

## SQUARE PHARMACEUTICALS LTD. BANGLADESH

## July, 2014 Volume : 7 Issue : 1

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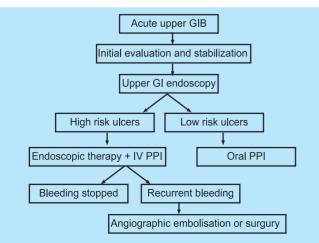
### Management of GI emergencies: Peptic ulcer acute bleeding

Peptic ulcers bleeding accounted for 36% of all causes of acute upper gastrointestinal bleeding. Changes in disease epidemiology have posed new challenges to clinical management. These include a larger proportion of elderly patients, and more patients taking novel anti-platelets, anti-coagulants, non-steroidal anti-inflammatory drugs (NSAIDs) and cyclo-oxygenase 2 (COX-2) inhibitors for various medical co-morbidities. Peptic ulcer bleeding is now predominantly a disease of the elderly, with over 60% of patients above the age of 60 years, and around 20% over the age of 80 years.

#### Risk stratification and pre-endoscopy management

Initial evaluation and risk stratification is important in the management of patients with upper gastrointestinal bleeding. In patients with exsanguinating haemorrhage and unstable haemodynamic status, intensive monitoring and prompt fluid and red cell replacement is mandatory. Although transfusion can be life-saving and may replace blood loss to enhance tissue perfusion, overzealous transfusion in haemodynamically stable patients was reported to be associated with higher rates of recurrent bleeding and death. Liberal transfusion was associated with higher rate of complications. Nevertheless, higher haemoglobin thresholds may be considered in patients with evidence of intravascular volume depletion, or other co-morbidities such as coronary artery disease(Fig. 1). Several risk classfication systems have been developed to help determine the level of intervention and predict disease outcome. The Rockall score is a composite score that combines clinical parameters with endoscopic findings to predict mortality; whereas the Glasgow-Blatchford score include several clinical and laboratory parameters. In a prospective cohort of 676 patients with acute gastrointestinal bleeding, the Glasgow-Blatchford score was shown to be superior to the Rockall score in predicting the need of intervention and death. Patients with a Glasgow-Blatchford score of 0 have a <1% chance of requiring intervention, and may be suitable for outpatient management. Among the many clinical parameters, age >70 years, presence of medical co-morbidities, haematemesis at presentation; systolic blood pressure <100 mmHg, in-hospital ulcer bleeding, recurrent bleeding and the need for surgery are independent predictors of mortality.

Pre-emptive acid suppressive therapy prior to endoscopic haemostasis is used. In a study involving 638 patients with upper GI bleeding randomized to receive high dose IV omeprazole or placebo, the need of endoscopic treatment was lower in the omeprazole group with less actively bleeding and more clean-based ulcers. The use of proton pump inhibitors should not replace urgent endoscopy in actively bleeding patients; although in situations where endoscopy may be delayed or contraindicated, proton pump inhibitor therapy may improve clinical outcomes.



**Fig. 1. Management of acute peptic ulcer bleeding.** GIB - gastrointestinal bleeding, PPI- proton pump inhibitor.

#### Endoscopic treatment

Endoscopic therapy has generally been recommended as the first-line treatment for upper gastrointestinal bleeding. It has been shown to reduce further bleeding, the need for surgery and mortality. The benefits of endoscopic therapy appear be most significant in actively bleeding ulcers and ulcers with a visible vessel. Patients with unstable haemodynamic status should undergo urgent endoscopy for primary haemostasis; whereas for stable patients, early endoscopy should be considered.

