</td>
</tr>
<tr>
<td>Number of other symptoms</td>
<td>Low (1–3)</td>
<td>Medium (4–6)</td>
<td>High (≥7)</td>
</tr>
<tr>
<td>Health-related quality of life</td>
<td>Good</td>
<td>Fair</td>
<td>Poor</td>
</tr>
<tr>
<td>Health-care use</td>
<td>0–1/yr</td>
<td>2–4/yr</td>
<td>≥5/yr</td>
</tr>
<tr>
<td>Activity restriction</td>
<td>Occasional (0–15 days)</td>
<td>More often (15–50 days)</td>
<td>Frequent/constant (&gt;50 days)</td>
</tr>
<tr>
<td>Work disability</td>
<td>&lt;5%</td>
<td>6–10%</td>
<td>≥11%</td>
</tr>
</tbody>
</table>

IBS, irritable bowel syndrome; IBS-C, constipation-predominant IBS; IBS-D, diarrhea-predominant IBS; IBS-M, mixed IBS; FODMAP, fermentable oligo-, di-, monosaccharides, and polyols.

### Multidimensional Clinical Profile of Irritable Bowel Syndrome

- Categorical diagnosis (symptom-based criteria)
- Clinical modifier (IBS-C, IBS-D, IBS-M, post-infectious, FODMAP sensitive)
- Impact (mild, moderate, severe)
- Psychosocial modifier
- Physiological dysfunction and biomarkers

### Treatment

An incorporative approach including patient education, cognitive behavioral therapy, diet, and lifestyle modification are required for the management of IBS.

This usually needs an involvement of the dietician and a clinical psychologist.

A step up approach depending on the severity of the predominant symptom and the multi-disciplinary clinical profile is helpful in guiding the treatment (Table 2).

The current first-line therapies are directed toward individual symptoms; however, the newer therapies are based on altering the micro-organic pathophysiology.
Newer Therapies for IBS

Lumen Directed Therapy: Targeting the Low Grade Inflammation Dysbiosis and Intestinal Permeability

Nonabsorbable Antibiotics

Multiple case control studies from around the globe have inferred microbial dysbiosis in patients with IBS. Thus, use of non-absorbable antibiotics for management of IBS was suggested.

Neomycin was initially used in patients with IBS; however, the use was limited due to adverse effects.

Rifaximin was tested initially in small scale trials in patients with IBS. Subsequently, in a large randomized trial, positive effects were found in 8–10% patients of IBS who did not have constipation. This effect was present during the 10 weeks of follow-up; however, the effect gradually decreased thereafter. Therefore in another retreatment trial repeat administration of rifaximin was assessed and it was found that retreatment was efficacious as in naïve patients without the concern of antibiotic resistance.

Rifaximin has pleiotropic effects on the gut apart from managing the gut dysbiosis. Variable effects include anti-inflammatory effects, restoring the gut barrier function...
and effects on visceral hyperalgesia through unknown mechanisms.

**Pre-Probiotics and Synbiotics**

Probiotics are live microorganisms, which when consumed in prescribed amounts confer multiple health benefits. The available data exhibit an overall positive effect of pre-probiotics on the symptoms of IBS; however, comparative analysis of the bacterial species is lacking.

Probiotics affect the luminal dysbiosis, low grade inflammation, and helps restoring the mucosal integrity in patients with IBS. Apart from the direct effects, probiotics also indirectly modulate the gut-brain interaction.

Synbiotics are combinations of pre- and probiotics with synergistic actions. Synbiotics are hypothesized to be beneficial in IBS; however, results are inconsistent and data is sparse.

**Fecal Microbiota Transplant (FMT)**

Alteration in gut microbiota is one of the proposed mechanisms in the pathogenesis of IBS. Fecal microbiota has been efficacious in treating patients with pseudomembranous colitis with great success. Hence, its role in other luminal as well as non-luminal disorders has been hypothesized. So far many small case series and randomized trials have been published and have assessed IBS severity score as the outcome measure. However, the results were conflicting.

Sahly et al. in 2020 published a double blind randomized controlled trial assessing the efficacy of single donor FMT in 30 gm and 60 gm doses as compared to placebo and found significant response (89.1% vs. 23.6% p<0.0001) in reduction in IBS symptoms. However, mild self limiting GI symptoms after FMT need a word of caution.

**Mast Cell Stabilizer and Other Anti-inflammatory Drugs**

Low grade inflammation in the gut as well as presence of inflammatory cells especially lymphocytes and mast cells have been found in patients with IBS and are considered as one of the microbiologic change.

Mesalazine, used as an anti-inflammatory drug in IBD was found to have no role in patients with IBS.

Mast cells being predominant inflammatory cells are one of the targets for recent therapies of IBS. Mast cells are also involved in pathogenesis of visceral hypersensitivity in patients with IBS. Mast cell stabilizer ketotifen was found to increase the discomfort threshold to rectal distension in patients with IBS and had significant effects on abdominal pain and QOL. This effects was hypothesized due to H1 receptor antagonism of ketotifen, which is a secondary action. Another H1 receptor antagonist, Ebastine, was also found to significantly decrease abdominal pain over a 12-week treatment period.

**Dietary Modifications**

Worsening of symptoms has been reported by many patients after ingestion of certain foods. It has been postulated that food acts through various mechanisms including osmotic, chemical, mechanical and neuroendocrine effects. These pathologic mechanisms can potentiate the already present microbiologic pathology present in the gut. It has also been found that food material containing incompletely digestible carbohydrates, fats, and high caloric diet are incompletely absorbed in the small intestine and are a cause of significant bloating and abdominal discomfort due to fermentation by the gut microbiota. Thus, current recommendations evaluate patients after modifying intake of such food as well as alcohol, caffeine, milk, or any lactulose containing diet.

If these recommendations are cashed on improving symptoms the FODMAP diet eliminating foods containing fermentable oligosaccharides, disaccharides, monosaccharides, and polyols are advised.

Food eliminating Gluten has also been advocated in non-celiac IBS patients on the basis of evidence of decrease in intestinal inflammation and mucosal injury on gluten free diet.

**Therapeutic Updates on Constipation**

**Predominant IBS**

**Guanylate Cyclase C Agonist**

The stimulation of enterocyte guanylate cyclase c (GCC) receptors activates the apical CFTR that leads to water secretion by the gut mucosa. *Linaclotide* is an orally administered 14 amino acid containing peptide that acts as an agonist of GCC. In a dose dependent manner linaclotide softens the stools and also improves symptoms of abdominal pain, bloating, and discomfort.
290 µg daily was shown to improve stool frequency and ease of defecation.37,38 The most common side effect is diarrhea, which can be managed by reducing the dose. Plecanatide is another 16 amino acid GCC agonist approved for management of chronic constipation and recently FDA approved for IBS-C.

**Lubiprostone**

It is a fat soluble molecule that activates type 2 chloride channels in the enterocytes releasing more water into the intestinal lumen increasing water content of the stool. At a dose of 8 µg twice daily lubiprostone has shown efficacy in reduction of symptoms and stool consistency.39 Most common side effects are nausea and diarrhea.

**5-HT4 Agonists**

Activation of 5-HT, enhances the gut motility by amplifying the release of acetylcholine from nerve endings.

5-HT4 agonist Tegaserod was shown to be efficacious in management of IBS-c; however, it was withdrawn owing to potential cardiovascular risks.40,41 A novel 5-HT4 receptor agonist Prucalopride has been approved for treatment of chronic constipation and has been evaluated in IBS-C considering the anecdotal reports of improvement in bloating, abdominal pain, and discomfort in the trials for constipation.42

**Ghrelin Receptor Agonists**

Ghrelin is a gut hormone involved in appetite control and gut motility in upper as well as lower GI tract. Relamorelin is a novel injectable ghrelin receptor agonist studied as a motility amplifier in patients with diabetic gastroparesis.43 It has also been evaluated in women with chronic constipation and has been found to improve gastric emptying rate and stool frequency but had no effect on stool consistency. Further studies are warranted in patients with IBS-C.

