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Contents

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Contents

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REVIEW

Diagnosis and treatment of gastroesophageal reflux disease

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Abstract

Gastroesophageal reflux disease (GERD) is a common disease with a prevalence as high as 10%-20% in the western world. The disease can manifest in various symptoms which can be grouped into typical, atypical and extra-esophageal symptoms. Those with the highest specificity for GERD are acid regurgitation and heartburn. In the absence of alarm symptoms, these symptoms can allow one to make a presumptive diagnosis and initiate empiric therapy. In certain situations, further diagnostic testing is needed to confirm the diagnosis as well as to assess for complications or alternate causes for the symptoms. GERD complications include erosive esophagitis, peptic stricture, Barrett's esophagus, esophageal adenocarcinoma and pulmonary disease. Management of GERD may involve lifestyle modification, medical therapy and surgical therapy. Lifestyle modifications including weight loss and/or head of bed elevation have been shown to improve esophageal pH and/or GERD symptoms. Medical therapy involves acid suppression which can be achieved with antacids, histamine-receptor antagonists or proton-pump inhibitors. Whereas most patients can be effectively managed with medical therapy, others may go on to require anti-reflux surgery after undergoing a proper pre-operative evaluation. The purpose of this review is to discuss the current approach to the diagnosis and treatment of gastroesophageal reflux disease.

Key words: Gastroesophageal reflux disease; Esophageal disease; Acid suppression; Fundoplication; Upper gastrointestinal tract disorder

Core tip: Given the high prevalence of gastroesophageal reflux disease (GERD) and the various complications which can result from inadequate treatment, it is important for practioners to have a proper understanding of the current approach to its diagnosis and management. Diagnostic tools including various methods of pH testing are discussed. Furthermore, it is important to understand the indications and contraindications to anti-reflux surgery in order to optimize our patient's surgical outcomes. Management of GERD in the obese patient may involve bariatric surgery and this is also further discussed.

Badillo R, Francis D. Diagnosis and treatment of gastroesophageal reflux disease. *World J Gastrointest Pharmacol Ther* 2014; 5(3): 105-112 Available from: URL: http://www.wjgnet.com/2150-5349/full/v5/i3.105.htm DOI: http://dx.doi.org/10.4292/wjgpt.v5.i3.105

SYMPTOMS AND EPIDEMIOLOGY

Gastroesophageal reflux disease (GERD) is defined as symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus or beyond, into the oral cavity (including larynx) or lung[1,2]. GERD can be classified as non-erosive reflux disease (NERD) or erosive reflux disease (ERD) based on the presence or absence of esophageal mucosal damage seen on endoscopy. The following document will provide a brief overview of the epidemiology, clinical symptoms and complications of GERD as well as a more comprehensive review of the current approach to diagnosis and management.

GERD is one of the most commonly encountered conditions by both primary care physicians and gastroen-

Table 1 Symptoms of gastroesophageal reflux disease

Typical Symptoms	Acid regurgitation, heartburn
Atypical Symptoms	Epigastric fullness, epigastric pressure, epigastric pain, dyspepsia, nausea, bloating, belching
Extraesophageal Symptoms	Chronic cough, bronchospasm, wheezing, hoarseness, sore throat, asthma, laryngitis, dental erosions

terologists. To illustrate, a 2005 systematic review found the prevalence of GERD (defined by at least weekly heartburn and/or acid regurgitation) to be as high as 10%-20% in the Western world compared to a prevalence of less than 5% in Asia. There is a trend for higher prevalence in North America compared to Europe, and a trend for higher prevalence in Northern over Southern Europe[3]. It should be noted, however, that there are limitations in the diagnosis of GERD based solely on patient symptoms as there are patients with endoscopic evidence of GERD (*e.g.,* esophagitis or Barrett's esophagus) who lack symptoms and patients who have symptoms but no objective evidence of GERD. The high prevalence of GERD in combination with the high cost of acid lowering medications results in the significant socioeconomic burden associated with the disease.

GERD can manifest in a wide range of symptoms which can be subdivided into typical, atypical and extraesophageal symptoms (Table 1). In general, symptoms tend to be more common after meals and are often aggravated by recumbency and relieved by acid lowering medications[1]. Typical symptoms include heartburn and acid regurgitation which have high specificity but low sensitivity for GERD[4]. Atypical symptoms such as epigastric pain, dyspepsia, nausea, bloating, and belching may be suggestive of GERD but may overlap with other conditions in the differential diagnosis such as peptic ulcer disease, achalasia, gastritis, dyspepsia and gastroparesis. Lastly, there are various extraesophageal symptoms including chronic cough, asthma, laryngitis and dental erosions[5]. The current belief is that these symptoms are caused by either microaspiration of refluxate or a vagally mediated reflex triggered by distal esophageal acid exposure. The shared vagal innervation of the cough reflex and esophagus is believed to act as the pathway through which distal esophageal acid exposure may lead to coughing, a process known as the esophagobronchial reflex[6]. However, extraesophageal symptoms could be secondary to a host of other conditions and should not uniformly be attributed to a diagnosis of GERD, especially when typical symptoms are absent.

GERD symptoms have a profound impact on health-related quality of life (HRQoL). A 2011 systematic review of nine studies, including a total of 14774 patients with GERD, showed that persistent reflux symptoms on PPI therapy are associated with reduced physical and mental HRQoL, while reduced mental HRQoL at baseline seemed to impair symptomatic response to PPIs. The authors recommended that one consider behavioral and psychological factors when making decisions about disease management in those patients with persistent reflux symptoms and reduced well-being despite PPI treatment[7]. It is therefore important to recognize, diagnose and properly treat patients with GERD in order to avoid detrimental effects on quality of life as well as numerous complications.

GERD-related complications include erosive esophagitis, peptic stricture, Barrett's esophagus, esophageal adenocarcinoma and pulmonary disease. Esophageal adenocarcinoma is thought to be more common in older white males with elevated body mass index and screening for Barrett's esophagus is recommended in this group[8,9].

DIAGNOSIS

The diagnosis of GERD is typically made by a combination of clinical symptoms, response to acid suppression, as well as objective testing with upper endoscopy and esophageal pH monitoring. For example, the combination of moderate to severe typical symptoms and endoscopic changes (erosive esophagitis or Barrett's esophagus) are highly specific (97%) for GERD (confirmed with pH testing)[10]. However, a well-taken history alone can prove very valuable in the diagnosis, especially in the setting of heartburn and acid regurgitation which have a very high specificity (89% and 95%, respectively), albeit low sensitivity (38% and 6%) for GERD[4]. This can allow one to make a presumptive diagnosis and begin empiric therapy, thereby avoiding a comprehensive and costly evaluation in every patient presenting with uncomplicated symptoms[11]. Additional testing may be necessary, however, for those who do not respond to acid suppression, those who have alarm symptoms (*e.g.,* dysphagia, odynophagia, iron deficiency anemia, weight loss, *etc.*) and those who have suffered from the disease for an extended period of time due to concern for Barrett's esophagus[1]. The rationale for pursuing additional testing includes confirmation of GERD as well as evaluation of GERD associated complications or alternate diagnoses (Table 2).

Empirical therapy

As mentioned above, those with a history suggestive of uncomplicated GERD manifesting in typical symptoms of heartburn and/or regurgitation can be offered empiric treatment (see treatment section). Typical symptoms that are responsive to acid suppression offer additional evidence for pathologic esophageal acid exposure and it is reasonable to assume a diagnosis of GERD in patients who respond to appropriate therapy[1]. On the other hand, typical symptoms that do not improve warrant further evaluation to demonstrate the existence of GERD and evaluate for an alternate diagnosis. Likewise, patients with atypical symptoms or non-cardiac chest pain as their primary complaint should also be considered for further diagnostic evaluation prior to empiric therapy. It should be remembered that a minority of patients on even high

Table 2 Diagnostic Testing for gastroesophageal reflux disease

Diagnostic test	Indication
PPI trial	Classic GERD symptoms with no alarm symptoms.
Esophageal pH monitoring	Refractory symptoms where GERD diagnosis is in question, pre-operative evaluation for non-erosive disease
Upper endoscopy	Alarm symptoms (*e.g.*, dysphagia), PPI unresponsive patients, high risk for Barrett's esophagus
Barium esophagram	Evaluation of dysphagia, otherwise not recommended for GERD evaluation
Esophageal manometry	Prior to anti-reflux surgery to rule out esophageal dysmotility (*e.g.*, achalasia, scleroderma), otherwise not recommended for GERD evaluation

GERD: Gastroesophageal reflux disease; PPI: Proton pump inhibitor.

dose proton pump inhibition will continue to have objective evidence of pathologic esophageal acid exposure on ambulatory pH monitoring[12], likely a result of medication non-compliance or PPI resistance.

Ambulatory pH monitoring

Ambulatory reflux monitoring is the only modality allowing direct measurement of esophageal acid exposure, reflux episode frequency and association between symptoms and reflux episodes. It is typically used to evaluate patients with persistent symptoms despite medical therapy, particularly those without endoscopic evidence of GERD, in order to confirm the diagnosis. It can also be employed to monitor the control of reflux in those on therapy with persistent symptoms[1] and is also recommended in endoscopy negative patients prior to undergoing anti-reflux surgery in order to confirm the diagnosis.

Reflux monitoring is typically performed using either a wireless capsule or a transnasal catheter (pH alone or combined pH-impedance) with the patient either on or off acid suppression. Though there is no uniform consensus regarding the most optimal method, each has its advantages and disadvantages. For either study, diet and activity should remain unchanged in order to capture an accurate depiction of day to day esophageal acid exposure.

Wireless capsule decreases patient discomfort, allows for longer recording time, and may improve accuracy by allowing the patient to resume normal activities without the presence of a transnasal catheter. The test involves endoscopic or transnasal placement of a radiotelemetry pH sensing capsule to the mucosa of the distal esophagus. The capsule (conventionally placed 6 cm above the squamocolumnar junction) measures pH and transmits the data via a radiofrequency signal to a small receiver clipped onto the patient's belt[13]. Unlike with traditional catheter-based systems, this approach allows the patient to resume normal activity without the conspicuous presence of a transnasal catheter and also allows for additional recording time (typically 48 h compared to 24 h recording with catheter-based monitoring). Another advantage of wireless capsule is the fixed position of the capsule on the esophageal wall in comparison to catheter-based systems where migration due to swallowing or talking has been shown to occur[14,15]. Potential disadvantages include additional expense due to endoscopic placement (as nasal passage can be difficult due to size of capsule), early detachment in a minority of patients, patient discomfort which could require removal via repeat endoscopy, as well as overdiagnosis of GERD due to ingestion of acidic foods[16]. There is also some data suggesting an increased number of reflux episodes during the first 6 hour period following propofol administration[17].

Transnasal catheter pH testing is limited by patient tolerance and 24 h monitoring but has the unique advantage of adding impedance which allows distinguishing between acid and non-acid (weakly acidic or weakly alkaline) gastroesophageal reflux. Impedance monitoring detects changes in the resistance to electrical current across adjacent electrodes, allowing it to differentiate the antegrade and retrograde bolus transit of both liquids and gas. Due to the ability to detect both acid as well as nonacid reflux, impedance-pH monitoring has greater sensitivity than pH monitoring alone in the detection of gastroesophageal reflux[18]. It is the test of choice for on-PPI testing, as these patients have lower rates of acidic reflux with continued episodes of weakly acidic reflux which can then be detected with this modality. In contrast, both wireless capsule and catheter-based systems can be used for evaluation of GERD in patients off acid suppression[19].

Regardless of the pH monitoring system used, a symptom-reflux correlation is made using either the symptom index (SI) or symptom association probability (SAP), the latter being the preferred statistical calculation[20]. This allows for measurement of the strength of the association between reflux events and symptoms. A positive association combined with abnormal esophageal acid exposure provides evidence that symptoms are being caused by GERD.

Upper endoscopy

Upper endoscopy is the primary modality used in the evaluation of the esophageal mucosa in patients with GERD and also allows for biopsies of concerning lesions (*e.g.,* Barrett's metaplasia, strictures or masses). It is important though to understand that there are limitations with the use of upper endoscopy in the diagnosis of GERD. For instance, while an endoscopy showing esophagitis or Barrett's esophagus essentially confirms the diagnosis of GERD (high specificity), a normal endoscopy does not refute the diagnosis. In fact, most patients with typical symptoms of GERD will have no endoscopic evidence

of GERD on esophagogastroduodenoscopy. Therefore, an upper endoscopy is not required for the diagnosis and is mostly performed for evaluation of GERD associated complications and alternative diagnoses as well as for placement of wireless capsule pH probes. Patients with multiple risk factors for esophageal adenocarcinoma (age 50 years or older, male sex, white race, chronic GERD, hiatal hernia, elevated BMI, and intra-abdominal distribution of body fat) should receive screening endoscopy for Barrett's esophagus[8].

