

# Tropical Sprue in 2014: the New Face of an Old Disease

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**Abstract** Tropical sprue (TS), once known to be a common cause of malabsorption syndrome (MAS) in India and other tropical countries, is believed to be uncommon currently in spite of contrary evidence. Several recent studies from India showed TS to be the commonest cause of sporadic MAS in Indian adults. TS is diagnosed in patients presenting with suggestive clinical presentation, which cannot be explained by another cause of MAS and investigations revealing malabsorption of two unrelated substances, abnormal small-intestinal mucosal histology, which responds to treatment with antibiotics such as tetracycline and folic acid. There is substantial overlap between TS and postinfectious irritable bowel syndrome. There have been several advances in epidemiology, pathogenesis, and diagnosis of TS, hitherto an enigmatic condition.

**Keywords** Malabsorption · Syndrome · Small-bowel bacterial overgrowth · Malnutrition · Chronic diarrhea · Postinfectious IBS

## Introduction

Tropical sprue (TS) or tropical malabsorption, believed to have disappeared even in tropical countries despite contradictory evidence, is the commonest cause of sporadic malabsorption syndrome (MAS) in northern, southern, and eastern parts

of India even currently [1•, 2•, 3, 4, 5•]. It is a condition in which malabsorption occurs in absence of an identified specific etiology primarily in the tropical regions of the world [6, 7•]. TS is diagnosed based on the following criteria: (a) compatible clinical presentation, (b) demonstration of malabsorption of two unrelated substances, (c) abnormal small-intestinal mucosal histology, which may be patchy, (d) exclusion of other specific causes for MAS (except small-intestinal bacterial overgrowth [SIBO]), and (e) persistent response to treatment with antibiotics such as tetracycline and folic acid [2•]. Compatible clinical presentation is very important as abnormal small-bowel mucosal histology has been reported in tropics even in asymptomatic subjects, a condition called as tropical enteropathy [8]. Tropical enteropathy, however, is not same as TS (Table 1).

## Epidemiology of TS

How Common Was TS in the Past?

In the past, most believed that TS was the commonest cause of MAS in Indian adults [9–11]. In fact, epidemics of chronic diarrhea and MAS following acute infective gastroenteritis (referred to as “postinfectious tropical malabsorption”) were reported from India [12•]. In a study from four villages from southern India in 1968, 8–20 % villagers, suffering from an attack of acute infective diarrhea continued to experience liquidity and frequency of stool who were diagnosed to have TS [1•]. Several other studies reported epidemics of diarrhea with features suggestive of TS in India [13–16]. The Madras State health reports recorded five epidemics of chronic diarrhea of unknown etiology that clinically resembled TS between 1930 and 1942 [17]. Epidemics of TS also occurred among soldiers and prisoners of war in the Indo-Burma region during the Second World War, in American military personnel serving

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**Table 1** Differences between tropical sprue and tropical enteropathy

Features	Tropical sprue	Tropical enteropathy
Gastrointestinal symptoms	Present	Absent
Natural history	Progressive worsening	Improves or worsens
Nutritional deficiency	Common	Less common
Migration to a temperate zone	Usually no improvement	Normalization of intestinal abnormalities
Response to treatment with folic acid and tetracycline	Dependable improvement in most patients	Variable

in the Philippines and in Bangladesh [6, 7, 18]. A similar condition was also reported sporadically from temperate countries where it was named “temperate sprue” [19].

#### How Common Is TS at Present?

It has been conventionally believed that with improvement in socioeconomic status and hygiene and increased use of antibiotics and probiotics, there has been a reduction in frequency of sporadic TS. There is, however, hardly any evidence in favor of this hypothesis; in contrast, there has been several studies reported recently that contradict this hypothesis. In a recent study on 275 patients with sporadic MAS from Lucknow, India, 101 (37 %) had TS, which was the single commonest cause of MAS [5]. In another study from a large teaching hospital in New Delhi, India, though celiac disease was the single commonest cause of MAS (62 %), 22 % had TS [3]. In a study reported from a hospital in Vellore, located in the southern region of India, 36 (29 %) of 124 adult patients with sporadic MAS had TS, which was the single commonest cause in this population [4]. In an earlier study from Lucknow, India, 39/99 (39 %) patients with MAS were diagnosed having TS using very rigorous criteria [2]. All these studies clearly contradict the belief that sporadic form of TS has disappeared currently. In fact, most reports have suggested that the sporadic form of TS is frequently seen in India even today [20]. Patients with TS have also been reported sporadically even recently from other parts of the world. Two American subjects living in Thailand and Vietnam were reported to have TS in 2013 [21]. Two other cases who developed TS after returning from Singapore, Thailand, Indonesia, and Peru were reported in 2010 from the USA [22].