---

**Fig. 1:** Low foodmap diet

<table>
<thead>
<tr>
<th>Food</th>
<th>Eat</th>
<th>Avoid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vegetables</strong></td>
<td>Lettuce, Carrot, Cucumber</td>
<td>Garlic, Beans, Onion</td>
</tr>
<tr>
<td></td>
<td>and more</td>
<td>and more</td>
</tr>
<tr>
<td><strong>Fruits</strong></td>
<td>Strawberries, Pineapple</td>
<td>Blackberries, Watermelon</td>
</tr>
<tr>
<td></td>
<td>Grapes and more</td>
<td>Peaches and more</td>
</tr>
<tr>
<td><strong>Proteins</strong></td>
<td>Chicken, Eggs, Tofu</td>
<td>Sausages, Battered Fish,</td>
</tr>
<tr>
<td></td>
<td>and more</td>
<td>Breaded meats and more</td>
</tr>
<tr>
<td><strong>Fats</strong></td>
<td>Oils, Butter, Peanuts</td>
<td>Almonds, Avocado, Pistachios</td>
</tr>
<tr>
<td></td>
<td>and more</td>
<td>and more</td>
</tr>
<tr>
<td><strong>Starches, cereals and grains</strong></td>
<td>Potatoes, Tortilla chips,</td>
<td>Beans, Gluten-based bread,</td>
</tr>
<tr>
<td></td>
<td>Popcorn and more</td>
<td>Muffins and more</td>
</tr>
</tbody>
</table>
**Tenapanor**
Small molecule inhibitor of GI \( \text{N}^+/\text{H}^+ \) exchanger isoform 3, tenapanor increases water secretion in the gut improving global symptoms of IBS-C. At a dose of 50 mg BD, tenapanor offers a newer mode of treatment in this class.\(^{44}\)

**Therapeutic Updates on Diarrhea**

**Predominant IBS**

**Eluxadoline**
This is a novel mixed \( \mu \) opioid receptor and \( \kappa \) receptor agonist and \( \delta \) agonist evaluated for treatment of IBS-D. It was studied in a dose of 75 mg and 100 mg per day for 26–52 weeks.\(^{45}\) Eluxadoline helps improve overall symptoms and particularly stool consistency and frequency.

However, pertaining to risk of pancreatitis due to sphincter of Oddi dysfunction it should not be used in patients with history of pancreatitis, SOD or alcohol abuse or any liver dysfunction.

**5-HT3 Antagonists**
Serotonin modulates the gut motility and sensitivity through a variety of receptors. Alosetron is a 5-HT\(_3\) antagonist found to be efficacious in treatment of IBS-D.\(^ {46}\) However, this drug was associated with risk of ischemic colitis and severe constipation.

Ramosteron is a novel 5-HT\(_3\) antagonist\(^ {47}\) found to be effective in improving global symptoms of IBS-D including pain scores, which were not improved by Ondansetron when compared for management of IBS-D.

**Drugs Acting on Bile Acids**
Bile acids are known to be important in stimulating secretion in the bowel and enhance gut motility that are relevant in causing diarrhea. Several studies have revealed the increase bile acid loss as a cause of IBS-D.\(^ {48}\) FGF19 is produced from the ileum that acts as an important factor in regulating bile acid synthesis in the liver. In bile acid diarrhea there is reduced feedback inhibition by FGF19. Cholestyramine is most commonly used bile acid sequestrant along with newer agents like colestipol and colesevelam.\(^ {49}\)

Farnesoid X activated receptor is also involved in inhibition of bile acid synthesis in liver by various mechanisms. Obeticholic acid is one of the various FXR receptor agonists that has been found to reduce bile acid synthesis and improve secondary bile acid diarrhea.\(^ {50}\)

**Modulating the Central Pain Mechanism**

**IBStim Device: The Cranial Nerve Stimulator (Fig. 2)**
Recently approved for use in patients for modulating abdominal pain in IBS patients, this device is approved for adolescents of age group 11–18 years. It modulates the pain pathways in the CNS by low frequency electrical stimulation of peripheral cranial nerves. It is single use device and works for 5 days.\(^ {53}\)

**Conclusion**

IBS is chronic relapsing remitting functional GI disorder. With enhanced understanding of the micro-organic basis of the disorder newer therapies are directed at modifying the pathology of the disease rather than the individual symptoms. It is however very necessary to clinically diagnose the patient with respect to the recent diagnostic criteria and order important battery of investigations for making a positive diagnosis of IBS.
References


Occult gastrointestinal bleeding signifies bleeding from the gastrointestinal tract that often goes unrecognized by the patient. It usually manifests as positive fecal occult blood test, or if continues for a long period of time, it may progress to iron deficiency anemia. A thorough evaluation of gastrointestinal tract including esophago-gastro-duodenoscopy and colonoscopy clinches the diagnosis in most of the cases. Recently, introduction of capsule endoscopy and balloon enteroscopy have made a major impact by identifying small bowel causes of bleeding. The primary concern is to rule out malignant causes, particularly in elderly. For patients with no identifiable pathology, long-term prognosis appears favorable with oral supplement of iron.

**Introduction**

Gastrointestinal (GI) bleeding can have a multitude of clinical presentation. The bleeding may be mild, moderate, or severe depending on the severity or rapidity of bleeding. Patient may present with clinically obvious symptoms of hematemesis, melaena, hematochezia, or, in some cases, fresh bleeding per rectum. Furthermore, bleeding may be hidden with patient totally unaware of its existence. This review will focus on this later type of bleeding called occult GI bleeding.

**Occult** GI bleeding is defined as bleeding that is unknown to the patient, and includes patients with positive fecal occult blood test (FOBT) and/or iron deficiency anemia (IDA). On the other hand, **obscure** GI bleeding is that which is evident to the patient but is from a source that is not readily identifiable by routine esophagogastrroduodenoscopy (EGD) and/or colonoscopy.

**Causes**

Any lesion presents anywhere in the GI tract may present with occult GI bleeding. In a review of five prospective studies on patients with occult GI bleeding, majority was found to have upper GI source (29–56%) followed colorectal source (20–30%). Surprisingly, synchronous lesions were found in up to 17% cases. All these studies used only OGD and colonoscopy, and hence, no source was identified in 29–52% cases. **Table 1** shows the potential causes of Occult GI bleeding.

**History and Physical Examination**

A detail history and targeted physical examination should form the basis of clinical evaluation. Abdominal pain with aspirin or other non-steroidal anti-inflammatory drug use suggests ulcerative mucosal injury. Unintentional weight loss suggests a malignancy. A past history of GI bleeding or abdominal surgery may give important diagnostic clues. Initiation of anticoagulants or antiplatelet medications in the preceding weeks may precipitate bleeding in an undiagnosed lesion. A family history of GI bleeding may suggest hereditary hemorrhagic telangiectasia (associated with vascular lesions on the lips, tongue, or palms) or blue rubber bleb nevus syndrome (a syndrome with venous
malformations in the GI tract, soft tissues, and skin). A history of gastric bypass surgery may suggest impaired iron absorption. Examination of skin may indicate the presence of an underlying condition like dermatitis herpetiformis (in celiac disease); erythema nodosum (in Crohn disease); an atrophic tongue and brittle, spoon-shaped nails (Plummer-Vinson syndrome); and freckles on the lips and in the mouth (Peutz-Jeghers syndrome).  

Stigmata of chronic liver disease may suggest bleeding due to portal hypertension. Anemia may be obvious on clinical examination. Palpable hard nodular liver or palpable abdominal lump may be signs of underlying advanced disease.

**Diagnostic Studies**

The choice of diagnostic modality should depend on clinical suspicion of potential site and probable cause of underlying disease, and any associated symptoms. Upper GI bleeding from lesions up to the second part of duodenum can be detected by EGD. Classically, small bowel bleedings are evaluated by enteroscopy. Older methods like Push enteroscopy reach only the proximal small intestine. However, bleeding sources in mid and distal small bowel need evaluation with wireless capsule endoscopy (WCE), deep enteroscopy, and computed tomography (CT) or magnetic resonance (MR) enterography. Lower GI bleeding (colonic and terminal ileal source) can be detected with colonoscopy. Laparotomy with intraoperative enteroscopy remains an option for those rare patients who have recurrent bleeding from a source not yet identified with the previously mentioned methods. Small bowel barium studies have a very low diagnostic yield and been largely replaced by capsule endoscopy. EGD and colonoscopy will find the bleeding source in 48–71% of patients. In patients with recurrent bleeding, repeat EGD and colonoscopy may find missed lesions in up to 35% of those who had negative initial findings. If a cause is not found after EGD and colonoscopy had been performed, capsule endoscopy has a diagnostic yield of 63–74%.

**Capsule Endoscopy and Different Methods of Enteroscopy**

These tools are particularly useful for establishing the source of bleeding in small intestine—a notoriously difficult site to examine with other methods.

Capsules used for endoscopy contain light-emitting diodes, a lens, a camera, batteries, and a radiofrequency transmitter. Captured images are transmitted to a data recording device worn by the patient, downloaded to a computer workstation, where the images are analyzed. The capsule is disposable and, because of its small size, readily passes through the GI tract. Capsule retention is a potential complication but, fortunately, occurs in less than 1%.