Barium esophagram

Barium esophagram was once recommended as a screening test for GERD, but is no longer part of the diagnostic evaluation. A 1996 study of 125 patients compared barium esophagram to esophageal pH monitoring to assess the accuracy of barium screening as a predictor of abnormal esophageal acid exposure. A significantly greater degree of abnormal esophageal acid exposure occurred in patients who had a hiatal hernia or spontaneous reflux on barium radiography. However, the sensitivity and specificity of barium radiography for abnormal degrees of acid reflux were insufficient and therefore this test is no longer recommended in the diagnosis of GERD[21]. On the other hand, it is frequently used in the evaluation of complications related to GERD (*e.g.,* peptic stricture) as well as in the evaluation of dysphagia in the post anti-reflux surgery patient, in conjunction with endoscopic evaluation.

Esophageal manometry

Esophageal manometry is most useful for the evaluation of dysmotility and has only limited utility in the evaluation of GERD. Although disruption of the anti-reflux barrier (gastroesophageal junction) and dysfunction of esophageal peristalsis are common in GERD patients, these findings are not diagnostic and therefore there is no manometric pattern which is pathognomonic for reflux[22]. The role of manometry in the evaluation of GERD remains limited to preoperative testing for exclusion of significant motility disorders such as achalasia or scleroderma (clear contraindications to anti-reflux surgery) as well as for assisting in proper positioning of transnasal pH probes. Otherwise, this test is not recommended for the diagnosis of GERD.

TREATMENT

GERD is a chronic disease that typically requires long term management in the form of lifestyle modification, medical therapy and, for a subset of patients, surgical therapy.

Lifestyle changes

Lifestyle and diet modification traditionally have included weight loss, head of bed elevation, avoidance of nighttime meals, and elimination of trigger foods such as chocolate, caffeine and alcohol. A 2006 systematic review of 16 randomized trials evaluated the impact of lifestyle measures on GERD and concluded that only weight loss and elevation of the head of the bed improved esophageal pH and/or GERD symptoms[23]. A 2006 systematic review and meta-analysis suggested a positive association between increasing BMI and the presence of GERD within the United States and possibly within other countries as well[24]. Interestingly, BMI was found to be associated with symptoms of GERD in both normal weight and overweight women and even moderate weight gain among those of normal weight was found to cause or exacerbate symptoms[25]. Therefore, weight loss is recommended for GERD patients who are overweight or who have had recent weight gain.

For nighttime reflux symptoms, patients should elevate the head of the bed and avoid recumbency 3 h postprandially. A recent study aimed to compare the recurrence rates of ERD and NERD, and determine the risk factors related to the recurrence. Recurrence was diagnosed when patients complained of GERD symptoms requiring additional medication after initial recovery with 4-8 wk of PPI treatment. The authors found that a shorter dinner-to-bedtime interval was the most significant factor influencing the recurrence of GERD and patients who usually slept within 3 h after eating had higher recurrence rates[26]. Despite strict compliance, lifestyle changes alone are frequently inadequate at controlling symptoms and medical therapy often becomes necessary.

Medical therapy

The mainstay of treatment of GERD is acid suppression which can be achieved with several classes of medications including antacids, histamine-receptor antagonists (H_2RAs) or proton-pump inhibitors (PPIs). Studies have shown more complete healing of erosive esophagitis and heartburn relief with PPIs *vs* H_2RA and this effect occurs nearly twice as fast (healing rate and heartburn relief of 11.7%/wk and 11.5%/wk *vs* 5.9%/wk and 6.4%/wk in the PPI and H_2RA groups, respectively)[27]. Additionally, studies show that ERD is more difficult to treat with H_2RA compared to PPIs[28] and patients with ERD tend to have a higher symptom response to PPIs compared to their NERD counterparts[29]. Therefore, it is recommended to treat erosive reflux disease with maintenance PPI therapy at the lowest effective dose as most will relapse after discontinuation of therapy[30]. In general, PPIs are felt to be equally effective and patients should be instructed to take these medications 30-60 min prior to meals; the exception to this is dexlansoprazole which can be taken irrespective of food intake.

In contrast, patients with NERD may potentially be managed successfully with on-demand PPI or, alternatively, with less costly therapy such as H_2RAs. A 2001 study set out to determine the feasibility of step-down therapy in patients with symptoms of GERD rendered asymptomatic with PPIs. After 1 year follow up, 58% of patients in the step-down group were asymptomatic on either non-PPI therapy or no therapy at all. Of those

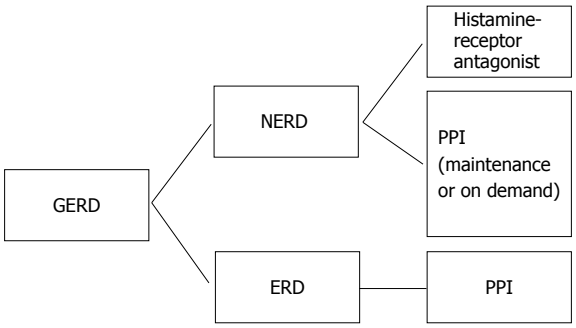

Figure 1 In general, patients with gastroesophageal reflux disease who are found to have evidence of erosive esophagitis on endoscopy should be placed on maintenance proton pump inhibitor due to the high risk of relapse off proton pump inhibitor. However, patients with NERD may achieve symptom control on H_2RAs or, alternatively, with on-demand PPI. If symptoms persist, maintenance PPI should be considered. GERD: Gastroesophageal reflux disease; PPI: Proton pump inhibitor; ERD: Erosive reflux disease; NERD: Non-erosive reflux disease.

who remained off PPIs, 59% required H_2RAs[31]. Given the high cost associated with indefinite PPI use, attempts should be made to treat patients with the least expensive yet effective medication, particularly in patient with NERD who may be able to be maintained on H_2RAs with control of symptoms. If symptoms recur, then maintenance PPI therapy should be reconsidered (Figure 1).

Patients with PPI-refractory GERD can be challenging to treat and are frequently referred to a gastroenterologist. First, compliance with medical therapy and proper dosing should be addressed. A study involving 10159 patients with Barrett's esophagus and 48965 GERD patients without Barrett's esophagus found that PPI prescriptions were filled by only 66.6% and 60.4% of patients with BE and GERD, respectively[32]. Given such high rates of noncompliance, an accurate history is important to obtain in order to avoid escalating therapy unnecessarily. If symptoms are truly refractory to proper medical therapy, the dosing can be increased or an alternate PPI can be used. Both methods may lead to further symptom improvement and both appear to be equally effective[33]. If a patient has predominantly nighttime symptoms, more effective nocturnal acid suppression may be achieved with bid or nighttime dosing of PPIs[34].

Another approach in the PPI-refractory patient involves the addition of nighttime H_2RAs to bid PPI therapy for persistent nighttime symptoms. Though a contested issue, the benefit from this approach would likely be temporary as studies have shown that after 1 mo of uninterrupted H_2RA therapy, gastric acidity returns to pre-H_2RA levels[35]. Another well studied medication is the GABAb agonist baclofen which has been shown to reduce postprandial reflux events and acid exposure in normal individuals and in patients with GERD by inhibiting transient lower esophageal sphincter relaxations, thought to be the primary cause of reflux events[36]. Unfortunately, side effects often preclude continued use of this medication and include drowsiness (up to 63%), dizziness (5%-15%), weakness (5%-15%), and fatigue (2%-4%)[37]. In a recent randomized, cross-over trial it was shown that administering baclofen at bedtime decreases sleep related reflux events and markedly improves objective and subjective sleep parameters compared with placebo. Thus, baclofen appears to have potential benefit for GERD patients with persistent symptoms on PPI therapy, especially those who have persistent nighttime heartburn and sleep complaints[37]. Finally, with respect to prokinetic therapy, a recent study randomized patients into an omeprazole plus mosapride (5HT4 agonist) group and omeprazole plus placebo group and found that the addition of mosapride to omeprazole was no more effective at controlling reflux symptoms than omeprazole alone in patients with NERD[38]. Based on this and several other studies, there is no clear role for the use of prokinetic therapy in the treatment of GERD.

If symptoms persist after attempts at maximizing medical therapy, an evaluation for non-GERD etiologies should be undertaken. An upper endoscopy should be performed next and may reveal an abnormality such as persistent erosive esophagitis, eosinophilic esophagitis, or Barrett's esophagus in roughly 10% of patients in whom empiric PPI therapy fails[39]. The finding of esophagitis would support the diagnosis of GERD and point towards noncompliance or failure of medical therapy. Most times, the esophagus will appear endoscopically normal and these patients should be further evaluated with pH monitoring to confirm or refute the diagnosis of GERD. Confirming pathologic acid reflux with a positive symptom correlation would indicate PPI failure and need for escalation of medical therapy or consideration of surgical options. The absence of GERD in a patient with typical heartburn symptoms would suggest a diagnosis of functional heartburn[2].

Surgical therapy

Surgical therapy is another treatment option for long-term therapy in patients with GERD and has become more appealing since the introduction of laparoscopic anti-reflux surgery. Indications for anti-reflux surgery, which typically include laparoscopic fundoplication or bariatric surgery, include unwillingness to remain on lifelong medical therapy, intolerance of medical therapy, medically refractory symptoms with evidence of GERD on endoscopy or pH monitoring, or GERD in the setting of a large hiatal hernia (Table 3).

Proper patient selection is critical to obtain the best possible surgical outcomes and it is imperative that there be objective documentation of GERD. Furthermore, it is well known that the highest surgical response is seen in those with typical symptoms who respond to a PPI or have abnormal pH testing with good symptom correlation. On the other hand, response rates to surgical intervention are lower in those with atypical or extraesophageal symptoms. To illustrate, one study showed that at 69 mo after laparoscopic fundoplication, the majority of patients maintained improvement or resolution of heart-

Table 3 Indications for anti-reflux surgery

Unwillingness to remain on lifelong medical therapy
Intolerance of medical therapy
Medically refractory symptoms with objective evidence of GERD
GERD in the setting of a large hiatal hernia
Medically refractory GERD in the setting of morbid obesity

GERD: Gastroesophageal reflux disease.

burn (90%), regurgitation (92%), and dysphagia (75%) when compared to before surgery. However, the results were less satisfactory in patients with extraesophageal symptoms such as hoarseness (69%) and cough (69%)[40]. In addition to upper endoscopy and esophageal pH testing, a preoperative workup should include a barium esophagram and esophageal manometry to ensure that there is normal esophageal motility. The combined results of this testing can establish the presence of disease and assist with planning the operative approach[41].

The short and medium term outcomes of laparoscopic anti-reflux surgery are quite good in terms of improving the typical symptoms of GERD[42]. However, in the long term it appears these results may diminish. During a follow-up period of 10 to 13 years, one study comparing long term outcomes in medical and surgical therapies for GERD found that 62% of surgical patients took anti-reflux medications on a regular basis, compared to 92% of medical patients. Anti-reflux surgery can be very effective but should not be advised with the expectation that patients will no longer take anti-secretory medications[43].

Complications from anti-reflux surgery include dysphagia of sufficient severity to require esophageal dilation in about 6% of patients treated with fundoplication surgery[44] as well as a significant increase in flatulence and inability to belch (gas bloat syndrome). This potential for complications underscores the importance of carefully selecting patients for anti-reflux surgery in order to optimize outcomes.

Due to concern for complications associated with traditional fundoplication, sphincter augmentation using the LINX Reflux Management System was developed. The surgery involves the laparoscopic placement of a bracelet of titanium beads with magnetic cores around the LES which serves to augment the physiologic barrier to reflux without altering gastric anatomy. Studies show that at four years following LINX implantation, 87.5% of patients were satisfied with their present condition, and 80% of patients were free from daily dependence on PPIs[45].

In view of the invasiveness of surgery, several endoscopic therapies for GERD have been attempted but due to inability to control GERD have been removed from the market. One of the latest endoscopic techniques for treatment of GERD is transoral incisionless fundoplication. A recent study showed that only a subgroup of patients experienced improved quality of life and reduced need for PPIs at 3 years follow-up, and an unacceptably high percentage of patients required additional medication or revisional laparoscopic fundoplication[46]. Additional studies in endoscopic therapy for GERD are ongoing.

Finally, when it comes to the obese patient with GERD, a different approach should be considered. Gastric bypass is the recommended treatment for GERD in the morbidly obese patient (BMI > 35 kg/m^2) due to concerns over higher failure rates following Nissen fundoplication in this population. Not only does bariatric surgery better address the mechanisms that lead to GERD in obese patients with the potential for a more durable response, but it also reduces obesity-related comorbidities and possibly reduces the long-term mortality risk associated with morbid obesity in an acceptably safe, minimally-invasive, and cost-effective manner[47]. Although all common bariatric procedures improve GERD, Roux- en-Y gastric bypass is superior to adjustable gastric banding and sleeve gastrectomy[48].