Most international guidelines recommend that upper gastrointestinal endoscopy should be performed within 24 hours in patients presented with upper gastrointestinal bleeding. Early endoscopy may facilitate rapid haemostasis for high risk patients and avoid unnecessary hospital of low risk patients. The endoscopic appearances of bleeding ulcers can be classified by the modified Forrest classification, which predicts the risk of rebleeding, the need for intervention and death. This classification can be used to stratify patients and guide management decisions. Ulcers with high risk features, i.e. those with active spurting (IA), active oozing (IB) or non-bleeding visible bleeding vessel (IIA) have high risk of further bleeding and warrant endoscopic therapy. In non-randomized cohorts of patients receiving only conservative therapy, the rate of further bleeding was as high as 70% in spurting ulcers and about 30-40% in oozing ulcers. A meta-analysis of endoscopic therapy shows a significant decrease in further bleeding for both actively bleeding ulcers and ulcers with non-bleeding visible vessels. For ulcers with adherent clot (IIB), endoscopic therapy may be performed by targeting the underlying lesion after clot removal. This has been shown to reduce recurrent bleeding as compared to medical therapy alone, although significant heterogeneity exists among the studies. Endoscopic therapy is generally not recommended for ulcers with a flat pigmented spot (IIC) or a clean base (III).

Endoscopic therapy can be divided into injection, thermal and mechanical methods. Adrenaline injection, when employed, should be coupled with a second modality as this reduces further bleeding and surgery. Thermal coagulation therapy is effective in achieving initial haemostasis, reducing further bleeding, surgery and mortality when compared to no endoscopic therapy. Although no randomized study has directly compared haemostatic clips versus no endoscopic therapy, this method is more effective than adrenaline injection and is similar to thermal coagulation in reducing further bleeding and the need for surgery

#### Post-endoscopy management

Gastric acid suppression favours haemostasis in peptic ulcer bleeding by enhancing platelet aggregation and clot formation. Apart from its preemptive use prior to endoscopy; proton pump inhibitor is also effective in reducing recurrent peptic ulcer bleeding after endoscopy. The optimal dosing of proton pump inhibitor after endoscopy is controversial. At present, the use of high dose intravenous infusion for high risk ulcers appears reasonable.

Recurrent bleeding occurs in a small but significant proportion of patients after initial haemostatic control. A randomized trial comparing repeated endoscopic therapy versus surgery revealed that 73% of patients with recurrent bleeding can be treated with repeated endoscopic therapy to achieve durable haemostasis, with a lower complication rate than surgery. Therefore it is reasonable to repeat endoscopic treatment may lead to perforations. If further bleeding occurs after the second endoscopic attempt, surgery or angiographic embolisation may be attempted.

#### Management after acute bleeding episode

Peptic ulcers have a high rate of recurrence, especially if no measure is taken to eliminate the causative agent or provide protective coverage. Depending on different aetiologies, studies have reported 1-year recurrent bleeding rates of 15–40%. Definitive treatment and preventive measures are employed to reduce the chance of ulcer recurrence.

Ref: Management of GI emergencies: Peptic ulcer acute bleeding. Sunny H. Wong, Joseph J.Y. Sung, Best Practice & Research Clinical Gastroenterology 27 (2013) 639–647

July 2014 Volume : 7 Issue : 1

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## American Gastroenterological Association Technical Review on Constipation

#### Definition and Classification of Chronic Constipation

Constipation is a syndrome that is defined by bowel symptoms (difficult or infrequent passage of stool, hardness of stool, or a feeling of incomplete evacuation) that may occur either in isolation or secondary to another underlying disorder (eg, Parkinson's disease). Although many physicians regard constipation as synonymous with reduced stool frequency, others also consider straining to defecate, hard stools, and the inability to defecate at will as constipation. Hence, the Rome III symptom criteria for constipation incorporate several bowel symptoms (Table 1); a diagnosis of defecatory disorders also requires abnormal anorectal test results. Constipation-predominant irritable bowel syndrome (IBS-C) is defined by abdominal discomfort that is temporally associated with 2 of the following 3 symptoms: relief of discomfort after defecation, hard stools, or less frequent stools. Although some patients with constipation also have abdominal discomfort, discomfort is not, in contrast to IBS-C, associated with these features. However, this distinction is of limited utility because patients are often uncertain about the temporal relationship between abdominal discomfort and these features. Moreover, compared with patients with constipation who do not have abdominal pain, patients with constipation who experience pain report poorer overall health and a greater impact of bowel symptoms on quality of life and more somatic symptoms regardless of whether the pain was or was not associated with characteristics of irritable bowel syndrome (IBS). Hence, the presence or absence of abdominal pain may be more useful than other associated features for characterizing phenotypes in chronic constipation.