Push enteroscopy consists of per oral insertion of a specialized, long, flexible tube up to 50–60 cm beyond the ligament of Treitz. This allows thorough examination of the distal duodenum and proximal jejunum, and biopsies can be taken if needed. It is rarely practiced nowadays. Deep enteroscopy has been a major advance in the evaluation of the small bowel as it offers scope for therapy and tissue biopsy, though multiple sessions may be needed for complete examination. There are several forms of deep enteroscopy, including double-balloon enteroscopy (DBE), single-balloon enteroscopy (SBE), and spiral

---

**TABLES 1** Causes of occult gastrointestinal bleeding

<table>
<thead>
<tr>
<th>Mass lesions</th>
<th>Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma (common)</td>
<td>Erosive esophagitis (common)</td>
</tr>
<tr>
<td>Adenoma (usually &gt; 1.5 cm)</td>
<td>Ulcer (any site, including peptic ulcer, common)</td>
</tr>
<tr>
<td></td>
<td>Cameron lesions</td>
</tr>
<tr>
<td></td>
<td>Erosive gastritis</td>
</tr>
<tr>
<td></td>
<td>Celiac disease</td>
</tr>
<tr>
<td></td>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td></td>
<td>Crohn’s disease</td>
</tr>
<tr>
<td></td>
<td>Colitis (non-specific)</td>
</tr>
<tr>
<td></td>
<td>Idiopathic cecal ulcer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular</th>
<th>Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular ectasia (common)</td>
<td>Hookworm</td>
</tr>
<tr>
<td>Varices (any site, rare)</td>
<td>Whipworm</td>
</tr>
<tr>
<td>Portal hypertensive gastropathy (PHG) (common)</td>
<td>Strongyloidiasis</td>
</tr>
<tr>
<td>Portal colopathy</td>
<td>Ascariasis</td>
</tr>
<tr>
<td>Gastric antral vascular ectasia (GAVE)</td>
<td>Tubercular enterocolitis</td>
</tr>
<tr>
<td>Dieulafoy’s ulcer (rare)</td>
<td>Amebiasis</td>
</tr>
<tr>
<td>Hemosuccus pancreaticus (rare)</td>
<td></td>
</tr>
<tr>
<td>Hemobilia (rare)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-distance running</td>
<td></td>
</tr>
<tr>
<td>Factitious</td>
<td></td>
</tr>
</tbody>
</table>
Evaluation of Occult GI Bleed

The principle of enteroscopy (SPIRUS) involves the use of an endoscope and an overtube, although procedures are emerging that may not require an overtube. Initially scopes are inserted as deep as possible; careful withdrawal of the scope then allows evaluation of the entire small bowel. With DBE, balloons are used to grip the intestine while inserting the endoscope. By inflating the overtube balloon enough to grip the intestinal wall, the endoscope can be inserted further without forming redundant loops in the small intestine and then the overtube can in turn be inserted while the endoscope balloon is inflated. The single balloon technique in theory is technically simpler than DBE. Spiral enteroscopy uses a special overtube with raised helices at the distal end, and clockwise rotation of the overtube pleats the small bowel onto the overtube and prevents looping. Data to date suggest that DBE allows greater depth of insertion than the other two.

Evaluation

There are two different clinical presentations of occult GI bleed:

- Positive FOBT without iron deficiency anemia
- Iron deficiency anemia with or without a positive FOBT

Positive FOBT without Iron Deficiency Anemia

Normal fecal blood loss varies from 0.5 to 1.5 mL/day. However, loss of up to 100 mL of blood per day may not cause any visible change in the color of the stool. FOBT, usually classic guaiac-based tests, is often used in day-to-day clinical practice by physicians. Other types of FOBT like fecal immunochemical tests and the heme porphyrin test are not available in India. The likelihood of positive test depends not only on the sensitivity of a particular test but also on the frequency and rate at which the causative lesion bleeds, bowel motility, and the anatomic site of the bleed. Guaiac-based tests are best at detecting blood from the lower rather than the upper GIT as the pseudoperoxidase activity of heme, detected by guaiac-based tests, is continuously degraded as it moves down the GIT.

Oral iron therapy is commonly believed to cause positive guaiac tests, but prospective studies have proven this belief to be wrong. Finally, bismuth (found in certain antacids and antidiarrheal drugs) makes the stool dark and even black in appearance, but does not cause a blue guaiac reaction and should not be mistaken for blood.

Flowchart 1 illustrates the approach proposed by the American Gastroenterological Association (AGA) for patients with positive FOBT. Colonoscopy is preferred because of its high sensitivity for detecting colonic mucosal lesions, and its intervention capabilities with biopsy, polypectomy, and treatment of bleeding lesions. Barium studies have lower sensitivity than colonoscopy and are generally not recommended. CT colonography may be an alternative to colonoscopy, if bowel preparation is a problem. However, it does not have therapeutic capabilities.
Identification of an abnormality consistent with the magnitude of bleeding makes further workup after colonoscopy unnecessary. If colonoscopy is negative, further studies are not required in the asymptomatic patient unless anemia develops. Exceptions are patients with upper GI symptoms, in whom EGD should be performed along with colonoscopy.

Fecal blood content in therapeutically anticoagulated patients is usually within normal limits. Hence, a positive FOBT should not be attributed to low-dose aspirin or anticoagulation, and as such, will require at least endoscopic evaluation.

Iron Deficiency Anemia with or without a Positive FOBT

Worldwide IDA is the most common cause of anemia. Under normal circumstances, iron balance is tightly regulated at the level of intestinal mucosa. Average daily loss of iron is 1 mg coming from microscopic GI bleeding and sloughed intestinal cells. In India, more than 50% of population is iron-deficient.

The approach recommended by AGA for evaluation of patients who have IDA with or without a positive FOBT has been illustrated in Flowchart 2. Men and postmenopausal women with IDA are assumed to have GI blood loss, unless proved otherwise. However, premenopausal women who have IDA that cannot be explained by heavy menses, or those who have GI symptoms, should be evaluated for a GI cause.

Endoscopic evaluation should start with EGD and colonoscopy. During EGD, biopsies should be taken from duodenal mucosa to look for celiac disease, an often ignored cause of IDA. If EGD and colonoscopy are normal, they are called obscure occult GI bleed.

Figs. 2A to C: Different types of deep enteroscopy: (A) Double-balloon enteroscopy; (B) Single-balloon enteroscopy; (C) Spiral overtube enteroscopy
The prevalent expert opinion suggests that they should undergo repeat upper endoscopy and colonoscopy, at least once. If these repeat studies are negative, capsule endoscopy should be the next investigative procedure with a focus on small bowel.

Whenever capsule endoscopy identifies a lesion on small bowel, further course of action depends on the nature of the lesion.

- If the identified lesion needs a tissue diagnosis or if the lesion requires endotherapy (like endoscopic hemostasis, endoluminal ablation, resection, or dilatation), balloon enteroscopy should be performed. The choice of route of balloon enteroscope insertion (either antegrade, i.e., orally or retrograde, i.e., inserted anally) will depend on the estimated site of lesion as observed on running the capsule endoscopy video.

- If capsule endoscopy shows a lesion that can be managed medically or that requires surgery, balloon enteroscopy is not justified.

If capsule endoscopy fails to identify a lesion, it may be repeated on another occasion (second-look capsule endoscopy). Alternatively, CT or MR enterography may be considered.

Sometimes, CT or MR enterography are performed before capsule endoscopy to check for luminal patency sufficient to allow unobstructed passage of the capsule.20

Surprisingly, in some cases, the diagnosis may be obvious on CT or MR precluding the need for capsule endoscopy. Radioisotope scan using radioactive technetium bound red blood cells (RBCs) are not favored due to significant radiation exposure, imprecise localization, and lack of therapeutic potential.21 Angiography and guided
intervention is reserved for acute brisk bleeding that do not fall in the category of occult GIB or IDA.20,22

A small percentage of cases may not have any lesion identified even after exhaustive evaluation. In them, covert non-GI blood loss should be considered. Also, the diagnosis and type of anemia need to be rechecked by a hematologist.1

Treatment
Essentially, the treatment should focus on the underlying cause of occult bleeding. Anemia is treated with oral ferrous sulfate in a dose of 325 mg twice or thrice daily. Ferrous fumarate or gluconate is acceptable alternative to ferrous sulfate in a dose of 325 mg twice or thrice daily.

The later often offers scope for curative intervention. The diagnosis and type of anemia needs to be rechecked by a hematologist.1 The later often offers scope for curative intervention. The outcome of therapy depends on identification of a specific bleeding lesion, severity of bleeding, and, finally, access to advanced diagnostic/therapeutic modalities.

Conclusion
A multitude of diseases of GIT can present as occult GI bleed, manifesting as a positive FOBT or IDA. Majority of these bleeds are caused by ulcerative diseases of the upper GIT while malignancy is rare. Routine endoscopy (UGI endoscopy and colonoscopy) is the first step in evaluation of these patients. Some patients have common lesions but with an unusual or atypical appearance; others may harbor rare/uncommon diseases. Capsule endoscopy and deep (often balloon-assisted) enteroscopy are useful to identify the diseases of small bowel. The later often offers scope for curative intervention. The outcome of therapy depends on identification of a specific bleeding lesion, severity of bleeding, and, finally, access to advanced diagnostic/therapeutic modalities.

References
Abstract
Endoscopic ultrasound (EUS) is a relatively new innovation in the field of gastrointestinal (GI) endoscopy that combines the endoscope and ultrasound transducer for examining the GI tract wall and structures beyond. The ability to place the ultrasound transducer very close to the structures/organs being evaluated allows use of high frequencies that provide very high resolution images. EUS is used for both diagnostic as well as therapeutic purposes. The diagnostic indications can be either for primary diagnosis where EUS is used as a primary diagnostic modality for diagnosing diseases like evaluation of idiopathic acute pancreatitis as well as diagnosis of chronic pancreatitis or as a secondary diagnostic modality for detailed evaluation of already diagnosed disease like submucosal lesions, dilated bile duct, and pancreatic cystic lesions or EUS guided FNA of GI as well as surrounding structures like lymph nodes or locoregional staging of GI cancers. Therapeutic EUS has phenomenally expanded in last one decade and a number of procedures like pseudocyst/walled off necrosis drainage, celiac plexus blockade/neurolysis, intra-abdominal abscess drainage, mediastinal abscess drainage, vascular interventions, intratumoral therapy, and biliary as well as pancreatic drainage can be safely done under EUS guidance. Development of newer technologies like EUS elastography and contrast EUS is going to further expand the role of EUS. It is important for an internist to be aware of the indications and strengths of EUS in various abdominal, thoracic as well as pelvic diseases.