REFERENCES

1 **DeVault KR**, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. *Am J Gastroenterol* 2005; **100**: 190-200 [PMID: 15654800 DOI: 10.1111/j.1572-0241.2005.41217.x]

2 **Katz PO**, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol* 2013; **108**: 308-328; quiz 329 [PMID: 23419381 DOI: 10.1038/ajg.2012.444]

3 **Dent J**, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 2005; **54**: 710-717 [PMID: 15831922 DOI: 10.1136/gut.2004.051821]

4 **Klauser AG**, Schindlbeck NE, Müller-Lissner SA. Symptoms in gastro-oesophageal reflux disease. *Lancet* 1990; **335**: 205-208 [PMID: 1967675 DOI: 10.1016/0140-6736(90)90287-F]

5 **Hom C**, Vaezi MF. Extra-esophageal manifestations of gastroesophageal reflux disease: diagnosis and treatment. *Drugs* 2013; **73**: 1281-1295 [PMID: 23881666 DOI: 10.1007/s40265-013-0101-8]

6 **Smith JA**, Abdulqawi R, Houghton LA. GERD-related cough: pathophysiology and diagnostic approach. *Curr Gastroenterol Rep* 2011; **13**: 247-256 [PMID: 21465223 DOI: 10.1007/s11894-011-0192-x]

7 **Becher A**, El-Serag H. Systematic review: the association between symptomatic response to proton pump inhibitors and health-related quality of life in patients with gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2011; **34**: 618-627 [PMID: 21770991 DOI: 10.1111/j.1365-2036.2011.04774.x]

8 **Spechler SJ**, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. *Gastroenterology* 2011; **140**: 1084-1091 [PMID: 21376940 DOI: 10.1053/j.gastro.2011.01.030]

9 **Lagergren J**, Bergström R, Nyrén O. Association between body mass and adenocarcinoma of the esophagus and gastric cardia. *Ann Intern Med* 1999; **130**: 883-890 [PMID: 10375336 DOI: 10.7326/0003-4819-130-11-199906010-00003]

10 **Tefera L**, Fein M, Ritter MP, Bremner CG, Crookes PF, Peters JH, Hagen JA, DeMeester TR. Can the combination of symptoms and endoscopy confirm the presence of gastro-

esophageal reflux disease? *Am Surg* 1997; **63**: 933-936 [PMID: 9322676]
11 **Giannini EG**, Zentilin P, Dulbecco P, Vigneri S, Scarlata P, Savarino V. Management strategy for patients with gastroesophageal reflux disease: a comparison between empirical treatment with esomeprazole and endoscopy-oriented treatment. *Am J Gastroenterol* 2008; **103**: 267-275 [PMID: 18289194 DOI: 10.1111/j.1572-0241.2007.01659.x]
12 **Katzka DA**, Paoletti V, Leite L, Castell DO. Prolonged ambulatory pH monitoring in patients with persistent gastroesophageal reflux disease symptoms: testing while on therapy identifies the need for more aggressive anti-reflux therapy. *Am J Gastroenterol* 1996; **91**: 2110-2113 [PMID: 8855731]
13 **Pandolfino JE**, Vela MF. Esophageal-reflux monitoring. *Gastrointest Endosc* 2009; **69**: 917-930, 930.e1 [PMID: 19249037 DOI: 10.1016/j.gie.2008.09.022]
14 **Kwiatek MA**, Pandolfino JE. The Bravo pH capsule system. *Dig Liver Dis* 2008; **40**: 156-160 [PMID: 18096447 DOI: 10.1016/j.dld.2007.10.025]
15 **Aksglaede K**, Funch-Jensen P, Thommesen P. Intra-esophageal pH probe movement during eating and talking. A videoradiographic study. *Acta Radiol* 2003; **44**: 131-135 [PMID: 12694094 DOI: 10.1034/j.1600-0455.2003.00033.x]
16 **Agrawal A**, Tutuian R, Hila A, Freeman J, Castell DO. Ingestion of acidic foods mimics gastroesophageal reflux during pH monitoring. *Dig Dis Sci* 2005; **50**: 1916-1920 [PMID: 16187197 DOI: 10.1007/s10620-005-2961-6]
17 **Chawla A**, Girda E, Walker G, Turcotte Benedict F, Tempel M, Morganstern J. Effect of Propofol on Acid Reflux Measured with the Bravo pH Monitoring System. *ISRN Gastroenterol* 2013; **2013**: 605931 [PMID: 23691337 DOI: 10.1155/2013/605931]
18 **Hirano I**, Richter JE. ACG practice guidelines: esophageal reflux testing. *Am J Gastroenterol* 2007; **102**: 668-685 [PMID: 17335450 DOI: 10.1111/j.1572-0241.2006.00936.x]
19 **Ravi K**, Francis DL. New technologies to evaluate esophageal function. *Expert Rev Med Devices* 2007; **4**: 829-837 [PMID: 18035949 DOI: 10.1586/17434440.4.6.829]
20 **Weusten BL**, Roelofs JM, Akkermans LM, Van Berge-Henegouwen GP, Smout AJ. The symptom-association probability: an improved method for symptom analysis of 24-hour esophageal pH data. *Gastroenterology* 1994; **107**: 1741-1745 [PMID: 7958686]
21 **Johnston BT**, Troshinsky MB, Castell JA, Castell DO. Comparison of barium radiology with esophageal pH monitoring in the diagnosis of gastroesophageal reflux disease. *Am J Gastroenterol* 1996; **91**: 1181-1185 [PMID: 8651167]
22 **DeVault K**, McMahon BP, Celebi A, Costamagna G, Marchese M, Clarke JO, Hejazi RA, McCallum RW, Savarino V, Zentilin P, Savarino E, Thomson M, Souza RF, Donohoe CL, O'Farrell NJ, Reynolds JV. Defining esophageal landmarks, gastroesophageal reflux disease, and Barrett's esophagus. *Ann N Y Acad Sci* 2013; **1300**: 278-295 [PMID: 24117649 DOI: 10.1111/nyas.12253]
23 **Kaltenbach T**, Crockett S, Gerson LB. Are lifestyle measures effective in patients with gastroesophageal reflux disease? An evidence-based approach. *Arch Intern Med* 2006; **166**: 965-971 [PMID: 16682569 DOI: 10.1001/archinte.166.9.965]
24 **Corley DA**, Kubo A. Body mass index and gastroesophageal reflux disease: a systematic review and meta-analysis. *Am J Gastroenterol* 2006; **101**: 2619-2628 [PMID: 16952280 DOI: 10.1111/j.1572-0241.2006.00849.x]
25 **Jacobson BC**, Somers SC, Fuchs CS, Kelly CP, Camargo CA. Body-mass index and symptoms of gastroesophageal reflux in women. *N Engl J Med* 2006; **354**: 2340-2348 [PMID: 16738270 DOI: 10.1056/NEJMoa054391]
26 **Yang JH**, Kang HS, Lee SY, Kim JH, Sung IK, Park HS, Shim CS, Jin CJ. Recurrence of gastroesophageal reflux disease correlated with a short dinner-to-bedtime interval. *J Gastroenterol Hepatol* 2014; **29**: 730-735 [PMID: 24224689 DOI: 10.1111/jgh.12455]
27 **Chiba N**, De Gara CJ, Wilkinson JM, Hunt RH. Speed of healing and symptom relief in grade II to IV gastroesophageal reflux disease: a meta-analysis. *Gastroenterology* 1997; **112**: 1798-1810 [PMID: 9178669 DOI: 10.1053/gast.1997.v112.pm9178669]
28 **Bate CM**, Keeling PW, O'Morain C, Wilkinson SP, Foster DN, Mountford RA, Temperley JM, Harvey RF, Thompson DG, Davis M. Comparison of omeprazole and cimetidine in reflux oesophagitis: symptomatic, endoscopic, and histological evaluations. *Gut* 1990; **31**: 968-972 [PMID: 2210463 DOI: 10.1136/gut.31.9.968]
29 **Dean BB**, Gano AD, Knight K, Ofman JJ, Fass R. Effectiveness of proton pump inhibitors in nonerosive reflux disease. *Clin Gastroenterol Hepatol* 2004; **2**: 656-664 [PMID: 15290657 DOI: 10.1016/S1542-3565(04)00288-5]
30 **Vigneri S**, Termini R, Leandro G, Badalamenti S, Pantalena M, Savarino V, Di Mario F, Battaglia G, Mela GS, Pilotto A. A comparison of five maintenance therapies for reflux esophagitis. *N Engl J Med* 1995; **333**: 1106-1110 [PMID: 7565948 DOI: 10.1056/NEJM199510263331703]
31 **Inadomi JM**, Jamal R, Murata GH, Hoffman RM, Lavezo LA, Vigil JM, Swanson KM, Sonnenberg A. Step-down management of gastroesophageal reflux disease. *Gastroenterology* 2001; **121**: 1095-1100 [PMID: 11677201 DOI: 10.1053/gast.2001.28649]
32 **El-Serag HB**, Fitzgerald S, Richardson P. The extent and determinants of prescribing and adherence with acid-reducing medications: a national claims database study. *Am J Gastroenterol* 2009; **104**: 2161-2167 [PMID: 19568229 DOI: 10.1038/ajg.2009.312]
33 **Fass R**, Sontag SJ, Traxler B, Sostek M. Treatment of patients with persistent heartburn symptoms: a double-blind, randomized trial. *Clin Gastroenterol Hepatol* 2006; **4**: 50-56 [PMID: 16431305 DOI: 10.1016/S1542-3565(05)00860-8]
34 **Hatlebakk JG**, Katz PO, Kuo B, Castell DO. Nocturnal gastric acidity and acid breakthrough on different regimens of omeprazole 40 mg daily. *Aliment Pharmacol Ther* 1998; **12**: 1235-1240 [PMID: 9882032 DOI: 10.1046/j.1365-2036.1998.00426.x]
35 **Fackler WK**, Ours TM, Vaezi MF, Richter JE. Long-term effect of H2RA therapy on nocturnal gastric acid breakthrough. *Gastroenterology* 2002; **122**: 625-632 [PMID: 11874994 DOI: 10.1053/gast.2002.31876]
36 **Zhang Q**, Lehmann A, Rigda R, Dent J, Holloway RH. Control of transient lower oesophageal sphincter relaxations and reflux by the GABA(B) agonist baclofen in patients with gastro-oesophageal reflux disease. *Gut* 2002; **50**: 19-24 [PMID: 11772961 DOI: 10.1136/gut.50.1.19]
37 **Orr WC**, Goodrich S, Wright S, Shepherd K, Mellow M. The effect of baclofen on nocturnal gastroesophageal reflux and measures of sleep quality: a randomized, cross-over trial. *Neurogastroenterol Motil* 2012; **24**: 553-559, e253 [PMID: 22404184 DOI: 10.1111/j.1365-2982.2012.01900.x]
38 **Miwa H**, Inoue K, Ashida K, Kogawa T, Nagahara A, Yoshida S, Tano N, Yamazaki Y, Wada T, Asaoka D, Fujita T, Tanaka J, Shimatani T, Manabe N, Oshima T, Haruma K, Azuma T, Yokoyama T. Randomised clinical trial: efficacy of the addition of a prokinetic, mosapride citrate, to omeprazole in the treatment of patients with non-erosive reflux disease - a double-blind, placebo-controlled study. *Aliment Pharmacol Ther* 2011; **33**: 323-332 [PMID: 21118395 DOI: 10.1111/j.1365-2036.2010.04517.x]
39 **Poh CH**, Gasiorowska A, Navarro-Rodriguez T, Willis MR, Hargadon D, Noelck N, Mohler J, Wendel CS, Fass R. Upper GI tract findings in patients with heartburn in whom proton pump inhibitor treatment failed versus those not receiving antireflux treatment. *Gastrointest Endosc* 2010; **71**: 28-34 [PMID: 19922918 DOI: 10.1016/j.gie.2009.08.024]
40 **Oelschlager BK**, Quiroga E, Parra JD, Cahill M, Polissar N, Pellegrini CA. Long-term outcomes after laparoscopic antireflux surgery. *Am J Gastroenterol* 2008; **103**: 280-287; quiz 288 [PMID: 17970835 DOI: 10.1111/j.1572-0241.2007.01606.x]

41 **Jobe BA**, Richter JE, Hoppo T, Peters JH, Bell R, Dengler WC, DeVault K, Fass R, Gyawali CP, Kahrilas PJ, Lacy BE, Pandolfino JE, Patti MG, Swanstrom LL, Kurian AA, Vela MF, Vaezi M, DeMeester TR. Preoperative diagnostic work-up before antireflux surgery: an evidence and experience-based consensus of the Esophageal Diagnostic Advisory Panel. *J Am Coll Surg* 2013; **217**: 586-597 [PMID: 23973101 DOI: 10.1016/j.jamcollsurg.2013.05.023]

42 **Rickenbacher N**, Kötter T, Kochen MM, Scherer M, Blozik E. Fundoplication versus medical management of gastroesophageal reflux disease: systematic review and meta-analysis. *Surg Endosc* 2014; **28**: 143-155 [PMID: 24018760 DOI: 10.1007/s00464-013-3140-z]