However, epidemics of TS have not been reported recently. This argument has been used to support the hypothesis that frequency of TS has reduced currently. An important issue to be reviewed here relates to a recently described entity called postinfectious irritable bowel syndrome (PI-IBS) [23]. In this condition, following an episode of acute gastrointestinal infection associated with at least two of the followings (a) diarrhea, (b) vomiting, (c) fever, and (d) isolation of enteropathogen on stool culture, patients develops IBS for the first time [23]. Most patients with PI-IBS have diarrhea-

predominant disease [23]. Initial studies on PI-IBS were reported from Sheffield, UK [24–27]. Subsequently, several studies have been reported from other temperate countries in the world such as Canada, North America, South Korea, and China [28–32]. Would this condition, in which stool continued to remain frequent and liquid after an episode of acute gastroenteritis, be called as temperate sprue if described five decades ago? The answer to this question would be affirmative if the patients were found to have biochemical evidence of mucosal malabsorption on D-xylose test, fecal fat estimation, and abnormal small-intestinal histology. However, in no study that described PI-IBS, tests for mucosal malabsorption and small-intestinal mucosal histology were reported. Hence, it is difficult to say whether a proportion of these patients with so-called PI-IBS could have suffered from postinfectious tropical malabsorption or TS. Obviously, this form of postinfectious tropical malabsorption is similar to epidemic form of TS.

There is considerable overlap in epidemiology, pathogenesis, clinical presentation, and treatment of postinfectious tropical malabsorption or TS and PI-IBS (Table 2). Briefly, 7–31 % patients with acute gastroenteritis have been reported to develop PI-IBS, a frequency quite similar (8–20 %) to that reported for postinfectious tropical malabsorption, whereas the latter condition was reported about five to six decades ago, interest in the former condition emerged primarily during last two decades [7, 33]. Both the conditions have similar pathogenesis and treatment (Table 2). Though several studies on PI-IBS have been reported from temperate countries recently, not a single study on this condition has been reported recently in the areas of the world where epidemic of TS was reported [23, 34]. Unfortunately, not a single study reported till date on PI-IBS performed tests for mucosal malabsorption and small-intestinal biopsy to exclude that these patients were suffering from PI-IBS and not postinfectious tropical malabsorption. In fact, a few studies reported abnormal small-intestinal permeability (SIP) in patients with diarrhea-predominant IBS (IBS-D) with or without SIBO [35, 36], some of whom might have PI-IBS; in fact, abnormal SIP might suggest presence of mucosal malabsorption; and abnormal SIP is well known in patients with TS [37]. Therefore, based on the above evidence, it is logical to believe that a disorder somewhat similar to that described from southern

**Table 2** Comparison between postinfectious tropical malabsorption or epidemic form of tropical sprue (TS) and postinfectious irritable bowel syndrome (PI-IBS)

Features	Postinfectious tropical malabsorption or epidemic form of TS	Postinfectious irritable bowel syndrome
<b>Epidemiology</b>		
Frequency of occurrence following an attack of gastroenteritis (%)	8–20	7–31
Time period when reported	Five to six decades ago	Mostly last two decades
Areas of the world from where reported	Tropics and temperate region (called tropical and temperate sprue)	Mostly from temperate regions
<b>Clinical presentation and diagnosis</b>		
Predominant clinical feature	Diarrhea as defined by liquidity and frequency of stool	Diarrhea as defined by Bristol stool form and frequency
Biochemical evidence of mucosal malabsorption (D-xylose test, fecal fat estimation, Schilling’s test for B <sub>12</sub> malabsorption)	Malabsorption of two unrelated substances is essential for diagnosis	Results of these tests have not been reported in any study
Abnormal small-intestinal histology	Required for the diagnosis	Has not been performed in any study
<b>Pathogenesis</b>		
Possible infective agents that might predispose	Bacteria, virus, protozoa	Bacteria, virus, protozoa
Change in gut flora and small-intestinal bacterial overgrowth	Often associated	Increasing reports among patients with diarrhea-predominant IBS
Small-intestinal permeability abnormality	Demonstrated	Demonstrated
Neurohumoral dysregulation <sup>a</sup>	Demonstrated <sup>a</sup>	Demonstrated
<b>Treatment</b>		
Agents used in the treatment	Antibiotics, folic acid, vitamin B <sub>12</sub>	Drugs modulating gut flora such as probiotics and antibiotics may be potential candidates