The American Gastroenterological Association (AGA) and Rome III criteria both emphasize the need to identify defecatory disorders. However, in contrast to the Rome III criteria, the last AGA technical review do not use the term "functional constipation" because a subset of patients with symptom criteria for functional constipation have slow colonic transit. Moreover, in several small studies, slow transit constipation (STC) was associated with a marked reduction in colonic intrinsic nerves and interstitial cells of Cajal, that is, it is not truly a functional disorder. Also, as detailed later, IBS-C is associated with various pathophysiological disturbances (eg, slow transit, abnormal colonic sensation). Hence, the AGA criteria rely on assessments of colonic transit and anorectal function to classify patients with constipation into one of 3 groups: normal transit constipation (NTC), STC, and pelvic floor dysfunction or defecatory disorders.

#### **Risk Factors for Constipation**

Lower socioeconomic status and lower parental education rates are associated with constipation, as are less self-reported physical activity, medications, depression, physical and sexual abuse, and stressful life events. Constipation was associated with low dietary fiber intake in some, but not other, studies.

#### **Clinical Evaluation**

The clinical assessment must, in particular, elicit specific symptoms of constipation, clarify which symptoms are distressing, and inquire about medications that can cause or are used to treat constipation. Alarm symptoms include a sudden change in bowel habits after the age of 50 years, blood in stools, anemia, weight loss, and a family history of colon cancer. The timing of symptom onset, particularly relative to potential risk factors (eg, onset during childhood, use of prescription and over-the-counter medications, inadequate dietary calorie and fiber intake, obstetric events, and a history of abuse), should be clarified. It is essential to characterize bowel habits and elucidate the specific symptoms of chronic constipation. Is the "call to stool" postprandial, initiated by

#### Table 1. Definitions of Constipation

abdominal discomfort and/or by a rectal sensation? Is the call always answered? What maneuvers (eg, straining to begin and/or to end defecation) are used to defecate? Although some symptoms (ie, anal digitation, a sense of anal blockage during defecation, or a sense of incomplete evacuation after defecation) suggest disordered defecation, the evaluation of these symptoms by a questionnaire is not particularly useful for discriminating patients with constipation who have a normal versus an abnormal rectal balloon expulsion test result. Pictorial representations of stool form (eg, by the Bristol Stool Form Scale) and bowel diaries are efficient and reliable methods to characterize bowel habits and are better predictors of colonic transit than self-reported stool frequency. Moreover, self-reported stool frequency is unreliable. Stool form also influences the ease of defecation. For example, among women with constipation in the community, straining to begin defecation is more frequent for hard stools than normal stools. When evacuatory deficits are pronounced, even soft stools and enema fluid may be difficult to pass. After a complete purge, it will take several days for residue to accumulate such that a normal fecal mass will be formed. Hence, it is not uncommon for patients to skip a bowel movement for a few days after a bout of diarrhea. Use of laxatives in patients with constipation can also predispose to alternating constipation and diarrhea, which is common in IBS

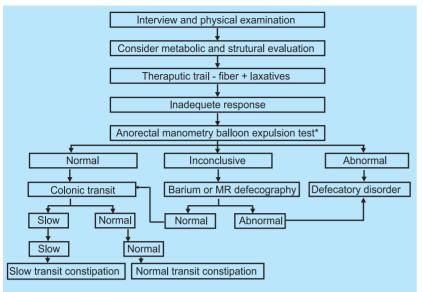
The clinical assessment should consider diseases to which constipation is secondary. A meticulous perineal and rectal examination is very useful for identifying defecatory disorders. Digital rectal examination can gauge anal resting tone. Pelvic contraction is normally accompanied by increased anal tone and a puborectalis "lift" (ie, anterosuperior motion toward the umbilicus); when patients are instructed to "expel the examining finger," both muscles should relax with perineal descent, which is normally 2 to 4 cm. Patients with defecatory disorders may have high anal resting tone, as evidenced by increased resistance to insertion of the examining finger into the anal canal, and/or impaired relaxation or paradoxical contraction of the sphincter complex with reduced perineal descent during simulated evacuation. Other possible findings include stool in the rectal vault, fecal soiling on the perianal skin, hemorrhoids, anal fissure(s), a rectocele, or puborectalis tenderness.