43 **Spechler SJ**, Lee E, Ahnen D, Goyal RK, Hirano I, Ramirez F, Raufman JP, Sampliner R, Schnell T, Sontag S, Vlahcevic ZR, Young R, Williford W. Long-term outcome of medical and surgical therapies for gastroesophageal reflux disease: follow-up of a randomized controlled trial. *JAMA* 2001; **285**: 2331-2338 [PMID: 11343480 DOI: 10.1001/jama.285.18.2331]

44 **Dominitz JA**, Dire CA, Billingsley KG, Todd-Stenberg JA. Complications and antireflux medication use after antireflux surgery. *Clin Gastroenterol Hepatol* 2006; **4**: 299-305 [PMID: 16527692 DOI: 10.1016/j.cgh.2005.12.019]

45 **Bonavina L**, Saino G, Lipham JC, Demeester TR. LINX(®) Reflux Management System in chronic gastroesophageal reflux: a novel effective technology for restoring the natural barrier to reflux. *Therap Adv Gastroenterol* 2013; **6**: 261-268 [PMID: 23814607 DOI: 10.1177/1756283X13486311]

46 **Witteman BP**, Strijkers R, de Vries E, Toemen L, Conchillo JM, Hameeteman W, Dagnelie PC, Koek GH, Bouvy ND. Transoral incisionless fundoplication for treatment of gastroesophageal reflux disease in clinical practice. *Surg Endosc* 2012; **26**: 3307-3315 [PMID: 22648098 DOI: 10.1007/s00464-012-2324-2]

47 **Prachand VN**, Alverdy JC. Gastroesophageal reflux disease and severe obesity: Fundoplication or bariatric surgery? *World J Gastroenterol* 2010; **16**: 3757-3761 [PMID: 20698037 DOI: 10.3748/wjg.v16.i30.3757]

48 **Pallati PK**, Shaligram A, Shostrom VK, Oleynikov D, McBride CL, Goede MR. Improvement in gastroesophageal reflux disease symptoms after various bariatric procedures: Review of the Bariatric Outcomes Longitudinal Database. *Surg Obes Relat Dis* 2014; **10**: 502-507 [PMID: 24238733 DOI: 10.1016/j.soard.2013.07.018]

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REVIEW

Use of methotrexate in inflammatory bowel disease in 2014: A User's Guide

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Abstract

Methotrexate has been used an immunomodulator in many autoimmune diseases, including inflammatory bowel disease. However, many physicians are unfamiliar or uncomfortable with its use in the management of inflammatory bowel disease. We summarize the data for use of methotrexate in common clinical scenarios: (1) steroid dependant Crohn's disease (CD); (2) maintenance of remission in steroid free CD; (3) azathioprine failures in CD; (4) in combination therapy with Anti-TNF agents in CD; (5) decreasing antibody formation to Anti-TNF therapy in CD; (6) management of fistulizing disease in CD; and (7) as well as induction and maintenance of remission in ulcerative colitis. An easy to use algorithm is provided for the busy clinician to access and safely prescribe methotrexate for their inflammatory bowel disease patients.

Key words: Methotrexate; Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Immunomodulators; Methotrexate user's guide

Core tip: Methotrexate can a be a useful adjunct to the treatment of inflammatory bowel disease, but many practitioners are unfamiliar with it's use. Here, we have provided a succinct summary of the data behind the use of methotrexate and a short "user's guide" and algorithm to allow for the busy clinician to become quickly familiar with the drug and information to help prescribe it safely.

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INTRODUCTION

Methotrexate (MTX) has a long history for effectively treating rheumatological conditions such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and sarcoidosis[1-3]. Over the past 25 years there have been numerous studies that evaluated its efficacy in Inflammatory Bowel Disease with varied results. It has to date remained in treatment algorithms as a salvage therapy for patients who have failed, or become intolerant of, azathioprine. The goal of our paper is to summarize the data behind methotrexate for common clinical situations and to provide a quick access guide on prescribing the drug.

MTX PHARMACOKINETICS

The landmark studies demonstrating efficacy of MTX in Crohn's disease (CD) have utilized *sq* or *im* at 25 mg/wk. Smaller non-randomized studies in both CD and UC patients have offered conflicting data and, to an extent

Table 1 Summary of methotrexate trials in Crohn's disease

Study	Dose MTX	Route of admin	*n*	Study design	Patients	Duration follow up (wk)	MTX response	MTX remission	Placebo or (Comparator) Response	AE MTX	AE Placebo
Kozarek	25 mg/wk	*sq*	14	Non-Randomized-open Label	CD	12	79%				
Feagan	25 mg/wk	*im*	141	Double-blind Placebo controlled multi center	Steroid dependent CD	16		39.4%[1]	19.1%	1%	2%
Oren	12.5 mg/wk	*po*	84	Randomized Double-Blind Placebo Controlled	Active CD	36		38%	46%		
Arora	22.5 mg/wk	*po*	33	Randomized Double Blind Placebo Controlled	Steroid Dependent CD	52	54%		20%	23%	0
Feagan	15 mg/wk	*im*	76	Double Blind Placebo Controlled Multi-Center	CD Maintenance	40		65%[1]	39%	1%	2%
Mate-Jimenez	15 mg/wk	*po*	38	Randomized Single Center	Steroid Dependent CD	76		80%[1] Induction 66.6%[1] Maintenance	14% Induction 0 Maintenance	11.5%	0
Lemann	25 mg/wk	*im*	49	Retrospective	Active CD			84%		49%	
Fraser	20 mg/wk (10-25)	*po*/*im*	48	Retrospective	Active CD-Maintenance			62%		27%	
Ardizzone	25 mg/wk	*iv*	54	Investigator Blind, randomized	Active CD	24		56%	63% AZA	11%	
Mahadevan	25 mg/wk	*im*	16	Retrospective case series	Fistulizing CD		56%			6%	
Wahed	25 mg/wk Induction 15 mg/wk Maintenance	*im*/*po*-Induction *po*-Maintenance	99	Retrospective	AZA Intolerance/ AZA non-responders		62%			8.3%	
Feagan	Wk0-10 mg/wk Wk3-20 mg/wk Wk5-25 mg/wk	*sq*	126	Double Blind Placebo Controlled Multi-center	Active CD	50		IFX + MTX 56%	IFX + PCBO 57%		

[1]$P < 0.05$ *vs* MTX response. MTX: Methotrexate; CD: Crohn's disease; AE: Adverse events; AZA: Azathioprine.

demonstrate, the relative ineffectiveness with low dose *po* regimens for induction or maintenance of remission (Table 1)[4,5]. Jundt demonstrated similar bioavailability between *po vs sq vs im* MTX in RA patients[6]. The bioavailability of *po* as compared to *im* was 0.85.

Kurnik *et al*[7] studied the bioavailability of MTX in adult patients with stable Crohn's disease. The patients were administered their weekly doses either orally or *sq* and the MTX levels were measured over the next 24 h. No information on extent of small bowel inflammation was provided. They found that oral bioavailability averages 73% (95%CI: 62%-86%) of that of subcutaneous administration[7]. Hoekstra demonstrated that the bioavailability of *po* MTX can be boosted by split dosing. RA patients were studied after single dosing of MTX by either *sq* or *po* method. Then the same patient underwent a second measurement after split dosing of MTX (50% of the dose taken 8 h later). The bioavailability of the split dose was 28% higher compared to the single dose ($P = 0.007$) and was statistically significant. The mean bioavailability after single-dose and split-dose MTX was 0.76 and 0.90, respectively, compared to subcutaneous administration[8].

Wilson *et al*[9] updated the Kurnik study using a more sensitive assay. They compared the pharmacokinetic profile of *po* and subcutaneous MTX (25 mg) in 11 CD patients. The bioavailability of *po* MTX compared with *sq* was found to be 0.86 (90%CI: 0.79-0.92). Of note, the 90%CI to meet definition of bioequivalency proposed by the FDA was not met, (lower end of the 90%CI would have had to be 0.80 rather than 0.79), and so this study could not claim true bioequivalency of the oral and *sq* routes of administration.

Although these are small studies and many patient factors were not provided (*i.e.,* extent and severity of bowel disease), the *po* route of administration does ap-

pear to be less bioavailable than *sq* dosing.

WHAT IS THE DATA FOR MTX IN INDUCTION OF REMISSION IN STEROID DEPENDENT CROHN'S DISEASE?

Although Kozarek *et al*[10] (NEJM 1980) had demonstrated the efficacy of 6-mercaptopurine in the induction of remission of Crohn's disease, the authors noted the response to be delayed and incomplete. The first report of successful induction with methotrexate was reported by Kozarek *et al*[10] in 1989. This non-randomized, open-label pilot study included 14 patients with Crohn's disease with an unidentified fraction described as failing immunomodulators. Eleven patients (79%) demonstrated a clinical response to 25 mg/wk *im* methotrexate as measured by objective decreases in CDAI, and 5 patients (36%) demonstrated endoscopic mucosal healing. Although this study lacked a control arm, it suggested MTX may have value in inducing remission in patients with Crohns' disease.

Feagan completed a prospective double-blind, placebo-controlled Canadian multicenter study of weekly *im* injections of methotrexate in patients who had chronically active Crohn's disease despite a minimum of 3 mo of prednisone therapy with the primary outcome being the induction of clinical remission[11]. A total of 141 patients assigned in a 2:1 ratio of MTX to placebo were included in the trial and 37 (39.4%) achieved clinical remission in the methotrexate group compared with 9 (19.1%) in the placebo group ($P = 0.025$). The response among patients requiring high dose prednisone (> 20 mg/d) was equally good as those requiring low doses at study initiation. Prednisone dose was appreciably lower by week 4 in the MTX group and demonstrated the largest difference from week 12 through 16. A greater number of patients withdrew from the treatment arm due to adverse events (17% *vs* 2%). The withdrawals from the MTX arm were due to asymptomatic elevation of serum aminotransferase concentrations (7), nausea (6), skin rash (1), atypical pneumonia (1), and optic neuritis (1).

Oren *et al*[5] conducted a prospective randomized, double blind, placebo-controlled Israeli multi-center trial to evaluate the effectiveness of oral methotrexate in patients who had required steroids or immunomodulators for at least 4 mo out of the year prior to enrollment. Although it would be difficult to characterize these patients as steroid dependant, they had active ongoing disease as measured by Harvey Bradshaw Index. The study randomized 84 patients to 12.5 mg *po* MTX/week *vs* 6-MP 50 mg/daily *vs* placebo. The lower dose of oral MTX (compared to 25 mg/wk *im* in the Feagan study) was based on reported efficacy in the rheumatoid arthritis literature. Remission rates were 39% and 41% in the MTX and 6-MP groups respectively. However, the rate of remission in the placebo group was 46%, thereby inferring no benefit for either the MTX or 6 MP treatment arm. Criticisms of this study included presumed underdosing of MTX and 6 MP. Also, no standard steroid tapering regimen was described in this study, although reduction in steroid dose was described as an outcome measure. Although improvement was seen based on intra-patient evaluation (each patient used as their own control), this was not a pre-specified analysis. Hence, these results should be viewed with caution.

A cohort of 38 patients with steroid dependant CD was evaluated by Mate-Jimenez, but the requirement to separate these patients into 3 arms (1.5 mg/kg per day 6MP, 15 mg/wk *po* MTX, or 5-ASA) resulted in a small number of patients in each arm[12]. However, the large differences in outcomes for induction of remission in both treatment arms (93.7% 6MP, 80%MTX) compared to placebo (14%) was statistically significant. Interestingly, these findings show a degree of benefit that has not been reproduced for either the 6MP or MTX treatment arms. Arora *et al*[13] evaluated 28 steroid-dependant Crohn's disease patients who received 15 mg/wk *po* MTX *vs* placebo. Dose escalation to 22.5 mg/wk was allowed at the discretion of the clinician. The primary endpoint was clinical exacerbation of Crohn's disease. Although fewer patients in the MTX group (6/13, 46%) experienced exacerbation of CD *vs* placebo (12/15, 80%), the findings did not reach statistical significance. Despite the 43% relative risk reduction in flare frequency between the treatment and placebo, this study was underpowered to find this difference to be significant.

Ardizzone evaluated the efficacy of *iv* MTX in comparison to AZA[4]. This randomized investigator-blind study enrolled 54 steroid-dependent active (CDAI > 200) CD patients on > 10 mg/d of steroid therapy. Patients were randomized to 25 mg *iv*/wk of MTX *vs po* AZA 2 mg/kg per day for 3 mo, after which MTX dosing was changed to 25 mg/wk *po* for an additional 3 mo follow up. The primary outcome considered was the proportion of patients entering steroid-free remission after 3 and 6 mo of therapy. No statistically significant difference was found between the two treatment regimens with respect to remission rate after 3 mo (methotrexate 44%, azathioprine 33%, $P = 0.28$, (95%CI: 0.369-0.147), and 6 mo (methotrexate 56%, azathioprine 63%, $P = 0.39$, 95%CI: 0.187-0.335), respectively. MTX and AZA demonstrated similar rates of adverse events leading to medication withdrawal. While there appeared to no additional benefit to providing MTX *via* the IV route, MTX at 25 mg/wk appeared to have similar efficacy as weight based azathioprine in inducing and maintaining remission in active Crohn's disease.