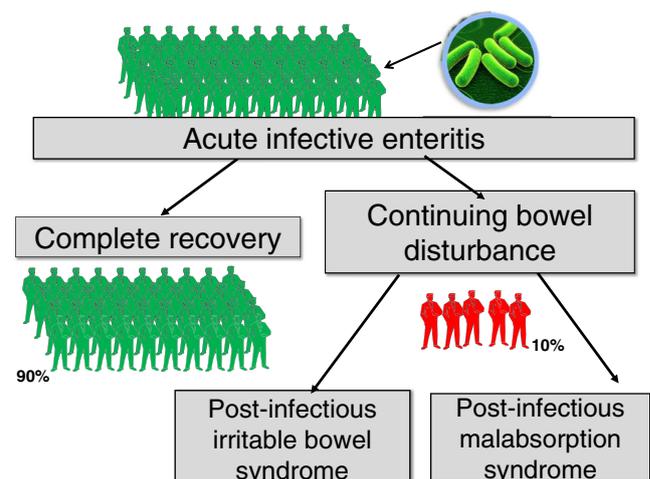
<sup>a</sup> Increase in peptide YY, glucagon-like peptide-1, and neurotensin and reduced motilin

Indian villages is being described from different parts of the world with a different name [1••]. We believe that following an acute gastroenteritis, though some patients recover completely, others may continue to have bowel dysfunction, which may be due to postinfectious tropical malabsorption or due to PI-IBS (Fig. 1). Tests for mucosal malabsorption and small-intestinal histology are essential to differentiate between these two conditions. Hence, we suggest that in the future iteration of Rome criteria for diagnosis of PI-IBS, it is important to consider this issue and modify the criteria for diagnosis of PI-IBS as suggested in Table 3.

**Pathophysiology**

Pathogenesis of TS is multifactorial [38]. These factors include, gut dysbiosis including small-intestinal bacterial colonization and overgrowth, dysregulated host’s immune response leading to protracted inflammation, reduced gut defense, abnormal SIP, villous atrophy, mucosal disaccharidase deficiency including that of lactase, bile acid de-conjugation, neuro-hormonal dysregulation, exaggerated fat-induced ileal

brake leading to slow mouth-to-cecum transit promoting bacterial colonization, deficiency of vitamin B<sub>12</sub> and folate causing megaloblastosis of small-intestinal epitheliums, and colonic dysfunction leading to reduced colonic water



**Fig. 1** Potential outcome of acute infective diarrhea and development postinfectious malabsorption (PI-malabsorption) and postinfectious irritable bowel syndrome (PI-IBS)



### Abnormalities in Gut Defense in TS

One study reported reduced secretion of gastric acid in patients with TS, though salivary IgA was normal [49]. In another study, a proportion of patients with TS were found to have hypogammaglobulinemia [50]. Obviously, these factors would result into reduced innate immunity of gut causing bacterial colonization and overgrowth in the small bowel in the presence of inadequate food hygiene, which is not uncommon in areas of the world where TS has been reported. Zinc supplementation is known to improve gut defense and improve SIP. Zinc supplementation reduced the severity and duration of diarrhea in infants and young children, in an earlier study from India [51]. But, there is no study of zinc in relation to TS. In a report on a single patient with TS developing following journey to Sri Lanka, low level of zinc was detected [52]. However, more studies using sophisticated immunological techniques may uncover many other aspects of reduced gut defense in patients with TS.