Introduction
Endoscopic ultrasound (EUS) is a relatively new innovation in the field of gastrointestinal (GI) endoscopy that combines the endoscope (for visualizing the mucosa of the GI lumen) and ultrasound transducer for examining the GI tract wall and structures beyond. The desire to see the structures beyond the GI lumen led on to development of EUS. Over last three decades, EUS has evolved tremendously from a research tool to important investigational tool in routine clinical practice. The ability to place the ultrasound transducer very close to the structures/organs being evaluated allows use of high frequencies that provide very high resolution images. These images are much better than those obtained by transabdominal ultrasound as well as other cross-sectional imaging techniques. Therefore, there has been gradual expansion in its clinical indications and it has evolved from a purely diagnostic modality to an important therapeutic tool. Its advent has made the locoregional staging of many GI cancers accurate and also made a number of GI therapeutic procedures safer. The advent of EUS guided fine needle aspiration (FNA) has made it the procedure of choice for tissue diagnosis of various benign as well as malignant GI lesions. It has changed the daily clinical practice of not only gastroenterologists, but also surgical gastroenterologists, oncologists, pulmonologists, radiologists, as well as internists. Therefore, it is very important for an internist to be aware of the current
indications, strengths as well as limitations of EUS. This review discusses in brief the diagnostic and therapeutic indications of EUS.

**Types of EUS Scopes**

Broadly, there are two types of EUS scopes (echoendoscopes). The first developed echoendoscope was a radial echoendoscope with a 360-degree transducer that has a scanning plane of ultrasound perpendicular to the long axis of the echoendoscope. This is a purely diagnostic echoendoscope and no intervention or FNA can be done with this scope. To overcome this limitation, linear echoendoscopes were developed in which the scanning plane of transducer is parallel to the long axis of the echoendoscope so that the entire needle can be seen in real time during FNA/interventions.3

Apart from these two commonly echoendoscopes, a new echoendoscope has recently been developed. The forward viewing echoendoscope has a forward endoscopic view instead of oblique endoscopic view of linear echoendoscope and has a shorter and more flexible tip. Therefore, it is more easily maneuverable and can be used instead of oblique viewing echoendoscope in difficult anatomical situations. However, absence of elevator at the tip of echoendoscope makes the interventions difficult with this scope. Therefore, this scope is usually used in those situations where linear echoendoscope cannot be used because of anatomical constraints.

**Indications of EUS**

The clinical indications for EUS can be divided into two broad categories: diagnostic and therapeutic (Table 1). The diagnostic indications can be either for primary diagnosis where EUS is used as a primary diagnostic modality for diagnosing diseases like evaluation of idiopathic acute pancreatitis as well as diagnosis of chronic pancreatitis or as a secondary diagnostic modality for detailed evaluation of already diagnosed disease like submucosal lesions (SMLs), dilated bile duct and pancreatic cystic lesions (PCL) or EUS guided FNA of GI as well as surrounding structures like lymph nodes or locoregional staging of GI cancers.

Therapeutic EUS has phenomenally expanded in last one decade and a number of procedures like pseudocyst/walled off necrosis drainage, celiac plexus blockade/neurolysis, intra-abdominal abscess drainage, mediastinal abscess drainage, vascular interventions, intratumoral therapy and biliary as well as pancreatic drainage can be safely done under EUS guidance.

**EUS as a Primary Diagnostic Modality**

**Idiopathic Acute Pancreatitis**

EUS provides high-resolution images of pancreas and biliary tract, and therefore is an important investigation for evaluation of patients with idiopathic acute pancreatitis. It is an excellent modality for diagnosis of occult cholelithiasis or choledocholithiasis, microlithiasis, or gallbladder sludge (Fig. 1), pancreatic duct anomalies like pancreas divisum, occult pancreatic neoplasm and importantly, exclude chronic pancreatitis.4 Studies have shown that EUS is a useful and minimally invasive tool for the diagnostic evaluation of idiopathic pancreatitis and in case of negative EUS examination relapses of pancreatitis are infrequent.5,6 EUS may also help in

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Indications for EUS</th>
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<tr>
<td><strong>Primary diagnostic modality</strong></td>
<td><strong>Secondary diagnostic modality</strong></td>
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<tr>
<td>- Idiopathic acute pancreatitis</td>
<td>- Dilated common bile duct</td>
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<tr>
<td>- Diagnosis of chronic pancreatitis especially early chronic pancreatitis</td>
<td>- Pancreatic cystic lesions</td>
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<td></td>
<td>- GI submucosal lesions</td>
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<td>- Locoregional staging of GI cancers</td>
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<td></td>
<td>- EUS guided fine needle aspiration or biopsy</td>
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<td></td>
<td>- EUS guided aspiration of minimal pleural effusion/ascites</td>
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<tr>
<td><strong>Therapeutic EUS</strong></td>
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<tr>
<td>- Drainage of pancreatic fluid collections</td>
<td>- Biliary and pancreatic duct drainage in cases of failed ERCP</td>
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<tr>
<td>- Biliary and pancreatic duct drainage in cases of failed ERCP</td>
<td>- Transmural gallbladder drainage</td>
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<tr>
<td>- Transmural gallbladder drainage</td>
<td>- EUS-guided celiac plexus neurolysis/blockade</td>
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<tr>
<td></td>
<td>- Drainage of mediastinal and intra-abdominal abscesses and collections</td>
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<td></td>
<td>- EUS-guided vascular interventions</td>
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<td></td>
<td>- EUS-guided palliative oncological interventions</td>
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<td></td>
<td>- EUS-guided gastrojejunostomy</td>
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</table>

ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; GI, gastrointestinal
diagnosing uncommon causes for AP such as pancreatico-biliary ascariasis and parathyroid adenomas.

**Diagnosis of Chronic Pancreatitis**

EUS has unique capability of demonstrating subtle structural alterations in the pancreatic parenchyma as well as ducts even before conventional imaging modalities demonstrate any abnormality (Fig. 2). The conventional imaging modalities like computed tomography (CT) and magnetic resonance cholangiopancreatography (MRCP) can pick up advanced morphological changes of chronic pancreatitis (CP) only, and therefore they have very low sensitivity for diagnosis of early CP. EUS by demonstrating early parenchymal and ductal changes can help in early diagnosis of CP. In patients with presumed acute recurrent pancreatitis, EUS can help in excluding underlying CP. However, EUS is not a panacea for diagnosis of CP. Being a highly sensitive imaging modality, there is a concern for overdiagnosis of CP. To overcome these limitations, advanced and complicated scoring systems incorporating multiple parenchymal and ductal EUS features have been used for diagnosis of CP. Despite these scoring systems, concerns about interobserver variability as well as aging, smoking, obesity, and chronic alcohol consumption causing EUS changes in pancreas mimicking CP persist. Therefore, EUS findings of CP should be interpreted in an appropriate clinical context and, if required, should be confirmed and followed up by serial EUS examinations. Newer EUS techniques like EUS elastography that evaluate the stiffness of pancreas appear to be promising techniques for confident diagnosis of early CP. However, further studies are required to determine their exact role in diagnosis of early CP.

**EUS as a Secondary Diagnostic Modality**

**EUS for Submucosal Lesions**

SMLs are usually asymptomatic lesions with normal overlying mucosa detected on routine endoscopy and require further evaluation for confirmatory diagnosis. Endoscopy and biopsy have limited role in evaluation of SMLs because of normal overlying mucosa. The ability of EUS to image structures beyond GI lumen makes it ideal modality for investigations of SMLs. EUS is an excellent modality to differentiate extramural compression and SML as well as determine the type and nature of SML. EUS can help in presumptive diagnosis of SML by accurately estimating the size, the layer of origin, the echo-pattern and the margins of the lesion. The diagnostic accuracy of EUS can further be enhanced by cytological or histological analysis of specimens obtained by EUS guided FNA/fine needle biopsy (FNB).