A 2011 meta-analysis of MTX in active Crohn's did not include either the Mate-Jiminez or Ardizzone studies (no placebo arm) or Arora studies (categorized the study patients as quiescent)[14]. Their conclusion that MTX was not better than placebo in active Crohn's was based only on the inclusion of Feagan's positive trial (25 mg/wk *im* MTX) and the negative orally administered MTX (12.5 mg/wk *po*) Oren trial. The Cochrane collaboration

reached similar conclusions a year later, but understood the limitations of the data on oral MTX and suggested further study[15].

WHAT IS THE DATA FOR MTX IN MAINTENANCE OF STEROID-FREE REMISSION IN CROHN'S DISEASE?

Feagan demonstrated the use of MTX in Crohn's disease for maintenance of remission in a large double-blind, placebo controlled multi-center study with 76 patients in 2000[16]. Some of these patients were enrolled from Feagan's trial for induction of remission using 25 mg *im*/wk MTX in 1995 and others from an open label trial of 25 mg/wk *im* MTX. The patients were randomized to 15 mg *im* MTX/weekly *vs* placebo and followed for 40 wk. Impressively, no other therapy for Crohn's disease was permitted. At the completion of the trial 65% (26/40) of the MTX group maintained remission compared to 39% (14/36) of the placebo group ($P = 0.04$). A majority (55%) of the relapsers could be re-induced with 25 mg/wk *im* MTX. Adverse events were minimal as only 1 patient discontinued MTX therapy for nausea and vomiting.

The efficacy of oral MTX (10-20 mg *po*) for maintenance of remission in Crohn's and ulcerative colitis was evaluated by a retrospective review by Fraser. Although 1 year remission rates approached 90%, the data for Crohn's and UC were combined and the clinical definition of remission was vague[17].

Given the dearth of high quality studies of MTX in maintaining remission in Crohn's, the only maintenance study used in the Kahn meta-analysis was Feagan's (15 mg *im*/wk MTX) suggesting benefit with a number needed to treat (NNT) of 4[14]. Interestingly, the Cochrane meta-analysis of MTX for maintenance of remission, included both the Mata-Jimenez study and Oren studies as part their analysis[18]. Their main conclusions track the benefit shown by the Feagan's 15 mg/wk *im* MTX and suggest that lower oral doses do not benefit maintenance of remission.

CAN MTX BE USED IN PATIENTS WHO FAIL AZA AND HOW DURABLE IS THE RESPONSE TO MTX?

Despite the widespread use of thiopurines, approximately one third do not respond and another 10% cannot tolerate the drugs[19]. In the United States, MTX is often reserved for AZA intolerance or failure and fewer physicians are comfortable prescribing it[20]. AZA Intolerance can include bone marrow suppression, upper GI symptoms, pancreatic dysfunction, abnormal LFT's and nonspecific symptoms including joint aches, hair loss, rash and flu like illness.

A study by Lemann in 2000 evaluated the durability of MTX for maintenance of remission in a population of patients who had (mostly) failed or were intolerant to AZA and had *already been treated* with MTX for period of at least 6 mo were followed for an additional 18 mo[21]. Out of 49 patients, 42 had previously failed AZA (85%). Out of the 41 achieving remission, 36 had previously failed AZA (87%). Most of the patients were administered 25 mg/wk *im* MTX, but some physicians changed the dose to oral administration and some were even able to taper it. Despite some patients with oral MTX dosing and despite a heavy proportion of AZA failures in the study population, 71% of the study population remained in remission for 1 year and up to 52% remained in remission after 3 years. Among patients who initially do well on MTX after AZA failure, they are likely to remain well on that therapy over the next several years.

Wahed *et al*[22] evaluated clinical response of 99 CD patients retrospectively who were placed on MTX due to AZA intolerance or nonresponse. The study suffers from a non-homogenous doses and method of administration of MTX for induction and maintenance. The range of induction dose of MTX was 2.5-25 mg/wk and administration varied as either *im* or *po*. Improvement was based on multiple variables as available from the charts, but was not standardized. With these caveats, clinical response occurred in 18 of 29 patients (62%) refractory to AZA/MP and 42 of 70 patients (60%) intolerant to AZA/MP. This suggests that MTX is effective in CD patients previously treated with AZA who experienced failure or nonresponse.

At present, there are no high quality trials (prospective, identical induction doses and method of administration, presence of control groups) on which to confidently choose to use MTX specifically in a population of AZA/6MP failures, but it would not be unreasonable to attempt MTX.

DOES COMBINATION MTX AND ANTI-TNF THERAPY TO TREAT CROHN'S DISEASE RESULT IN BETTER OUTCOMES?

The landmark SONIC study demonstrated that patients with moderate-to-severe Crohn's disease who were treated with combination infliximab plus azathioprine were more likely to have a corticosteroid-free clinical remission than those receiving azathioprine or infliximab monotherapy[23]. Concomitant immunosuppressive therapy also reduces the magnitude of the immunogenic response of infliximab[24]. It follows that methotrexate, as part of combination therapy with anti-TNF agents, may provide similar benefits.

Feagan *et al*[25] studied this hypothesis in the COMMIT trial. They performed a 50-wk double-blind, placebo-controlled trial of MTX + IFX *vs* IFX monotherapy in Crohn's patients who had started prednisone therapy within the preceding 6 wk. Patients were not permitted to use any other therapy with the exception of antibiotics for 14 d in the case of active perianal disease. Patients

were initiated on IFX 5 mg/wk and 10 mg *sq* MTX/week (escalating to 25 mg/wk by week 5) or IFX 5 mg/wk and placebo injections. Prednisone was force tapered in all patients by week 14. The primary outcome evaluated steroid free-remission by week 14 or maintenance of remission by week 50. Steroid-free remission at week 14 was 76% (48/63) in combination therapy compared to 78%(49/63) with IFX mono therapy ($P = 0.83$). At week 50, 56%(35/63) *vs* 57%(36/63) maintained remission in the combination arm *vs* monotherapy arm. Mean methotrexate doses at week 50 in the treatment arm was 22.3 mg/wk. This study found that combination therapy with IFX and MTX had no more benefit than IFX alone.

Based on the strongest current body of evidence (SONIC, COMMIT), it seems reasonable to prefer combination therapy using AZA/6MP rather than MTX in those Crohn's patients able to tolerate it.

IS MTX EFFECTIVE IN PREVENTING AUTO-ANTIBODY FORMATION WHEN USED IN COMBINATION WITH BIOLOGIC THERAPY?

A prospective study by Vermeire evaluated the development of antibodies to infliximab (ATI) when combined with AZA, MTX, or placebo[26]. The concomitant use of immunosuppressive therapy (MTX or AZA) was associated with a lower incidence of antibodies to IFX (53/115, 46%) compared with patients not receiving concomitant immunosuppressive therapy (43/59, 73%; $P < 0.0001$). Furthermore, the incidence of antibody formation was not different between the MTX and AZA groups, 44% compared to 48% respectively. Patients not taking IS therapy had lower IFX levels (median 2.42 mcg/mL) 4 wk after any follow-up infusion than patients taking concomitant IS therapy (median 6.45 mcg/mL) ($P = 0.065$), but there was no difference between MTX or AZA. Sokol *et al*[27] confirm that patients using co-treatment with immunosuppressives experienced less IBD activity and less need to switch Anti-TNF therapy due to secondary loss of response. In fact, their data suggest efficacy of AZA over MTX, though their patient population included both CD and UC patients, and it is not clear whether any of the UC patients were treated with MTX and included in the analysis.

Although the COMMIT study did not show an improvement in 50 wk outcomes using combination therapy (IFX + MTX *vs* IFX alone), the MTX combination group did achieve statistically significant lower antibody levels (4% compared with 20%, $P = 0.01$) and demonstrated higher median serum trough levels of IFX (6.35 μg/mL *vs* 3.75 μg/mL, $P = 0.08$), similar to what is seen with azathioprine combination therapy[25]. Whether this would result in fewer instances of infusion reactions or secondary non-response to IFX beyond 50 wk remains to be seen.

CAN MTX BE USED TO MANAGE SECONDARY NONRESPONSE TO BIOLOGIC MONOTHERAPY?

Absah retrospectively evaluated 14 pediatric patients with moderate to severe (CD) eventually failing anti-TNF-α therapy (13 ADA and 1 IFX) who then received concomitant methotrexate (median dose 17.5 mg *sq*/wk)[28]. Most (12/14) patients had also previously failed AZA therapy (though it is not made clear whether this was as part of combination with biologic). Clinical remission was achieved in 7/14 (50%) of patients on average of 6 wk after MTX initiation with no additional improvement in the other 7 patients during 10 mo of follow up. Unfortunately, no levels of biologic or antibody to biologic were measured in this study, so the mechanism of improvement remains unknown. Further research focusing on the adult population along with mechanism of action would serve to direct therapy in this refractory population often seen in tertiary centers.

DOES MTX TREAT FISTULIZING CROHN'S DISEASE?

To date, only small retrospective series are available to evaluate the efficacy of MTX monotherapy in fistulizing Crohn's disease. A research conducted a retrospective chart review of all Crohn's disease receiving methotrexate 15-25 mg *im* MTX/weekly. This group of patients that had failed or were intolerant to 6MP and were made up of perianal fistulae (9), abdominal wall (3), rectovaginal (1), bladder (1), perianal + rectovaginal (2). Overall, 4/16 (25%) experienced complete fistula closure and 5/16 (31%) had partial fistula closure. Fourteen of sixteen patients received full dose 25 mg *im*/wk of MTX for 3 mo and were switched to *po* for maintenance. The time to response could not be determined in half of the patients, but ranged from 4-13 wk in the other half. Another study found that 8/18 (44%) patients with Crohn's-related fistulas achieved partial or complete response using MTX for 6 mo, but information about success and failure based on oral or *im* administration was not provided[29]. A pilot study of 12 patients using combination infliximab and MTX found 7 patients had total or partial response to fistula, but there was no MTX only arm and the data seem similar to the benefit achieved with IFX monotherapy[30,31].

Approximately 10% of peri-anal and abdominal fistulas in Crohn's heal spontaneously[31]. Given a closure rate well above the spontaneous closure rate, we consider MTX a potentially useful adjunct in management of Crohn's fistulas.

METHOTREXATE AND ULCERATIVE COLITIS

Does MTX work for induction of remission in UC?

Evidence pertaining to the utility of methotrexate in

Table 2 Evidence for induction of remission of ulcerative colitis with methotrexate

Study	Dose (mean)	Route	No. of patients	Study design	Follow-up (wk)	MTX response	MTX remission	Placebo response
Kozarek	25 mg	*im*	7	Open label	12	5/7 (71.40%)		N/A
Baron	15 mg	Oral	8	Open label	18	3/8 (37.5%)	0	N/A
Oren	12.5 mg	Oral	67	Placebo control	36	14/30 (46.7%)		18/37 (48.6%)
Egan	15 mg	*sc*	18	Open label	16	7/18 (39%)	3/18 (17%)	N/A
	25 mg	*sc*	12			4/12 (33%)	2/12 (17%)	N/A
Mate-Jimenez	15 mg	Oral	34	6-MP control	30		7/12 (58.30%)	11/14 (78.6%)
Paoluzi	12.5 mg	*im*	10 thiopurine resistant/ intolerant	Open label	26	10/10 (100%)	6/10 (60%)	N/A
Cummings	1 9 . 9 m g mean	Oral	11 AZA failure 31 AZA intolerant	Retrospective	30	3/11 (27%) 18/31 (58%)	14/31	N/A
Nathan	20-25 mg	*sc*/ oral	23	Retrospective	N/A		11/23 (48%)	N/A
Wahed	10-25 mg	Oral, *sc*	9 thiopurine ineffective 23 thiopurine intolerant	Retrospective	26	7/9 (78%) 15/23 (65%)	N/A	N/A
Manosa	25 mg	Oral *sc*	7 33	Retrospective	26		24/40 (60%) remission	N/A
Saibeni	20 mg	Oral/ *sc*/*im*	23	Retrospective	N/A	11/23 (47.8%)		N/A
Khan	14 mg	Oral	68	Retrospective	60	25/68 (37%)		N/A
	25 mg	*sc*/*im*	23			7/23 (30%)		

MTX: Methotrexate; CD: Crohn's disease; AE: Adverse events; SC: Subcutaneous; PO: Oral; AZA: Azathioprine.

induction of remission for ulcerative colitis is conflicting (Table 2). Disparate results reflect disagreement over appropriate dosing and route of administration. To date, only one prospective, randomized placebo-controlled trial examining the efficacy of methotrexate in the treatment of ulcerative colitis exists; Oren *et al*[5] in 1996 compared 12.5 mg oral methotrexate to placebo in the induction of remission of 67 patients with moderate/severe UC[5,14]. All patients had active disease with a Mayo score of >7, and were taking steroids for at least 4 mo in the preceding year. The results were disappointing, with clinical remission rates of 46.7% (14/30) in the methotrexate arm in comparison to 48.6% (18/37) for the placebo arm, a non-significant difference. Of those who entered clinical remission, 64.3% of patients in the methotrexate arm had a relapse requiring steroid induction compared to 44.4% of placebo patients, again, an insignificant difference.