### Is TS a Specific Infectious Disorder?

Two earlier studies suggested that protozoa and fungi may play an important role in the pathogenesis of TS [53, 54]. *Cryptosporidium parvum*, *Isoospora belli*, *Blastocystis hominis*, and *Cyclospora cayentanensis* have been identified in fecal samples and small-intestinal biopsy specimens of people suffering from various forms of prolonged diarrhea in the tropics [53–55]. Moreover, viral particles resembling orthomyxo and coronaviruses have been demonstrated in the feces of 90 % of patients with TS from southern India [56].

### Small-Bowel Permeability in TS

Normal SIP is necessary for physiological function of the small bowel including absorption [57]. SIP is abnormal in several diseases associated with altered small-intestinal functions such as IBS-D, PI-IBS, inflammatory bowel disease, and celiac disease [58–62]. Postdysenteric gut dysfunction might result from persistent low-grade inflammation in enteric submucosal and neuromuscular compartments, as shown from studies in animals and human [63]. In patients with IBS-D and PI-IBS, increase in permeability could promote neuromuscular inflammation that disturbs enteric sensation and motility. Abnormal SIP has been reported in patients with TS. A study on estimation of SIP using urinary excretion of lactulose and mannitol by <sup>1</sup>H-NMR spectroscopy on a small number of patients with MAS ( $n=18$ ), including eight patients with TS and healthy controls ( $n=28$ ), showed that the urinary excretion ratio of lactulose to mannitol was higher in patients with MAS as compared to healthy controls [64]. Also, urinary excretion of lactulose was higher in patients with TS but excretion of mannitol was the same as compared with healthy

controls [64]. Another study on SIP using urinary excretion of lactulose and L-rhamnose showed that urinary excretion of lactulose was higher in TS patients as compared with healthy controls [65]. The magnitude of the absorption defects demonstrated in patients with TS was more severe than would be anticipated from the jejunal mucosal abnormalities [65]. In another study, abnormal SIP among patients with TS persisted in spite of treatment in a proportion of patients; [37••] those with persistently abnormal SIP continued to pass more frequent stool and gained less weight than those in whom it got normalized [37••].

### Is TS Related to Neuro-Hormonal Dysregulation?

TS is known to be associated with small-bowel stasis, which predispose to small-intestinal bacterial colonization and overgrowth [39••]. Small-bowel stasis in patients with TS may result from exaggerated ileal brake induced by malabsorbed fat passing through the ileum, which liberate gut hormones like peptide YY, neurotensin, and glucagon-like peptide-1 (Fig. 2) [39••, 66••]. Gut hormones play a major role in intestinal motility. Hormones such as enteroglucagon, peptide YY, and neurotensin slow transit while motilin enhances the rate of gastric emptying and hastens small-intestinal motility [67, 68]. In an earlier study, patients with TS had raised basal plasma motilin and enteroglucagon concentrations, but their postprandial release of both gastric inhibitory polypeptide and insulin was significantly reduced [69]. In two earlier studies, oro-caecal transit time (OCTT) was found to be longer in patients with TS than in controls [39••, 66••]. In one of these studies, OCTT correlated with degree of steatorrhoea [39••]. However, successful treatment of TS led to normalization of fecal fat excretion reducing OCTT [39••]. Lactulose hydrogen breath test was used to measure OCTT whereas glucose hydrogen breath test and quantitative jejunal aspirate culture were used to evaluate for SIBO in this study. Patients with SIBO with malabsorption are known to have longer OCTT than those without [70]. In a recent study, infusion of fat into the proximal small intestine was shown to inhibit antroduodenal motility, delay duodeno-cecal transit time, and increase plasma levels of peptide YY and neurotensin than among controls [66••]. Though the same mechanism of fat-induced ileal brake may operate in patients with MAS and steatorrhoea due to any cause, such as celiac disease and chronic pancreatitis, it has been studied only in patients with TS [66••].