Physiological testing should be performed in patients with chronic constipation refractory to dietary fiber supplementation and/or over-the-counter laxatives. When the clinical index of suspicion for disordered defecation is high, anorectal testing may be considered sooner, perhaps even before a trial of fiber and overthe-counter laxatives. In addition, a complete blood cell count should be performed. Although fasting serum glucose, sensitive thyroid-stimulating hormone, and calcium levels are often measured, the diagnostic utility and costeffectiveness of these tests are probably very low. Testing for colon cancer with imaging or endoscopy should be considered for all patients with alarm clinical features (eg, blood in stool, unexplained anemia, weight loss >10 lb, abdominal or rectal mass), for all patients with constipation refractory to medical management, and for patients aged 50 years or older; this age specification is lower in some patients with a family history of colon cancer. Testing should also be considered in patients with an abrupt change in bowel habits without an obvious cause. Routine colonoscopy is not warranted for most patients with constipation.

Defecatory disorders, which are by far the most common cause of medically refractory chronic constipation, can often be recognized by a careful clinical assessment and substantiated by anorectal test results. In general, IBS-C is characterized predominantly by abdominal pain, bloating, or feelings of incomplete evacuation in addition to bowel disturbances. Thereafter, assessments of colonic transit, as well as intraluminal assessment of colonic motor activity in selected patients, are useful for identifying when constipation is caused by colonic motor dysfunction.

Rome III creteria		Criteria used in pharmacologic studies		
Constipation	IBS-C	Constipation	IBS-C	
, I	Recurrent abdominal pain or discomfort at least 3 days per month in the past 3 months associated with 2 or more of the following:	3 SBMs per week and 1 of the following symptoms for at least 12 weeks during the preceding 12 months:		
<ul> <li>Straining</li> <li>Lumpy or hard stools</li> <li>Sensation of incomplete evacuation</li> <li>Sensation of anorectal obstruction/blockade</li> <li>Manual maneuvers to facilitate defecations; 3 defecations/wk</li> <li>Loose stools are not present, and there are insufficient criteria for IBS</li> </ul>	<ul> <li>Improvement with defecation</li> <li>Onset associated with change in frequency of stool</li> <li>Onset associated with change in form (appearance) of stool</li> <li>25% of bowel movements were loose stools</li> </ul>	<ul> <li>Straining in more than one-fourth of defecations</li> <li>Lumpy or hard stools in more than one-fourth of defecations</li> <li>Sensation of incomplete evacuation in more than one-fourth of defecations</li> <li>No loose or watery SBMs (Bristol Stool Form Scale score of 6–7)</li> </ul>	<ul> <li>Straining in one-fourth or more of defecations</li> <li>Lumpy or hard stools in one-fourth or more of defecations</li> <li>Sensation of incomplete evacuation in one-fourth or more of defecations</li> <li>Mean score of 2.0 for daily nonmenstrual abdominal pain or discomfort (5-point scale ranging from 1 none to 5 very severe)</li> <li>Mean of 3 complete SBMs and 6 SMBs per week</li> </ul>	





#### Figure 1.Treatment algorithm for chronic constipation. MR, magnetic resonance.

#### **Diagnostic Tests**

Figure 1 from the medical position statement summarizes a preferred approach to diagnostic testing in patients with chronic constipation who have not responded to a high-fiber diet and/or over-the-counter laxatives after organic disorders have been excluded. Anorectal testing with manometry and a rectal balloon expulsion test are at the top of the pyramid and may be considered even before trying laxatives in patients with symptoms that are highly suggestive of pelvic floor dysfunction. In contrast to the previous medical position statement, assessment of colonic transit is not recommended in the early assessment.