Overall, a low remission rate relative to placebo, long time to remission, and a high relapse rate in Oren's study all suggest a lack of efficacy for methotrexate in either the induction or maintenance of remission in ulcerative colitis. Of course, important criticism may be directed at the relatively low dose of MTX used and the oral route of administration.

Otherwise, a number of small open-label and larger retrospective analyses have been conflicting, not least due to differing definitions of response, length of follow up (12 wk-2 years), dose of MTX (7.5-25 mg/wk), and route administered (*po vs im*). None of these studies were considered of sufficient quality to be included in the meta-analysis by Khan *et al*[14].

The most comprehensive of these was published last year by Khan *et al*[32], presenting retrospective data regarding experience with methotrexate in the Veterans Affairs (VA) system. A total of 91 patients with ulcerative colitis who were steroid dependent or refractory were commenced on oral (mean 14 mg) or parenteral (mean 25 mg) methotrexate. In the oral MTX cohort, 37% (25/68) were able to successfully wean from steroid therapy, compared to 30% (7/23) of the parenteral cohort.

Overall, looking specifically at induction of remission in ulcerative colitis, response to methotrexate ranged from 27%-100%, and remission rates ranged from 0%-63%. Considering the retrospective nature of most studies, it is impossible to determine the true impact of dose or route of administration. In prospective, open label or randomized controlled trials, response rates similarly ranged from 33%-100%, with remission rates ranging 17%-60%. There are no clear signals regarding the impact of dose, route of administration, or indication for step-up in therapy on remission or response rates in UC.

Does MTX work for maintenance of remission in UC?

Regarding the maintenance of remission, the results are equally confusing - maintenance of remission rates range from 14%-75% (Table 3). Unfortunately, two open-labeled studies suggesting successful maintenance rates > 60%[10,33] using parenteral methotrexate did not include a placebo arm as comparison[10,33]. Oren *et al*[5] and Mate-Jimenez *et al*[12] included control arms, but provided disappointing results for the efficacy of oral methotrexate. Whether the route is a factor for better response rates remains to be seen.

There has been no data to date investigating the utility of combining methotrexate with biologic therapy in UC. Increasing interest in using methotrexate as a "synergistic enhancer" - to augment and prolong biologic efficacy -

Table 3 Evidence for maintenance of remission of ulcerative colitis with methotrexate

Study	Dose (mean)	Route	No. of pts	Study design	Follow-up period (mo)	MTX response maintained?	Control response	Significantly effective?
Kozarek	> 7.5 mg	*sc*	5	Open label	24	3/5 (60%)	N/A	N/A
Oren	12.5 mg	oral	32	Placebo-controlled	9	5/14 (36%)	10/18 (56%)	No
Mate-Jimenez	15 mg	oral	12	6-MP control	18	1/7 (14%)	7/11 (64%)	No
Paoluzi	12.5 mg	*im*	10	Open label	24	6/8 (75%)	N/A	N/A
Manosa	25 mg	Oral/ *sc*	7 33	Retrospective	24	35%		N/A

MTX: Methotrexate.

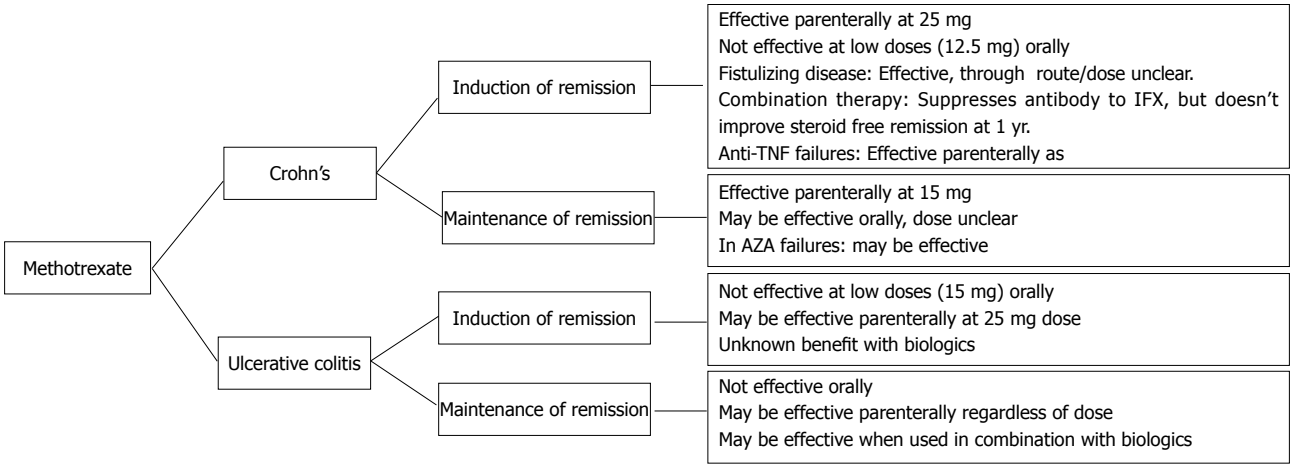

Figure 1 Algorithm for evidence-based use of methotrexate in inflammatory bowel disease. AZA: Azathioprine.

may help define its role in this disease.

PRACTICAL ADVICE ON HOW TO PRESCRIBE MTX IN THE US

Injectable MTX is available in 50 mg/2 mL vials. We prescribe one vial (2 loading dose equivalents) as well as a supply of "tuberculin" 1 mL syringes with 27 guage, 1/2" needles. The patient draws 25 mg weekly from the vial and injects subcutaneously in either lower quadrant of the abdomen or inner thighs as their preference. After 12 wk, if they have a response, they can be transitioned to oral methotrexate maintenance. A patient friendly resource on injecting MTX is available *via* the Canadian rheumatology association (http://rheuminfo.com/wp-content/uploads/2011/04/METHOTREXATE_INJECTION_SHEET.pdf).

Oral methotrexate is available in 10 and 15 mg strengths as Trexall™. If using oral methotrexate in the induction of remission of IBD, we would recommend starting with 25 mg weekly, reverting to the subcutaneous route in non-responders and those who develop nausea attributed to the oral route.

All patients should be prescribed folic acid 1mg daily as it significantly reduces hepatic toxicity, an infrequent occurrence, and gastrointestinal toxicity associated with MTX[34,35]. At present, our target population for MTX are CD patients who are unable to tolerate azathioprine or 6Mercaptopurine due to adverse events, homozygous TMPT mutations, or inefficacy. In the event that methotrexate is required in a woman of child bearing age, we counsel regarding the need for effective contraception (*i.e.,* IUD) and recommend a discussion with their obstetric physician. We advocate obtaining routine blood labs (complete blood count, basic chemistry panel, hepatic function panel) 1 wk after initiation as well as every 8-12 wk subsequently.

CONCLUSION

Given the current evidence an algorithm for MTX can be elucidated (Figure 1). Providers should no longer shy away from using MTX due to concerns of hepatotoxicity and intolerance. Methotrexate demonstrates a similar rate of drug withdrawal as AZA, and may be considered favorable in young males in whom practitioners are reluctant to use AZA (due to concerns of hepato-splenic T-cell lymphoma risk). Determining the optimal dose and route of administration in the various indications for use in IBD is the current priority. MTX is largely used as a second line therapy after AZA failure. It may be useful in combination with Anti-TNF therapy to reduce the risk of immunogenicity and subsequent secondary loss of response to anti-TNF therapy. We eagerly await the results

of two studies that will shed further light; the METEOR trial and MERIT-UC, both randomized, controlled trials of parenteral MTX 25 mg weekly in the induction and maintenance of remission in steroid dependent or refractory ulcerative colitis.

REFERENCES

1 **Lower EE**, Baughman RP. Prolonged use of methotrexate for sarcoidosis. *Arch Intern Med* 1995; **155**: 846-851 [PMID: 7717793 DOI: 10.1001/archinte.1995.00430080088011]
2 **Suarez-Almazor ME**, Belseck E, Shea B, Wells G, Tugwell P. Methotrexate for rheumatoid arthritis. *Cochrane Database Syst Rev* 2000; **(2)**: CD000957 [PMID: 10796399 DOI: 10.1002/14651858.CD000957]
3 **Wenzel J**. Methotrexate in systemic lupus erythematosus. *Lupus* 2005; **14**: 569 [PMID: 16130518 DOI: 10.1191/0961203305lu2175xx]
4 **Ardizzone S**, Bollani S, Manzionna G, Imbesi V, Colombo E, Bianchi Porro G. Comparison between methotrexate and azathioprine in the treatment of chronic active Crohn's disease: a randomised, investigator-blind study. *Dig Liver Dis* 2003; **35**: 619-627 [PMID: 14563183 DOI: 10.1016/S1590-8658(03)00372-4]
5 **Oren R**, Arber N, Odes S, Moshkowitz M, Keter D, Pomeranz I, Ron Y, Reisfeld I, Broide E, Lavy A, Fich A, Eliakim R, Patz J, Bardan E, Villa Y, Gilat T. Methotrexate in chronic active ulcerative colitis: a double-blind, randomized, Israeli multicenter trial. *Gastroenterology* 1996; **110**: 1416-1421 [PMID: 8613046 DOI: 10.1053/gast.1996.v110.pm8613046]
6 **Jundt JW**, Browne BA, Fiocco GP, Steele AD, Mock D. A comparison of low dose methotrexate bioavailability: oral solution, oral tablet, subcutaneous and intramuscular dosing. *J Rheumatol* 1993; **20**: 1845-1849 [PMID: 8308768]
7 **Kurnik D**, Loebstein R, Fishbein E, Almog S, Halkin H, Bar-Meir S, Chowers Y. Bioavailability of oral vs. subcutaneous low-dose methotrexate in patients with Crohn's disease. *Aliment Pharmacol Ther* 2003; **18**: 57-63 [PMID: 12848626 DOI: 10.1046/j.1365-2036.2003.01614.x]
8 **Hoekstra M**, Haagsma C, Neef C, Proost J, Knuif A, van de Laar M. Splitting high-dose oral methotrexate improves bioavailability: a pharmacokinetic study in patients with rheumatoid arthritis. *J Rheumatol* 2006; **33**: 481-485 [PMID: 16463431]
9 **Wilson A**, Patel V, Chande N, Ponich T, Urquhart B, Asher L, Choi Y, Tirona R, Kim RB, Gregor JC. Pharmacokinetic profiles for oral and subcutaneous methotrexate in patients with Crohn's disease. *Aliment Pharmacol Ther* 2013; **37**: 340-345 [PMID: 23190184 DOI: 10.1111/apt.12161]
10 **Kozarek RA**, Patterson DJ, Gelfand MD, Botoman VA, Ball TJ, Wilske KR. Methotrexate induces clinical and histologic remission in patients with refractory inflammatory bowel disease. *Ann Intern Med* 1989; **110**: 353-356 [PMID: 2492786 DOI: 10.7326/0003-4819-110-5-353]
11 **Feagan BG**, Rochon J, Fedorak RN, Irvine EJ, Wild G, Sutherland L, Steinhart AH, Greenberg GR, Gillies R, Hopkins M. Methotrexate for the treatment of Crohn's disease. The North American Crohn's Study Group Investigators. *N Engl J Med* 1995; **332**: 292-297 [PMID: 7816064 DOI: 10.1056/NEJM199502023320503]
12 **Maté-Jiménez J**, Hermida C, Cantero-Perona J, Moreno-Otero R. 6-mercaptopurine or methotrexate added to prednisone induces and maintains remission in steroid-dependent inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2000; **12**: 1227-1233 [PMID: 11111780 DOI: 10.1097/00042737-200012110-00010]
13 **Arora S**, Katkov W, Cooley J, Kemp JA, Johnston DE, Schapiro RH, Podolsky D. Methotrexate in Crohn's disease: results of a randomized, double-blind, placebo-controlled trial. *Hepatogastroenterology* 1999; **46**: 1724-1729 [PMID: 10430331]
14 **Khan KJ**, Dubinsky MC, Ford AC, Ullman TA, Talley NJ, Moayyedi P. Efficacy of immunosuppressive therapy for inflammatory bowel disease: a systematic review and meta-analysis. *Am J Gastroenterol* 2011; **106**: 630-642 [PMID: 21407186 DOI: 10.1038/ajg.2011.64]
15 **McDonald JW**, Tsoulis DJ, Macdonald JK, Feagan BG. Methotrexate for induction of remission in refractory Crohn's disease. *Cochrane Database Syst Rev* 2012; **12**: CD003459 [PMID: 23235598 DOI: 10.1002/14651858.CD003459.pub3]
16 **Feagan BG**, Fedorak RN, Irvine EJ, Wild G, Sutherland L, Steinhart AH, Greenberg GR, Koval J, Wong CJ, Hopkins M, Hanauer SB, McDonald JW. A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. North American Crohn's Study Group Investigators. *N Engl J Med* 2000; **342**: 1627-1632 [PMID: 10833208 DOI: 10.1056/NEJM200006013422202]
17 **Fraser AG**, Morton D, McGovern D, Travis S, Jewell DP. The efficacy of methotrexate for maintaining remission in inflammatory bowel disease. *Aliment Pharmacol Ther* 2002; **16**: 693-697 [PMID: 11929386 DOI: 10.1046/j.1365-2036.2002.01227.x]
18 **Patel V**, Macdonald JK, McDonald JW, Chande N. Methotrexate for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2009; **(4)**: CD006884 [PMID: 19821390 DOI: 10.1002/14651858.CD006884.pub2]
19 **Krishnareddy S**, Swaminath A. When combination therapy isn't working: emerging therapies for the management of inflammatory bowel disease. *World J Gastroenterol* 2014; **20**: 1139-1146 [PMID: 24574790]
20 **Swaminath A**, Lebwohl B, Capiak KM, Present DH. Practice patterns in the use of anti-tumor necrosis factor alpha agents in the management of Crohn's disease: a US national practice survey comparing experts and non-experts. *Dig Dis Sci* 2011; **56**: 1160-1164 [PMID: 21181440 DOI: 10.1007/s10620-010-1530-9]
21 **Lémann M**, Zenjari T, Bouhnik Y, Cosnes J, Mesnard B, Rambaud JC, Modigliani R, Cortot A, Colombel JF. Methotrexate in Crohn's disease: long-term efficacy and toxicity. *Am J Gastroenterol* 2000; **95**: 1730-1734 [PMID: 10925976 DOI: 10.1111/j.1572-0241.2000.02190.x]
22 **Wahed M**, Louis-Auguste JR, Baxter LM, Limdi JK, McCartney SA, Lindsay JO, Bloom SL. Efficacy of methotrexate in Crohn's disease and ulcerative colitis patients unresponsive or intolerant to azathioprine /mercaptopurine. *Aliment Pharmacol Ther* 2009; **30**: 614-620 [PMID: 19552632 DOI: 10.1111/j.1365-2036.2009.04073.x]
23 **Colombel JF**, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, Lichtiger S, D'Haens G, Diamond RH, Broussard DL, Tang KL, van der Woude CJ, Rutgeerts P. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010; **362**: 1383-1395 [PMID: 20393175 DOI: 10.1056/NEJMoa0904492]
24 **Baert F**, Noman M, Vermeire S, Van Assche G, D' Haens G, Carbonez A, Rutgeerts P. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med* 2003; **348**: 601-608 [PMID: 12584368 DOI: 10.1056/NEJMoa020888]
25 **Feagan BG**, McDonald JW, Panaccione R, Enns RA, Bernstein CN, Ponich TP, Bourdages R, Macintosh DG, Dallaire C, Cohen A, Fedorak RN, Paré P, Bitton A, Saibil F, Anderson F, Donner A, Wong CJ, Zou G, Vandervoort MK, Hopkins M, Greenberg GR. Methotrexate in combination with infliximab is no more effective than infliximab alone in patients with Crohn's disease. *Gastroenterology* 2014; **146**: 681-688.e1 [PMID: 24269926 DOI: 10.1053/j.gastro.2013.11.024]
26 **Vermeire S**, Noman M, Van Assche G, Baert F, D'Haens G, Rutgeerts P. Effectiveness of concomitant immunosuppressive therapy in suppressing the formation of antibodies to infliximab in Crohn's disease. *Gut* 2007; **56**: 1226-1231 [PMID:

17229796 DOI: 10.1136/gut.2006.099978]
27 **Sokol H**, Seksik P, Carrat F, Nion-Larmurier I, Vienne A, Beaugerie L, Cosnes J. Usefulness of co-treatment with immunomodulators in patients with inflammatory bowel disease treated with scheduled infliximab maintenance therapy. *Gut* 2010; **59**: 1363-1368 [PMID: 20587545 DOI: 10.1136/gut.2010.212712]
28 **Absah I**, Faubion WA. Concomitant therapy with methotrexate and anti-TNF-α in pediatric patients with refractory crohn's colitis: a case series. *Inflamm Bowel Dis* 2012; **18**: 1488-1492 [PMID: 21882301 DOI: 10.1002/ibd.21885]
29 **Soon SY**, Ansari A, Yaneza M, Raoof S, Hirst J, Sanderson JD. Experience with the use of low-dose methotrexate for inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2004; **16**: 921-926 [PMID: 15316419 DOI: 10.1097/00042737-200409000-00018]
30 **Schröder O**, Blumenstein I, Schulte-Bockholt A, Stein J. Combining infliximab and methotrexate in fistulizing Crohn's disease resistant or intolerant to azathioprine. *Aliment Pharmacol Ther* 2004; **19**: 295-301 [PMID: 14984376 DOI: 10.1111/j.1365-2036.2004.01850.x]
31 **Bressler B**, Sands BE. Review article: Medical therapy for fistulizing Crohn's disease. *Aliment Pharmacol Ther* 2006; **24**: 1283-1293 [PMID: 17059510 DOI: 10.1111/j.1365-2036.2006.03126.x]
32 **Khan N**, Abbas AM, Moehlen M, Balart L. Methotrexate in ulcerative colitis: a nationwide retrospective cohort from the Veterans Affairs Health Care System. *Inflamm Bowel Dis* 2013; **19**: 1379-1383 [PMID: 23542534 DOI: 10.1097/MIB.0b013e31828133e8]
33 **Paoluzi OA**, Pica R, Marcheggiano A, Crispino P, Iacopini F, Iannoni C, Rivera M, Paoluzi P. Azathioprine or methotrexate in the treatment of patients with steroid-dependent or steroid-resistant ulcerative colitis: results of an open-label study on efficacy and tolerability in inducing and maintaining remission. *Aliment Pharmacol Ther* 2002; **16**: 1751-1759 [PMID: 12269968 DOI: 10.1046/j.1365-2036.2002.01340.x]
34 **Prey S**, Paul C. Effect of folic or folinic acid supplementation on methotrexate-associated safety and efficacy in inflammatory disease: a systematic review. *Br J Dermatol* 2009; **160**: 622-628 [PMID: 18945303 DOI: 10.1111/j.1365-2133.2008.08876.x]
35 **Te HS**, Schiano TD, Kuan SF, Hanauer SB, Conjeevaram HS, Baker AL. Hepatic effects of long-term methotrexate use in the treatment of inflammatory bowel disease. *Am J Gastroenterol* 2000; **95**: 3150-3156 [PMID: 11095334 DOI: 10.1111/j.1572-0241.2000.03287.x]

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REVIEW

Visceral hypersensitivity and electromechanical dysfunction as therapeutic targets in pediatric functional dyspepsia

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Abstract

Functional gastrointestinal disorders (FGID) are common clinical syndromes diagnosed in the absence of biochemical, structural, or metabolic abnormalities. They account for significant morbidity and health care expenditures and are identifiable across variable age, geography, and culture. Etiology of abdominal pain associated FGIDs, including functional dyspepsia (FD), remains incompletely understood, but growing evidence implicates the importance of visceral hypersensitivity and electromechanical dysfunction. This manuscript explores data supporting the role of visceral hypersensitivity and electromechanical dysfunction in FD, with focus on pediatric data when available, and provides a summary of potential therapeutic targets.

Key words: Motility; Visceral hypersensitivity; Functional dyspepsia

Core tip: Functional dyspepsia (FD) is a common disorder of upper gastrointestinal symptoms in adults and children. Etiology and mechanisms of FD are complex, and improved understanding could help direct therapy. Visceral sensitivity and intestinal electromechanical function both are demonstrated to be altered in some FD patients and are potential targets for treatment. Limited studies in pediatric FD are available, but available evidence supports adult data that targeting visceral hypersensitivity and electromechanical dysfunction is warranted, particularly in the context of the biopsychosocial model. Future studies in pediatrics are needed to determine optimal therapy and appropriate patient application.

Rosen JM, Cocjin JT, Schurman JV, Colombo JM, Friesen CA. Visceral hypersensitivity and electromechanical dysfunction as therapeutic targets in pediatric functional dyspepsia. *World J Gastrointest Pharmacol Ther* 2014; 5(3): 122-138 Available from: URL: http://www.wjgnet.com/2150-5349/full/v5/i3.122.htm DOI: http://dx.doi.org/10.4292/wjgpt.v5.i3.122

INTRODUCTION

Functional gastrointestinal disorders (FGIDs) account for more than 80% of chronic abdominal pain complaints in children. Although additional studies are needed, pediatric FGID prevalence and impact are described broadly in North America[1,2] and Europe[3,4], and with increasing recognition in other parts of the world[5-7]. The impact of pediatric FGIDs on patients and health-care systems cannot be overstated. In one epidemiologic study, 38% of school-aged children in the United States reported abdominal pain weekly and 24% reported abdominal pain persisting for more than 8 wk[8]. Further, FGIDs frequently are associated with somatic symptoms[9], decreased quality of life[10,11], psychological comorbidities[12], and school absenteeism[8]. Consequently, the burden on public health care[13] and associated financial costs are enormous[14,15].

In the late 1950s, Apley and Naish described an entity of recurrent abdominal pain (RAP)[16]. RAP was defined

by 3 or more bouts of pain severe enough to interfere with activities and occurring over at least a 3 mo period. Children with a wide variety of clinical presentations and etiologies were included under the single entity of RAP. This entity was rendered inadequate for clinical practice due to broad inclusivity. Over the past decade there was an effort to reclassify RAP into discrete groups that are known as FGIDs. FGIDs are defined by symptom-based clinical criteria set forth by an expert panel generally referred to as the Rome Committee. The committee met for the third time in 2006 (Rome Ⅲ) to update the criteria[17]. Rome Ⅲ defines abdominal pain associated FGIDs in children as pain occurring at least weekly for longer than 2 mo and without identifiable biochemical, structural, or metabolic abnormalities to explain symptoms. However, abdominal pain associated FGIDs are diagnosed even in the absence of laboratory, radiologic, and endoscopic testing, or in the presence of mild chronic inflammation of the intestinal mucosa[18,19]. Functional dyspepsia (FD) and irritable bowel syndrome (IBS) are among the most common pediatric FGIDs[20]. FD is diagnosed in children by: (1) upper abdominal pain or discomfort several times a week or more often; (2) upper abdominal pain or discomfort longer than 2 mo duration; (3) pain "sometimes" or less relieved by defecation; and (4) pain "once in a while" or less associated with a change in stool form or frequency. FD is differentiated from IBS in that IBS pain can be upper or lower abdomen, is more often relieved with defecation, and is often associated with change in stool form or frequency. Although distinctions are made within the criteria, it is debatable whether the two disorders are truly distinct in etiology or mechanism and ultimately may be symptom-defined diagnoses sharing a common underlying pathophysiology[21,22].

In adults, FD is further delineated by two subtypes: postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS). PDS is defined by the presence of upper abdominal fullness or early satiety after normal size meals, whereas EPS is defined by predominance of epigastric pain or burning. PDS and EPS are not included within the pediatric FD symptom definition due to lack of supportive evidence in children. However, subsequent to Rome Ⅲ, evidence emerged that adult subtypes also may be relevant in the pediatric population. For example, children with PDS-type symptoms have been found to have increased anxiety[23,24], a phenotype demonstrated in adults with PDS[25].

FD, as true of other FGIDS, is considered to be etiologically multi-factorial. The biopsychosocial model proposes contributions from and interactions between biologic, psychologic, and social systems. Factors within any of these systems may initiate, exacerbate or alter the course of the pain syndrome. In addition, adverse events early or later in life may lead to brain-gut axis changes, including long-term alterations in visceral electromechanical function, sensitivity, immunity, and brain-gut stress response. Examples of early adverse events span the biopsychosocial spectrum to include infection[26], inflammation, surgery[27,28], abuse[29], and wartime exposure[30].

We previously reviewed the role of inflammation (specifically eosinophils and mast cells) in pediatric FD[31]. In this companion review, we explore the role of visceral hypersensitivity and gastrointestinal electromechanical dysfunction in generation and maintenance of FD symptoms or subtypes (Table 1), as well as their potential as therapeutic targets (Table 2). Although they will generally be treated as separate entities in this discussion, visceral sensation, motor function and inflammation interrelate and should be considered as such when pursuing patient diagnosis and treatment.