### TS and Colon—Is There Colonic Abnormality in TS?

In patients with MAS such as TS, a larger amount of fluid passes through the ileocecal valve than the healthy subjects [66••]. Colon can increase its capacity to absorb electrolytes and water to compensate for the higher amount of fluid

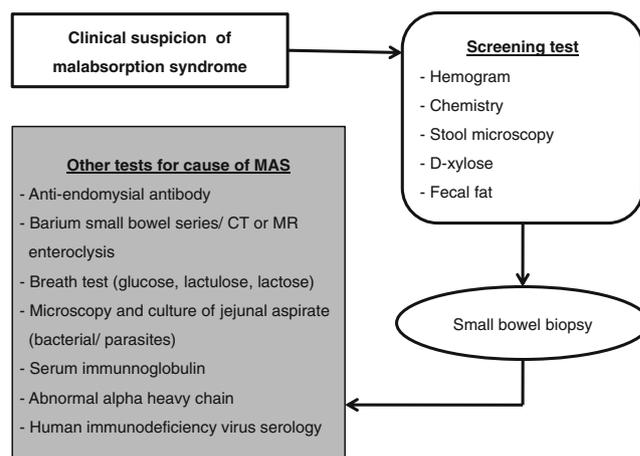
coming to the colon to prevent occurrence of diarrhea. Ramakrishna et al. showed that in patients with TS, there is abnormality in the colon that prevents this compensatory mechanism predisposing to occurrence of diarrhea [71–73].

### Is TS Due to Vitamin B<sub>12</sub> and Folate Malabsorption?

Deficiencies of folate and vitamin B<sub>12</sub> may favor the development of TS by causing megaloblastosis of small-intestinal epithelium [74]. Vegetarians are at risk for vitamin B<sub>12</sub> deficiency due to suboptimal intake [75]. A large proportion of Indian subjects are vegetarian, which may predispose to the deficiency of vitamin B<sub>12</sub>. Moreover, SIBO may predispose to vitamin B<sub>12</sub> deficiency as occurring in blind loop syndrome [76]. Although vitamin B<sub>12</sub> absorption is frequently improved by antibiotics, it may not return to normal levels despite prolonged therapy [77]. There may be, therefore, a coexistent mucosal lesion as previously described in *E. coli*-contaminated rats and small-intestinal diverticulosis in man [78, 79]. In a previous study on 38 patients with vitamin B<sub>12</sub> malabsorption, antibiotic therapy resulted in a rapid return of vitamin B<sub>12</sub> absorption to normal in 50 % of the patients [12•]. In another study, vitamin B<sub>12</sub> absorption returned to normal and there was a marked decrease in total luminal flora in all three subjects who were treated with tetracycline [79]. Furthermore, there was some correlation between the bacteriological findings in both the jejunum and ileum and vitamin B<sub>12</sub> malabsorption [80]. In the jejunal aspirates of patients with vitamin B<sub>12</sub> malabsorption, the mean log counts of aerobic flora, total flora, and bacteroides were greater than the counts in the controls and in the ileal aspirates, all except one of the patients with vitamin B<sub>12</sub> malabsorption had bacteria present in counts greater than 10<sup>4</sup> colony forming units/milliliter (CFU/mL) [80]. Whereas in those with normal vitamin B<sub>12</sub> absorption, only one fourth had bacterial growth and none had more than 10<sup>3</sup> CFU/mL [80]. This might suggest that bacteria to produce toxins altering small-intestinal physiology. Such a mechanism has been postulated for *E. coli* in a case of diverticulosis [79]. However, further studies to examine the nature of the cellular lesion responsible for the vitamin B<sub>12</sub> absorptive defect in TS and the possible role of bacteria in its pathogenesis are required.

### Management of TS

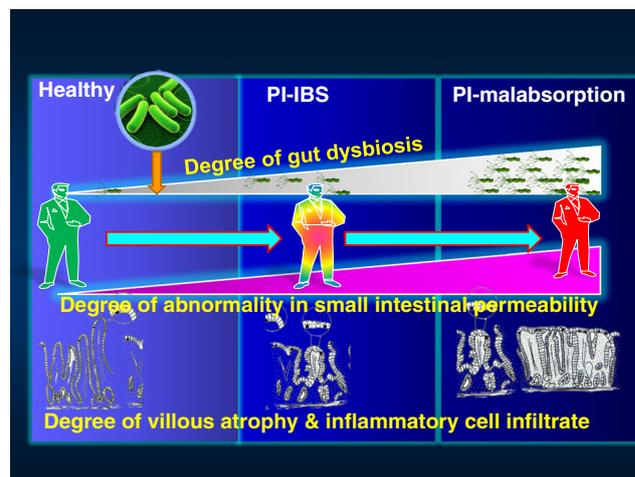
**Diagnosis** Patients with TS presents with chronic diarrhea, anorexia, weight loss, malnutrition, anemia, signs of vitamin deficiency, fatigue, neuropathy, bone disease due to calcium and vitamin D malabsorption, and symptoms of potassium deficiency such as proximal muscle weakness. Clinically, it is difficult to differentiate between different causes of MAS. However, in a recent study, we found that