#### **Putting It Together**

At the conclusion of the initial clinical evaluation of patients with constipation, it should be possible to tentatively classify patients into one (or possibly more) of the following categories:

1. NTC with normal colonic transit and defecation; some patients in this group have symptoms of  $\ensuremath{\mathsf{IBS}}$ 

 STC when pelvic floor function is normal and there is evidence of slow transit
 Defecatory disorders (anismus/dyssynergia [failure of relaxation] or descending perineal syndrome and other flaccid disorders)

4. Combination of 2 and 3; clinical observations suggest that some patients also have features of IBS

5. Organic constipation (mechanical obstruction or adverse drug effect)

6. Secondary constipation (metabolic disorders).

#### **Medical Management**

The treatment algorithms in the medical position statement encapsulate our suggestions. Tables 2 summarize common over-the-counter laxative agents and newer pharmacologic agents for chronic constipation. There is new evidence supporting the use of common laxative agents.

#### **Management of Defecatory Disorders**

Defecatory disorders should be managed by biofeedback-aided pelvic floor retraining. Although therapy may also include measures to improve pelvic floor contraction (ie, Kegel exercises), the emphasis in patients with defecatory disorders is on appropriately coordinating abdominal and pelvic floor motion during evacuation.

#### **Role of Surgery**

Patients with STC who fail to respond to optimal medical management are candidates for colectomy and ileorectostomy. In a referred population undergoing stringent physiological testing, only about 3% are actually candidates for this procedure. Thus, among the population at large with constipation, only a tiny fraction will ever be suitable candidates for ileorectostomy. Patients with both pelvic floor dysfunction and STC should have their pelvic floor function addressed by pelvic floor retraining and, if constipation persists, should be offered IRA. Patients with a physiologically significant rectocele should undergo a repair, and patients with rectal intussusception should undergo pelvic floor retraining.

Ref: GASTROENTEROLOGY 2013;144:218-238. GASTROENTEROLOGY 2013;144:211-217

Туре	Generic name	Dosage	Side effects	Time of ons	et Mechanism of action
Fiber	Barn	1 cup/day	Bloating, flatulence, iron and calcium malabsorption		Stool bulk increases, colonic transit tmie decdreases, gastrointestinal motility increase
Psylliu	Psyllium	1 tsp up to 3 times daily	Bloating, flatulence		
	Methylcellulose Calcium polycarbophi	1 tsp up to 3 times daily 2–4 tablets once daily	Less bloating Bloating, flatulence		
Stool softene	er Docusate sodium	100 mg twice daily		12-72	
Hyperosmola agents	ar Sorbitol	15–30 mL once daily or twice daily	Sweet tasting, transient abdominal cramps, flatulence	24-48	Nonabsorbable disaccharides metabolized by colonic bacteria into acetic acid and other short-chain fatty acids
	Lactulose	Same as sorbitol	Same as sorbitol	24-48	
	PEG	8–32 oz once daily	Incontinence due to potency	0.5-1	Osmotically increases intraluminal fluids
	Glycerin	Suppository; up to once daily	Rectal irritation	0.25-1	Evacuation induced by local rectal
	Bisacodyl, Picosulfate	10-mg suppositories or 5–10 mg by mouth up to 3imes/wk	Incontinence, hyperkalemia,abdominal cramps, rectal burning with daily use of suppository form	0.25-1	Bisacodyl, Picosulfate & sodium picosulfate are are hydrolyzedto active metabolite, which has antiabsorptive/secretory and prokinetic effects
	Anthraquinones (senna, cascara)	2 tablets once daily to 4 tablets twice daily	Degeneration of Meissner's and Auerbach's plexus (unproven), malabsorption, abdominal cramps, dehydration, melanosis coli	8-12	Electrolyte transport altered by increased intraluminal fluids; myenteric plexus stimulated; motility increases
Saline laxativ	e Milk of magnesia	15–30 mL once daily or twice daily	Magnesium toxicity, dehydration, abdominal cramps, incontinence	1-3	Fluid osmotically drawn into small bowel lumen; cholecystokinin stimulated; colon transit time decreases
Lubricant	Mineral oil	15 - 45 ml	Lipid pneumonia, malabsorption of fat-soluble vitamins, dehydration, incontinence	6-8	Stool lubricated

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#### Editorial Note:

Dear Doctor, It's our immense pleasure to inform you that we have published the first issue, Vol: 7, of GI Café. In this newsletter, we have highlighted the GI bleeding and Constipation management. The articles give you some interesting thoughts.

Your comments and suggestions will enrich our upcoming issues. Please participate in quiz competition and win prizes.

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