**EUS for Unexplained Dilated Common Bile Duct**

EUS transducer from duodenum closely images the CBD, and therefore has very high diagnostic accuracy for lower and mid CBD lesions. Isolated CBD dilatation is commonly encountered in clinical practice because
of widespread use of cross-sectional imaging modalities for patients with non-specific abdominal symptoms. In many of these patients cross-sectional imaging modalities like ultrasound, CT, and MRCP fail to identify the etiology of dilated CBD and many of these patients required endoscopic retrograde cholangiopancreatography (ERCP) for confirming the diagnosis. ERCP is an invasive procedure with inherent risks of serious adverse effects like post ERCP pancreatitis. In these clinical situations EUS has been demonstrated to be an excellent diagnostic modality for identifying underlying etiology of unexplained CBD dilatation (Fig. 3). More importantly, if EUS is normal, there is extremely less likelihood of presence of any significant underlying disease and patient therefore should be reassured and no further follow-up is required.11-13

**EUS in Pancreatic Cystic Lesions**

Evaluation of patients with PCL requires a confident differentiation of malignant, potentially malignant and benign PCL. EUS is a useful modality for evaluation of PCL as it can provide information about the detailed morphology of cysts (Fig. 4) as well as enable guided FNA to obtain cyst fluid for cytological, biochemical as well as molecular analysis.14-17 Cyst fluid carcinoembryonic antigen (CEA) levels more than 192 ng/mL have been shown to have highest sensitivity and specificity for differentiating mucinous from non-mucinous PCL.18 Cyst fluid molecular markers hold considerable promise for proper evaluation of PCL. New EUS based technologies like contrast-enhanced EUS, EUS guided cystoscopy, needle-based confocal laser endomicroscopy, and through-the-needle forceps biopsy provide important information for accurate diagnosis of PCL.

**EUS for Locoregional Staging of GI Cancers**

EUS can accurately define the walls of the GI tract and thus is an accurate modality to assess the transverse spread of malignant lesion. It can also accurately assess the extraluminal involvement of the malignant lesion by identifying lymph nodal as well as arterial and venous involvement. Therefore, over last decade EUS has thus become an important investigation for preoperative assessment for majority of the GI cancers including esophageal, gastric, pancreaticobiliary, as well as rectal cancers.18 EUS from esophagus can also evaluate the mediastinum, and therefore EUS is an important imaging modality for accurate staging of non-small cell lung cancer. Combining EUS with endobronchial ultrasound (EBUS) allows access to all mediastinal lymph node stations, and therefore is an important staging modality for lung cancer.18,19

**EUS-guided Tissue Acquisition**

Linear echoendoscope is used to perform EUS-guided FNA with great precision in real time as the needle is visualized in real time throughout the procedure. The advantage of EUS-guided FNA is its ability to acquire
tissue from difficult to access anatomical locations in abdomen, retroperitoneum, mediastinum, and perirectal spaces. EUS guided FNA is now routinely used in clinical practice to acquire tissue for histological diagnosis from pancreas, lymph nodes in mediastinum and abdomen (Fig. 5), GI SMLs, perirectal lesions, left lobe of liver, left adrenal, and mediastinal masses. EUS can also be used for aspirating minimal amount of ascites and pleural effusion. It can also be used for visualizing as well as sampling peritoneal as well as pleural deposits in patients with undiagnosed pleural effusion as well as ascites. Despite being in GI endoscopy practice for more than a decade, EUS FNA has important limitations like false positivity in pancreatic masses in CP and autoimmune pancreatitis and false negativity because of technical difficulty, marked desmoplastic background, sampling error, or interpretative errors. Moreover, certain diseases like lymphoma and autoimmune pancreatitis require core biopsy for confident diagnosis. To overcome these limitations of EUS FNA, newer FNB needles have been developed for use with EUS. EUS guided FNB has been demonstrated to provide samples with increased cellularity along with preserved histologic architecture, and therefore seems to be an ideal tissue acquisition technique for histological as well as molecular testing.

**Therapeutic EUS**

EUS has the ability to visualize organs and lesions adjacent to GI tract and thus provide an opportunity to target them for various therapeutic procedures. The advantages of EUS is its ability to provide a real time imaging of the targeted area and also, importantly, avoiding adjacent vascular and other structures. Various EUS guided interventional procedures that are being performed are drainage of pancreatic fluid collections, biliary and pancreatic duct drainage in cases of failed ERCP, transmural gallbladder drainage, celiac plexus neurolysis (CPN)/blockade, drainage of mediastinal and intra-abdominal abscesses and collections, various vascular interventions, endoscopic gastrojejunostomy and is useful for targeted chemotherapy and radiotherapy.

CPN is a procedure of chemical ablation of the celiac plexus using absolute alcohol or phenol for relief of intractable pain because of pancreatic cancer. It is usually done under ultrasound, or CT guidance or surgically. Advent of EUS guided CPN has made this procedure very safe with rare adverse effects. Although EUS, CPN is safe and effective, but the pain relief is usually short lasting and patient may require repeated procedures for effective pain relief.

EUS guided transmural drainage of pancreatic fluid collections including pseudocysts (Fig. 6) as well as walled off necrosis has evolved as its treatment of choice and is preferred over surgical as well as percutaneous drainage. Being minimally invasive, safe, effective, and absence of external percutaneous drainage catheter are important advantages of EUS guided drainage of pancreatic fluid collections. Developments of fully covered lumen apposing metal stents (LAMS) have further improved results of EUS guided drainage of pancreatic fluid collections.
fluid collections. Similarly, abscesses or collections in locations adjacent to GI tract like mediastinal, left lobe of liver, lesser sac, and pelvic collections can be drained under EUS guidance.\textsuperscript{27} 

EUS-guided transmural drainage of biliary tract and pancreatic duct is an effective alternative to percutaneous or surgical drainage of these ducts in patients with failed ERCP.\textsuperscript{27} Although these procedures are effective but are technically challenging, and therefore should be performed only by experts in centers with radiological and surgical back up. Similarly, EUS can be used for draining gallbladder in cases of acute cholecystitis not responding to antibiotics and has been shown to be safer and effective alternative to percutaneous drainage of gallbladder with added advantage of absence of percutaneous drain. 

Advancement in accessories for EUS has led on to exploration of unthinkable therapeutic areas. Various palliative oncological interventions like EUS-guided brachytherapy, fiducial marker placement, ethanol ablation, and EUS-guided delivery of antitumor agents can be performed and studies have shown them to be safe and effective.\textsuperscript{27} EUS has expanded into vascular interventions field also with various EUS guided interventions like EUS guided glue or coil injections into gastric/ectopic varices as well as pseudoaneurysms being safely performed. EUS-guided intrahepatic portosystemic shunt has also been performed as an alternative to TIPS (transjugular intrahepatic portosystemic shunt) for the treatment of consequences of portal hypertension. Advancement in EUS had made it possible to perform various surgical procedures like gastrojejunostomy safely in a minimally invasive fashion under EUS guidance.\textsuperscript{31} 

**Conclusion**

EUS is an important investigation in the armamentarium of an endoscopist. EUS has been shown to have a significant impact in management of patients with various GI disorders with significant change in both the diagnosis as well as management.\textsuperscript{3} The advent of EUS-guided FNA for tissue diagnosis as well as therapeutic EUS has led on to wider clinical applications of EUS. Locoregional staging of various GI cancers is one of the important clinical applications of EUS in clinical practice. Development of newer technologies like EUS elastography and contrast EUS is going to further expand the role of EUS. It is important for an internist to be aware of the indications and strengths of EUS in various abdominal, thoracic, as well as pelvic diseases.

**References**

Gastroesophageal reflux disease (GERD) is a frequently encountered disease in clinical practice that significantly hampers the quality of life of patients. Long-term complications of GERD are another area of concern that necessitates timely diagnosis and treatment. Both acid and non-acid reflux have been implicated into the pathophysiology of GERD. Ambulatory 24-hour pH monitoring is the gold standard test for diagnosis. Proton pump inhibitors (PPIs) along with lifestyle modifications are the mainstay of treatment. However, they have their own range of side effects, which precludes their long-term use. Moreover, 20–40% patients show persistent symptoms despite adequate PPI therapy. Management of refractory GERD requires optimization of PPI therapy, addition of a nighttime H₂ receptor antagonist, baclofen and neuromodulators. However, promising results have not been obtained with any of these so far. Newer enantiomers of PPI, potassium-competitive acid blockers, and TLESR-reducers are under trial phase. However, due to the disturbing recurrent nature of symptoms, patients’ preference for surgical and endoluminal therapies is apparent. This chapter briefly outlines the pathophysiology and current treatment options for GERD with focus on recent advancements in medical, endoluminal, and surgical management strategies of the disease.

Introduction
Gastroesophageal reflux disease (GERD) is a global disease. While the prevalence in western population is 18.1–27.8%, it is believed to be lower in the East Asian population (<10%). The overall prevalence of GERD in India is 7.6%.

GERD is associated with deleterious effects on day-to-day activities, reduced work efficiency, and sleep, ultimately affecting the quality of life. Further, long-term complications like stricture, Barrett’s esophagus, and adenocarcinoma also necessitate timely diagnosis and treatment.