**Fig. 3** Outline of investigations of patients with malabsorption syndrome in the tropics

younger age (<35 years) and longer duration of diarrhea were more often associated with celiac disease than TS [5••]. Clubbing of fingers, which may sometimes occur in patients with MAS due to various causes, has rarely been reported in patients with TS [5••]. The protocol for work-up of patients presenting with MAS is outlined in Fig. 3.

**Treatment** Treatment of TS involves treating malnutrition, vitamin supplementation, particularly vitamin B<sub>12</sub> and folic acid, and correcting the possible etiology viz. intestinal bacterial colonization and overgrowth. Ideal body weight should be calculated and a diet plan made according to it. A few patients may be too sick and require hospitalization for proper management. Fluid and electrolyte balance should be achieved as early as possible. Vitamins should be supplemented as most of the patients with TS have multiple vitamin deficiencies. In severely malnourished patients, parenteral vitamins may be required. Similarly, minerals like iron, calcium, and magnesium should be supplemented.



**Fig. 4** A unifying hypothesis for pathogenesis of tropical sprue and postinfective (PI) irritable bowel syndrome (IBS)

Empirical antibiotic treatment has been shown to improve diarrhea and associated malnutrition in most patients with TS [77, 81]. Most studies have been done with tetracycline and sulfonamides [81, 82]. It has been shown that folate and vitamin B<sub>12</sub> absorption improves markedly and symptoms resolve early with antibiotics [83]. Treatment with folic acid alone can be curative early in the course of the disease [84]. It has been proposed that antibiotics reduce the overall bacterial load in the gut leading to reduced inflammation and thus improving diarrhea [85]. Prolonged treatment with tetracycline may be required for complete resolution of symptoms. Tetracycline is generally given for 2 months. In a recent study, rifaximin was tried in treatment of TS without encouraging result [86]. More studies, however, are needed on this issue.

Adequate dietary management is the key for the management of TS. Steatorrhea is a common feature of TS and contributes significantly to diarrhea [87, 88]. Antibiotics and vitamins may not completely cure steatorrhea. Cause of steatorrhea is multifactorial—mucosal malabsorption of fat, bacteria-splitting bile acids, and impaired enterohepatic recirculation of bile salts [89]. Restriction of long-chain fatty acids may help in reducing steatorrhea. It should be replaced by medium-chain triglycerides. Coconut oil, which is rich in medium-chain fatty acids, may be helpful in reducing diarrhea [90]. Moreover, malabsorbed fat might cause exaggerated ileal brake reducing gut motility, promoting SIBO and malabsorption in TS [39••]. Protein and carbohydrate intake should be guided by the weight and body mass index.

Long-term prognosis of patients with TS with proper dietary management and antibiotics plus vitamins is good. However, in endemic regions, the disease may have relapsing course requiring repeated cycles of antibiotics. Also, not all patients who improve symptomatically have complete resolution of small-intestinal histology and functions such as SIP [39••, 91].

### Conclusion and Future Direction

TS, once thought to be a common cause of MAS, is now believed to be uncommon, though the evidence contradicts this belief. There is significant overlap between TS and PI-IBS. In fact, PI-IBS and TS may be continuing spectrum of response of the gut to an episode of infectious gastroenteritis (Fig. 4). Since pathogenesis of TS and PI-IBS is similar, we may need to learn about management of PI-IBS from our knowledge on management of TS. More research is needed on this issue.

### Compliance with Ethics Guidelines

**Conflict of Interest** Uday C. Ghoshal, Ujjala Ghoshal, Deepakshi Srivastava, and Abhai Verma declare no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by the author.

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- Of major importance

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