Definitions
- **GERD**—Troublesome symptoms sufficient to impair an individual's quality of life or injury or complications that result from the retrograde flow of gastric contents into the esophagus, oropharynx, and/or respiratory tract.
- **NERD**—GERD symptoms without erosions on endoscopy in absence of recent acid-suppressive therapy.
- **Erosions on endoscopy (EE)**—EE with/without GERD symptoms.
- **Barrett’s esophagus (BE)**—Endoscopic presence, confirmed histologically of columnar-lined esophagus. It is known to have malignant potential.
- **Extraesophageal GERD syndrome**—This includes:
  - Conditions with established association with GERD (cough, laryngitis, asthma, and dental erosions).
  - Conditions with only a proposed association (pharyngitis, sinusitis, idiopathic pulmonary fibrosis).
Causative and Protective Factors

- **Causative Factors**
  - Older age
  - Pregnancy
  - Obesity
  - Smoking and alcohol
  - Anxiety/depression
  - Less physical activity
  - Large meals just before sleep
  - High dietary fat intake
  - Certain medication like NSAIDs, calcium channel blockers

- **Protective Factors**: Helicobacter pylori infection and physical activity seem to play a protective role.

Pathophysiology

GERD is the disease of lower esophageal sphincter (LES). The acid reflux is most commonly caused due to transient relaxation of lower esophageal sphincter (TLESRs), which is a physiological phenomenon and increases in frequency postprandially.

Other factors that contribute to acid reflux include:
- Decreased LES pressure
- Increased intra-abdominal pressure
- Hiatal hernia
- Poor esophageal acid clearance
- Delayed gastric emptying

Non-acid Reflux

Undoubtedly, acid reflux is the chief cause of symptoms in GERD patients, making gastric acid suppressive therapy (proton pump inhibitor, PPI) the mainstay of treatment.

In patients with symptoms despite acid suppression, the culprit in more than 80% cases is non-acid reflux (pH>4).

Three types of refluxes have been defined based on pH:
- Acid reflux—pH<4
- Weakly acidic reflux—pH 4–7
- Weakly alkaline reflux—pH>7

The proposed mechanisms are:
- Duodenogastric-esophageal reflux—Regurgitation of duodenal contents, containing biliary and pancreatic secretions into stomach and esophagus.
- Large volume of reffluce triggering symptoms irrespective of its acidity by mechanical stimulation of esophagus.
- Greater proximal esophageal extent of reflux resulting in increased likelihood of symptoms.

Clinical Features

- GERD symptoms can be classified into typical and atypical:

<table>
<thead>
<tr>
<th>Typical symptoms</th>
<th>Atypical symptoms</th>
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<tbody>
<tr>
<td>Heartburn</td>
<td>Nausea, vomiting</td>
</tr>
<tr>
<td>Regurgitation</td>
<td>Belching</td>
</tr>
<tr>
<td>Water brash</td>
<td>Early satiety</td>
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<tr>
<td></td>
<td>Epigastric pain</td>
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<tr>
<td></td>
<td>Hoarseness</td>
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<tr>
<td></td>
<td>Globus sensation</td>
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<tr>
<td></td>
<td>Dental enamel loss</td>
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<tr>
<td></td>
<td>Chest pain</td>
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<tr>
<td></td>
<td>Nocturnal awakening</td>
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<tr>
<td></td>
<td>Chronic cough</td>
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<tr>
<td></td>
<td>Asthma</td>
</tr>
<tr>
<td></td>
<td>Chronic sinusitis</td>
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<td>Recurrent sore throat</td>
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</table>

- Atypical extraesophageal symptoms lead to difficult and delayed diagnosis.
- They have poor response to conventional therapy.

Diagnosis

The initial diagnosis is usually made on the basis of cardinal symptoms and response to PPI therapy.

In presence of atypical symptoms, it is important to rule out other gastrointestinal disorders (e.g., ulcers, malignancy) and non-gastrointestinal diseases (e.g., ischemic heart disease).

PPI Diagnostic Test

- Patients with typical symptoms can be put on PPI therapy and followed up to 8 weeks.
- Almost 20–40% patients continue to be symptomatic even on adequate PPI treatment.
- The patients with inadequate response and those with alarm symptoms need further evaluation.

<table>
<thead>
<tr>
<th>Alarm features</th>
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<tbody>
<tr>
<td>Dysphagia</td>
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<tr>
<td>Odynophagia</td>
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<td>Gastrointestinal bleeding</td>
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<tr>
<td>Weight loss</td>
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<tr>
<td>Iron deficiency anemia</td>
</tr>
<tr>
<td>Early satiety</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Age &gt; 55 years</td>
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<tr>
<td>Family history of upper GI malignancy</td>
</tr>
</tbody>
</table>

Upper Gastrointestinal (UGI) Endoscopy

- UGI endoscopy should be done in all patients with
  - Alarm features
  - Suboptimal response to PPI therapy.
**Los Angeles classification of erosive esophagitis**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>One or more mucosal breaks, ≤5 mm, none of which extends between the tops of the mucosal folds</td>
</tr>
<tr>
<td>B</td>
<td>One or more mucosal breaks, &gt;5 mm long, none of which extends between the tops of two mucosal folds</td>
</tr>
<tr>
<td>C</td>
<td>Mucosal breaks that extend between the tops of two or more mucosal folds, but which involve &lt;75% of the esophageal circumference</td>
</tr>
<tr>
<td>D</td>
<td>Mucosal breaks that involve at least 75% of the esophageal circumference</td>
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</table>

- Long standing GERD, endoscopy is necessary to assess for complications.
- Erosive esophagitis should be graded on the basis of endoscopy findings as follows:

**Ambulatory 24-hour pH Monitoring**

- It is the gold standard for diagnosis of GERD
- It is used to quantify:
  - Esophageal acid exposure time (EAT)
  - Number of reflux events (events when pH decreases to <4)
  - Nature of refluxate (acidic/neutral/alkaline)
- An EAT of more than 6% and a total of more than 80 reflux episodes in 24 hours are considered abnormal.
- Normally carried out for 24 hours, the test can be extended up to 96 hours using Bravo esophageal pH recorder capsule.
- It is done:
  - **Off PPI:**
    - In patients with unproven GERD (no or LA grade A/B esophagitis)
    - Before surgery
    - Atypical presentations
  - **On PPI:**
    - In proven GERD (LA grade C/D esophagitis) or BE > 1 cm or prior abnormal pH study
    - To establish causation of refractory symptoms

**EndoFLIP (Endoscopic Functional Luminal Imaging Probe) System**

- It assesses the distensibility of esophageal body and GE junction at various volume-controlled (usually 20–30 mL) distending pressures
- GERD patients seem to have increased GE junction distensibility
- FLIP can also identify esophageal motility disorders
- It serves as a useful tool in anti-reflux procedures

**Multichannel Intraluminal Impedance Monitoring**

- To diagnose non-acid reflux, pH monitoring is not quite helpful as it uses acidity as marker of reflux but not the actual reflux.
- Multichannel intraluminal impedance monitoring combined with pH monitoring can reliably identify non-acid reflux.
- The technique uses changes in resistance to electrical currents to detect the presence of intraluminal liquid.

**Treatment**

**Lifestyle Modifications**

In patients with uncomplicated GERD, the initial step of management is lifestyle modifications which include:

- Elevation of head end of bed by 4–8 inches
- Dietary changes
  - Avoiding fatty, spicy, large meals
  - Avoiding late evening snacks
  - Avoiding chocolate, citrus foods, caffeine, carbonated drinks
- Minimizing smoking and alcohol
- Weight reduction
- Avoid NSAIDs

**Medical Management**

This comprises of acid-neutralizing (antacids) and acid-suppressing (H2RA, PPI) agents.

- **Antacids**:
  - Mostly used for occasional or short-term symptoms
— Include sodium, calcium, aluminum, magnesium salts, and alginate containing agents

- **Histamine type-2 receptor antagonists (H2RA):**
  - Better efficacy and prolonged action than antacids
  - However, tachyphylaxis (usually within 2 weeks) is an issue
  - Should not be given at same time as PPI
  - Currently, there are four FDA-approved H2RAs: cimetidine, famotidine, nizatidine, and ranitidine
  - Lavoltidine and lafutidine are under trial

- **Proton pump inhibitors:**
  - Most potent and hence, the mainstay of treatment
  - PPIs have a better, faster, and long-lasting effect in both NERD and EE
  - Most effective when taken 30 minutes before meals

Acid suppression can be achieved in the following three ways:

- **Step-up therapy:**
  - Starting with less potent agent and moving up for response
  - Patient is first started on H2RA
  - If no response is seen for 2 weeks, patient is shifted to PPI followed by double dose of PPI

- **Step-down therapy:**
  - Patient is started with twice daily dose of PPI
  - When response is achieved, he is switched to once daily dose followed by on-demand dose

- **On-demand therapy:**
  - Here patient is given standard dosage of H2RA or PPI as and when needed

### Side Effects of PPI

- The efficacy and ease of availability of PPI has led to its misuse
- Patients either self-treat themselves or once prescribed, continue them for prolonged periods without re-evaluation
- This leads to excessive cost of therapy as well as adverse effects
- Most of the side effects are mild and self-limiting like headache, nausea, abdominal pain, and flatulence
- Recent studies, however, reveal association of PPI with some serious adverse effects

### Refractory GERD

Refractory heartburn is defined as symptoms of reflux of gastric content that do not respond to a double dose of a PPI given for at least 8 weeks.

Functional heartburn and reflux hyper-sensitivity are the most common underlying mechanisms. Other less common mechanisms include psychological factors, functional bowel disorders, delayed gastric emptying, bile reflux, rapid PPI metabolism, PPI resistance or improper PPI timing.

Every patient with refractory GERD should also be evaluated for Eosinophilic esophagitis (EoE), achalasia and Zollinger-Ellison syndrome.

The management of refractory GERD includes:

- Optimization of PPI therapy
  - Lifestyle modifications
  - Better compliance
  - Proper dosing time
  - Splitting the dose
  - Shifting to another PPI
- Adding a night-time H2 receptor antagonist.
- Baclofen- A gamma-aminobutyric acid-B agonist (5-20 mg three times a day) reduces gastroesophageal reflux by decreasing TLESR rate.
- Neuro-modulators (like tricyclic-antidepressants, selective serotonin-reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors and trazodone) are effective in patients with functional heartburn or reflux hypersensitivity.
- Endoscopic treatment
- Antireflux surgery.

### Recent Developments in Medical Management

- **Extended-release PPIs:** In order to increase their potency, PPIs have been modified into enantiomers that undergo slower hepatic metabolism and maximum absorption and thus increased bioavailability.
  - Dexlansoprazole MR:
Dual delayed-release formulation of dexlansoprazole (R-enantiomer of lansoprazole)

Two peaks of drug release; at 1–2 hours and at 4–5 hours

Can be given irrespective of meal timings

- Tenatoprazole and S-Tenatoprazole:
  - Contain an imidazopyridine molecule (not a benzimidazole molecule like other PPIs)
  - Offer better night-time control, due to prolonged half-life

- Esomeprazole strontium delayed-release (Esomezol)

- Ilaprazole

- **PPI combinations:**
  - **PPI-VB101 (Vecam):** Combination of omeprazole and succinic acid that increases activation of proton-pumps in parietal cells
  - **OX-17:** Omeprazole plus famotidine
  - **NMI-826:** Nitric-oxide-enhanced PPI
  - **Secretol:** Omeprazole plus lansoprazole

- **Potassium-competitive acid blockers (P-CABs):**

- **Act by reversibly inhibiting gastric H+/K+-ATPase by competing with K+**

- Do not need prior proton pump activation

- Have a faster onset of action; hence, useful as on-demand therapy

- Linaprazan, Soraprazan, Revaprazan, and TAK-438 are P-CABs under trials

- Associated with side effects like hepatotoxicity.

- **TLESR reducers:**

- **Cannabinoid Receptor-agonists:** Delta-9-tetrahydrocannabinol (CB1/CB2 receptor agonist), Rimonabant (CB1 receptor antagonist)

- **Cholecystokinin/Gastrin Receptors-antagonist:** Itriglumide, Loxiglumide

- **GABA-B agonists:** Baclofen, Lesogaberan

**Endoscopic Management**

- Endoluminal procedures offer a less invasive means of treating GERD

- Patients suitable for endotherapy are those with:
  - Typical symptoms of GERD
  - Low-grade EE (Los Angeles Grades A and B)
  - Endoscopy negative with abnormal esophageal acid exposure
  - No or small hiatal hernia (<3 cm)

- At least a partial response to PPI treatment

- Preference for nonmedical, nonsurgical therapy

- **Contraindications:**
  - Morbid obesity
  - Esophageal motility disorder (e.g., achalasia, scleroderma)
  - Prior esophageal/gastric surgery
  - Esophageal stricture or Barrett esophagus
  - Esophageal/gastric varices
  - Pregnant/lactating women

- **Basic techniques of endotherapy:**
  - Constriction of LES by using thermal energy
  - Augmenting LES pressure by injecting bulking agent
  - Mechanical alteration of gastroesophageal junction (GEJ)

- Currently, three endoluminal methods are in practice:

  - **Stretta procedure:**
    - Here, compliance of LES is reduced by using radiofrequency ablation
    - This decreases frequency of TLESRs and hence, reflux

  - **Transoral incisionless fundoplication (TIF):**
    - Here using the Esophyx Z device, an anterior full thickness fundoplication is done
    - This constructs a valve 3–5 cm in length and greater than 270 degrees circumferential wrap around LES

- **Ultrasonic surgical endostapler**

- This technique makes use of a modified endoscope that incorporates a miniature camera, an ultrasound probe, and a stapler on its tip

- With the use of this endoscope, an anterior full-thickness fundoplication is done

- Endoscopic procedures still under development are:
  - Anti-reflux mucosectomy
  - Endoscopic full thickness plication
  - Submucosal injection of a biocompatible substance

**Surgical Management**

- The anti-reflux surgery is said to have only marginal long-term benefit over PPI therapy

- Patients with typical symptoms respond better to surgery than those with atypical or extra-esophageal symptoms
- Approximately half of the patients will still need anti-reflux medications, post-surgery
- Further, postoperative complications like solid food dysphagia, diarrhea, and early satiety have been reported in 7–10% patients
- Surgery does not prevent progression to adenocarcinoma
- Patients who will be benefitted the most from surgery are those with:
  - No response, non-compliance or intolerance to medical therapy
  - Complications like refractory esophagitis, stricture, and BE
  - Large hiatus hernia (>5 cm)
  - Documented acid reflux with defective anti-reflux barrier
  - Cardiac dysfunction
  - Normal gastric emptying and esophageal motility
- **Linx™ reflux management system:**
  - This device is in the form of a ring made by series of titanium beads with a magnetic core connected with titanium wires
  - This ring is placed, laparoscopically, around the lower end of distal esophagus
  - It prevents reflux by augmenting LES
  - Short-term studies are promising with more than 90% patients reporting improvement in quality of life
  - However, dysphagia was seen in 68% patients

**Conclusion**

GERD is a common gastrointestinal disorder with significant impact on quality of life. PPIs, though mainstay of treatment, have got serious long-term side-effects and are less promising in patients with non-acid reflux and extra-esophageal manifestations. There may be a rise in patient’s interest in anti-reflux surgery and endoluminal therapy in future; thus, highlighting the need to explore beyond the conventional therapy.

**References**

Abstract

Post-infectious irritable bowel syndrome (PI-IBS), a subclass of IBS, where this clinical entity has been linked with occurrence of various gastrointestinal infections, bacterial, protozoal, viral, etc. Studies have clearly shown its occurrence in different ethnicity and every part of the world. As it starts after an episode of GI infection, a few studies throw some light toward its mechanism. Its pathophysiology, clinical features, prognosis, and possible treatment have been discussed here.

Introduction

Many patients of IBS, on being enquired, when did their symptom begin, will struggle to give a correct date. But some occasional patients would come out with an answer, suggest a specific date, saying I was fine until.......Such patients who connect onset of their symptoms to an episode of disorder infectious gastroenteritis, appear to be a little different from others. This subset of patients may be labeled as post-infectious irritable bowel syndrome (PI-IBS). However, most patients of PI-IBS cannot recognize their illness by the past events because either they do not remember or they do not give much importance to any such episode. The clinical syndrome, PI-IBS, denotes persistence of abdominal discomfort, bloating, and constipation diarrhea, which continue despite absence of inciting pathogens. A met analysis in the past concluded that the risk of developing PI-IBS increases sixfold after GI infection and remains elevated for next 1–3 years.1

Epidemiology

A link between enteric infection and IBS dates back to the Second World War when numerous cases of GI discomfort were seen in British troupes that had earlier suffered from enteric infection. Since then a number of studies in various parts of the world have reported such illnesses. The incidence or prevalence of PI-IBS, 5–32%, in such studies tell us that it is a global phenomenon and not related to a particular ethnic group or environment (Box 1).2,3 The wide variation in this reported incidence or prevalence may be because of differences in study methodology, inclusion criteria, definition of IBS, etc.

Table 1 describes the prevalence of PI-IBS in some of these countries.4 The prevalence rate of PI-IBS (11.5%) does not vary much, if we take into account the post-infection period, that is, 3, 6, 12, 13–59, or more than 60 months.5 But initial infective organisms matter and overall, the rate

<table>
<thead>
<tr>
<th>BOX 1</th>
<th>Factors involved in PI-IBS</th>
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<tr>
<td>• Genetic susceptibility</td>
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<tr>
<td>• Intestinal inflammation</td>
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<tr>
<td>• Intestinal permeability</td>
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<tr>
<td>• Altered visceral sensitivity</td>
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<tr>
<td>• Severity of infection</td>
<td></td>
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<tr>
<td>• Psychiatric disturbances</td>
<td></td>
</tr>
<tr>
<td>• Pathogens involved</td>
<td></td>
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<td>• Host factors</td>
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of PI-IBS was the highest after protozoa/parasitic infective enteritis, followed by bacterial and the lowest rates were seen with viral infection.6

Pathophysiology

IBS is a disease where diagnosis is based on clinical criteria in absence of any organic changes. Though gut mucosa of patients of IBS are endoscopically normal, recently complex alteration in digestive mucosa has been identified in PI-IBS patients. These changes mainly alter the integrity of intestinal epithelial barrier. It results in paracellular permeability, which can encourage exposure and migration of microflora or food borne antigens. This in turn stimulates intestinal mucosal immunity, leading to persistent intestinal microinflammation. The possibility of inflammatory state of intestinal mucosa is substantiated by the occurrence of infiltration of T lymphocytes, mast cells, and enterochromaffin cells. These cells are responsible for release of cytokines and mediators of inflammation. In one study, increased intestinal permeability was associated with increased stool frequency and was proved by demonstrating increased lactulose-mannitol fractional excretion ratio in patients, 2 years after a water borne outbreak of gastroenteritis involving Campylobacter jejuni and Escherichia coli.7,8 These changes suggest a pathophysiological model of PI-IBS and genesis of symptoms of IBS, where symptoms start after a bout of infection rather than its absence. An increased number of mast cells in rectal mucosa and mucosal cellularity were significantly higher in patients of PI-IBS as compared to patients of IBS, a fact confirmed by rectal-sigmoid and ileal mucosal biopsy.

Risk Factors for Development of PI-IBS

Female sex is associated with 2.2 times higher risk. Smoking is not considered a risk factor. Prevalent anxiety and depression at the time of infective enteritis is associated with PI-IBS development more often. Similarly, somatization and neuroticism, at the time of infection, are risk factors.6,9 Host immune status of elderly persons protects against infection and thus lowers risk of its development.2

The nature of pathogen too influences the risk of developing IBS, post infection. The hazard ratio is 4.3 for E. coli, 2.9 for C. jejuni, 2.5 for Salmonella spp, and 2.2 for viral gastroenteritis. The mechanism of low-hazard ratio for viral etiology is poorly understood. It is possible that viral enteritis is associated with less mucosal damage and poor structural and immunological alteration.10 However, the high incidence of PI-IBS after an attack of protozoal enteritis (Giardiasis) merits attention as it shows the prevalence much higher, i.e. 39–89%.11

Clinical Features

The diagnosis of IBS is always symptom based and is mostly challenging. Similarly, there are no definite diagnostic criteria for post-infectious IBS. The element of “new onset IBS after an episode of acute gastroenteritis in patients who never had IBS previously” should always be given significance. There is strong relation between traveler’s diarrhea (TD) and PI-IBS. Self reported TD was associated more often than laboratory confirmed TD (1.5-fold rise in RR).

There might be some subtle differences in PI-IBS from IBS, which has greater stool frequency and loose stools as compared to IBS. All different subtypes of IBS are recognized, and the frequency is IBS-mixed, 46%, IBS diarrhea, 39%, and IBS constipation, 15% in some studies.11,12 Emphasis should be laid before making a diagnosis of PI-IBS to exclude alarm signs and checking for preliminary investigations, that is, CBC, ESR, CRP, stool culture, etc. in one study, PI-IBS was found to be associated with post-infectious malabsorption syndrome (PI-MAS), popularly known as tropical sprue.14 Small

<table>
<thead>
<tr>
<th>Table 1: Prevalence of PI-IBS in different areas</th>
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<tbody>
<tr>
<td>Country</td>
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<tr>
<td>Canada</td>
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<td>Bangladesh</td>
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intestinal bacterial overgrowth (SIBO) has been linked with IBS, particularly IBD-D type.

Other similar conditions like acquired lactase deficiency following gastroenteritis, bile acid malabsorption, inflammatory bowel disease, or lymphocytic colitis should always be taken into account as differential diagnosis.

### Prognosis

PI-IBS too lasts for a long time. In one study, the rate of spontaneous remission was 27% in a year. The proportion of patients who improved (as assessed by ROME III criteria) varied across the age group (23% in younger population of 21–30 years and 37.5% in older population if more than 70 years (p=0.18). Other factors responsible for poor recovery are female sex, patients from North America and Europe, and those with history of somatization. Patients with longer history of IBS symptoms exhibited poor recovery. Despite different pathogenesis, surprisingly, prognosis in PI-IBS does not differ much from non PI-IBS with recovery of one in four patients in first year. Still, it is very encouraging to learn that over half of patients of PI-IBS return to their preinfection state. However, it may take years for symptoms to disappear completely.

### Treatment

It is legitimate to think that traditional approach of treatment aiming only at attenuating symptoms, must give place to addressing new pathological targets (intestinal permeability, microinflammation, mast cells, serotonin, visceral hypersensitivity, etc.) However, approaches to tackle such anomalies have not met with much success. In a small study, treatment with prednisolone, in PI-IBS, on presumption of immunological genesis has not shown any benefit. Another RCT of an anti-inflammatory agent, mesalazine, showed overall no benefit in IBS patients with IBS with diarrhea, but a post hoc subgroup analysis did suggest some response in PI-IBS. Furthermore, treatment with *E. coli* 0147 infection with mesalazine appeared to reduce the risk of developing PI-IBS. Increased 5HT available in small intestine in PI-IBS patients enhances visceral hypersensitivity which can be blocked by 5HT receptor antagonist, ondansetron. This theory encouraged randomized trial of ondansetron in IBS with diarrhea, which showed relief of symptoms, particularly urgency.

SIBO is seen in rats of PI-IBS after campylobacter infection. A recent study in India suggested that PI-IBS might overlap with tropical sprue in which SIBO is common. Rifaximin is a locally acting antibiotic, which targets SIBO, has shown benefit in IBS-D patients. Bile salt malabsorption may develop following acute gastroenteritis. Several studies have demonstrated that PI-IBS can respond to cholecystokinin. However, intolerance to this drug discourages its use.

Despite all these novel and experimental therapies, treatment of PI-IBS is frequently symptom directed and matches closely with treatment of IBS. Table 2 summarizes measures, which help treating patients of PI-IBS.

### Diet

Many patients describe a chronological link between onset and worsening of symptoms with a particular food. However, in majority of patients there is no compelling data to recommend an exclusion diet. The knowledge of enhanced intestinal permeability may suggest food allergy on the premise of penetration of food antigens and their contact with immunocompetent cells. Possible exclusion of such items by patients may be helpful rarely. A low fiber diet with soluble fiber will help to some extent. The consumption of poorly absorbed fermentable oligo-, di-, mono-saccharide and polyols (FODMAPs) may be a trigger for symptoms too. FODMAPs and insoluble

### Table 2

<table>
<thead>
<tr>
<th>IBS symptom</th>
<th>Drugs in therapy</th>
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<tbody>
<tr>
<td>Abdominal pain</td>
<td>• Antispasmodics</td>
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</table>
| Diarrhea | • Loperamide<sup>a</sup>  
• Diphenoxylate<sup>a</sup>  
• Cholestyramine<sup>a</sup>  
• Probiotics<sup>a</sup> |
| Constipation | • Bulking agents  
• Polymethyl glycol  
• Osmotic or stimulating laxatives<sup>a</sup>  
• Prucalopride<sup>a</sup>  
• Lubiprostone<sup>a</sup>  
• SSRIs<sup>a</sup>  
• Probiotics<sup>a</sup> |
| Bloating/abdominal distension/meteorism/flatulence | • Probiotics<sup>a</sup>  
• Rifaximin<sup>a</sup> |

<sup>a</sup>Recommended in a few patients based on individual clinical profile SSRIs, selective serotonin reuptake inhibitors.

fibers may enhance osmotic pressure in large intestine and provide a substrate for bacterial fermentation. Low FODMAPs can change intestinal microbiota and reduce IBS symptoms (Table 3). More so, different gastrointestinal cell types that produce hormones, which regulate appetite and food intake, show dysfunction too. This, in turn, increase food intake and weight gain. Though, linkage of IBS and obesity is poorly understood, low FODMAPs and insoluble fibers, probiotics, and regular exercise are to be recommended.21

**Probiotics and Fecal Microbial Transplantation**

A number of probiotics are tested in IBS. The results are encouraging, particularly in relieving excessive flatulence. In fact, administration of probiotics during an attack of acute gastroenteritis of bacterial origin has a protective effect on intestinal epithelial barrier. The role of probiotics is seen in animal model of PI-IBS in a favorable manner. Fecal microbial transplantation (FMT) may be, probably, more beneficial as human feces is the ultimate human probiotic. A number of studies have proved its beneficial role in diseases like IBS, IBD, chronic constipation, etc. In one study role of FMT was studied in recurrent Clostridium difficile infection (CDI) by Mattila et al.22 In this study, symptoms resolved in all patients who did not have strain 027 CDI during the first three months Out of 36 patients who had 027 infection, 32 (89.7%) had a favorable response. Unfortunately rest four patients had history of long standing diarrheal disease with comorbidities did not improve and died. However, no human trial of FMT is available in PI-IBS but success in other areas offers legitimacy for using this therapy and conducting a large trial.

**Conclusion**

Post-infectious IBS represents a frequently occurring new clinical entity which has led to better understanding of the factors involved in pathophysiology of IBS. ROME IV recognizes post-infectious IBS, a multidimensional clinical chronic inflammation triggered by enteric infection. Present literature on IBS is very descriptive and large randomized trials are lacking. Future research is needed to establish a link between hosts and microbes in which participants are subdivided according to underlying mechanisms. The response of each subgroup will provide new tools for prevention and management.

**References**