VISCERAL HYPERSENSITIVITY

Visceral sensory output from organs (*e.g.*, intestine, bladder) to the central nervous system occurs continuously. Signals result from stimuli including hollow organ distension, inflammation, traction on the mesentery, and ischemia. Normal physiologic function of the visceral organs, including gastrointestinal distension and contraction, is typically nonpainful. However, the subjective interpretation may change due to increased frequency or amplitude of the visceral stimulus, or increased sensitivity to a typically painful (hyperalgesia) or nonpainful (allodynia) stimulus. Visceral hypersensitivity may result from alterations in the peripheral or central nervous system and has complex but increasingly understood etiology[32]. Human and animal studies have identified numerous contributing factors to this alteration, with visceral hypersensitivity now considered one of the central mechanisms of FGIDs.

Visceral hypersensitivity in FD may result in early satiety, abdominal pain, and nausea. Results from pediatric and adult investigations strongly suggest that sensory thresholds in FD patients are different than in subjects with other intestinal disorders and healthy controls. Visceral hypersensitivity was studied in 11 FD, 8 IBS and 11 FD-IBS overlap adults utilizing gastric and rectal barostats[33]. FD patients had predominant gastric (91% of subjects) over rectal (18%) hypersensitivity, IBS patients had only rectal (75%) hypersensitivity, and overlap patients had hypersensitivity to both (82% gastric, 91% rectal). Findings from this study suggest that hypersensitivity in FD may be localized to the stomach. However, other studies have failed to demonstrate these location-specific findings[34,35]. Differences in findings across studies may be related, at least in part, to heterogeneity in patient selection and/or in hypersensitivity definition.

Assessment of visceral hypersensitivity

Visceral sensitivity of the intestine is measured using a variety of methods in clinical studies. Patients undergo specific interventions, then either subjective pain reports or objective clinical data (*e.g.*, biometrics, functional brain imaging) are collected and analyzed. Tests utilized include water load, balloon distension, and inflammatory/nociceptive challenge. In many studies, tests of visceral sensitivity are conducted in a multimodal design, both to

Table 1 Selected studies of visceral sensitivity and electromechanical function in pediatric FD and related disorder

Assessment method	Cohort (*n*, symptom type)	Ref.
Visceral sensitivity		
Water load	71 RAP	Schurman *et al*[36]
	28 FD	Hoffman *et al*[37]
	15 FD	Chitkara *et al*[38]
	101 CAP	Anderson *et al*[39]
Gastric barostat	16 FD	Hoffman *et al*[47]
	10 RAP, 10 IBS	Di Lorenzo *et al*[48]
Electromechanical function		
Gastric emptying breath test	28 FD	Hoffman *et al*[37]
	15 FD	Chitkara *et al*[38]
Gastric emptying scintigraphy	57 FD	Chitkara *et al*[76]
	30 FD	Friesen *et al*[77]
Gastric Emptying ultrasound	41 FD	Devanarayana *et al*[78]
	42 FD	Boccia *et al*[79]
Accommodation ultrasound	20 RAP	Olafsdottir *et al*[94]
	20 RAP	Olafsdottir *et al*[95]
	20 non-ulcer dyspepsia	Cucchiara *et al*[96]
SPECT	15 FD	Chitkara *et al*[38]
Electrogastrogram	30 FD	Friesen *et al*[77]
	15 FD	Chen *et al*[106]
	7 non-ulcer dyspepsia	Di Lorenzo *et al*[114]
Antroduodenal manometry	11 non-ulcer dyspepsia	Cucchiara *et al*[109]
	34 non-ulcer dyspepsia	Di Lorenzo *et al*[110]
	7 non-ulcer dyspepsia	Di Lorenzo *et al*[114]
Wireless motility capsule	22 mixed upper GI symptoms	Green *et al*[118]

FD: Functional dyspepsia; RAP: Recurrent abdominal pain; IBS: Irritable bowel syndrome.

Table 2 Selected studies of therapy directed at visceral hypersensitivity or electromechanical dysfunction in pediatric FD and related disorders

Therapy	Cohort (*n*, symptom type)	Ref.
Amitriptyline	90 FGID; 12 FD	Saps *et al*[138]
Citalopram	25 RAP	Campo *et al*[140]
Famotidine	25 RAP with dyspepsia	See *et al*[148]
Omeprazole	169 FD	Dehghani *et al*[149]
Cisapride	10 non-ulcer dyspepsia	Riezzo *et al*[154]
Erythromycin	7 FD	Cucchiara *et al*[172]
Cyproheptadine	44 FD	Rodriguez *et al*[187]
Peppermint oil	42 IBS	Kline *et al*[191]
Gut-directed hypnotherapy	52 FAP or IBS	Vlieger *et al*[200]
	34 FAP	van Tilburg *et al*[201]
Yoga	25 IBS	Kuttner *et al*[202]
Biofeedback	20 FD	Schurman *et al*[203]
Gastric electrical stimulator	24 FD	Lu *et al*[10]

FD: Functional dyspepsia; RAP: Recurrent abdominal pain; IBS: Irritable bowel syndrome.

determine correlation and to validate outcomes. Water load testing requires subjects to drink a maximal amount of water in a brief discrete time period (typically 5 min). Outcomes include subjective symptoms and quantity of water ingested. Balloon distension of hollow organs, including gastric barostat, measures distension thresholds and corresponding signs and symptoms. Of note, balloon distension also is used in animal models of visceral pain, with electromyographic recording included as an additional objective outcome. Inflammatory/nociceptive challenges directly stimulate intestinal mucosal sensory nerves by application of a chemical (*e.g.*, acid or lipid) and measuring subjective pain thresholds. Both water load and balloon distension tests are affected by gastric accommodation and emptying, further demonstrating that separating sensation from function is a practical but artificial distinction.

Water load test: The water load test is advocated as a means of identifying patients with visceral hypersensitivity. Although the water load test may not be useful for identification of pediatric FD due to suboptimal sensitivity, children diagnosed with FD often have abnormal test results[36]. In a controlled study by Schurman *et al*[36], 68 pediatric patients with FGIDs and 26 healthy children completed the Behavioral Assessment Scale for Children-

Self-Report Form (BASC-SR) and underwent a rapid water load test (maximal tolerable volume within 3 min). Children with FD, with or without corresponding IBS, had lower water consumption than healthy controls. This was not true of children with IBS only. Using the 10th percentile for water volume consumption in the control group as a lower limit of normal, the water load test had 28% sensitivity and 100% specificity in identifying patients with the diagnosis of FD as determined by the clinician. Consistent with the biopsychosocial model, self-reported anxiety was negatively correlated with volume of water intake; however, it accounted for only 6% of the variance.

A variation on the water load test measuring satiety was evaluated in 28 pediatric patients diagnosed with FD using Rome Ⅲ criteria[37]. Participants drank a liquid meal at a constant rate and repeatedly scored satiety until reaching maximal possible score or 5 min time. Total intake volume was decreased in dyspeptic patients compared to healthy controls. Another study of 15 adolescents with FD who consumed a liquid meal at a constant rate to maximal tolerable volume found no statistical difference in total ingested volume or time to satiation compared to controls[38]. However, total volume was over 10% less and time to satiation over 20% sooner in FD subjects. Additionally, postprandial nausea and bloating were greater in dyspeptics, with 7/15 subjects reporting postprandial pain scores > 99th percentile of scores for healthy adolescents. Of note, in a study of 101 children with functional abdominal pain that utilized multiple validated questionnaires in addition to a water load test, children believing they could modify their own pain (high problem-focused pain efficacy) had decreased visceral sensitivity compared to those who perceived little control over pain[39]. Although the direct application to children with FD is unclear given different inclusion criteria, findings support consideration of visceral sensitivity to gastric distension as a possible pathophysiologic mechanism and, further, the potential beneficial role of CNS-mediated inhibition.

Measures of visceral sensitivity are studied more extensively in adult patients with FGIDs including FD. While water load testing in adults with FD has yielded similar results[40-44] to those reported above for pediatric studies, studies in adults contain expanded data investigating other upper GI conditions, demographic and psychosocial factors, and liquid composition. In one study of adults, patients with FD (n = 59), GERD (n = 101), and ulcer (n = 55) all demonstrated decreased maximal ingested volume of water over 5 min compared to 30 healthy controls[45]. Although this again supports visceral sensitivity mechanisms, it also raises concern regarding the specificity of the water load test as an assessment for FD. Strid *et al*[43] evaluated 35 FD adults and 56 controls. Depressed mood and poor overall health correlated with lower tolerated volumes in FD patients only, again reinforcing the brain-gut connection/biopsychosocial model and the useful but artificial construct of measuring visceral sensitivity in isolation. In contrast, Jones *et al*[44] found no correlation between psychological measures and specific water load test outcomes. Composition of the liquid also appears to affect the postprandial symptom profile in FD. Lee *et al*[46] compared 30 adults with FD to 12 healthy controls and found that symptoms of bloating and abdominal pain within 30 min following ingestion were greater in FD patients after a nutrient drink as compared to water, while there was no symptom difference between the two liquids in healthy controls[46]. Interpretation of liquid loading needs to take into consideration the psychologic state of the subject and the nutrient content of the ingested liquid.

Gastric barostat: Barostat testing is the traditional "gold standard" for evaluating mechanical hypersensitivity in adults. In FD, the evaluation utilizes balloon distension of the fundus and subjective scoring of discomfort. Hoffman *et al*[47] found that FD children had abdominal discomfort at lower gastric distension pressures compared to healthy young adults. This is consistent with a separate study utilizing barostat testing in which visceral hypersensitivity was identified at a higher frequency in children with RAP as compared to healthy controls[48]. The RAP group likely included children with FD as well as other abdominal pain disorders.

Gastric barostat studies in adult FD generally replicate, and also extend, pediatric findings. Evaluation of 8 dyspeptic adults found lower sensation threshold to gastric distension compared to controls, although maximal tolerated distension pressure and volume were similar[49]. These 8 patients had not previously consulted health care professionals regarding symptoms, suggesting that visceral hypersensitivity to balloon distension is independent of referral bias and certain psychosocial characteristics (such as high anxiety regarding symptoms). FD patient heterogeneity was demonstrated in two other studies, however, suggesting that sensitivity to balloon distension is not universal. Specifically, relative pressure (intraballoon pressure/intraabdominal pressure) to produce discomfort was abnormal in only 37% of 160 consecutive patients with FD when compared to 80 healthy controls and gastric hypersensitivity was found in only 44% of "pain-predominant" and 25% of "discomfort-predominant" FD adults[50]. Hypersensitivity to balloon distention is enhanced in the postprandial state in FD patients (but not controls) and correlates with preprandial sensitivity, impaired accommodation, and the severity of meal-related symptoms[51]. Taken together, studies suggest that mechanical hypersensitivity may be associated with an increased prevalence of postprandial pain.

Duodenal infusion: Although chemosensitivity has not been evaluated in children with FD, adults with FD have demonstrated increased symptoms to both duodenal[52] and gastric[53] acid infusion. Duodenal acid infusion has most often been associated with nausea but also bloating and pain[52,54-56]. Duodenal acid infusion decreases antral

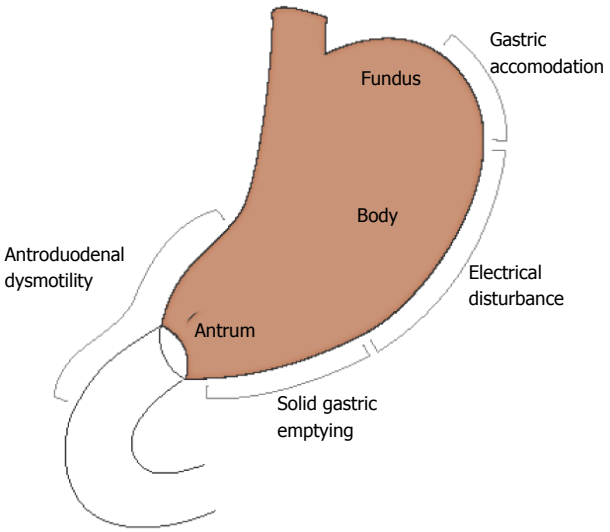

Figure 1 Overview of electromechanical disturbances in functional dyspepsia.

motility and alters response to balloon distention[46,55]. In a study of adults with FD, Feinle *et al*[57] showed that duodenal lipid exposure affects gastric sensitivity to balloon distension supporting the effect of lipids and cholecystykinin on visceral sensitivity. Lipid infusion, but not glucose infusion, enhances perception to gastric distention and lipid infusion is associated with nausea[58]. In addition to mechanical sensitivity, chemosensitivity represents another potential therapeutic target.

Mechanisms of hypersensitivity

Visceral hypersensitivity is a complex process which may occur both within the CNS and at the level of the peripheral nervous system. Mechanisms of increased visceral sensitivity to balloon distension have been studied extensively in animal models[59,60] and in several cohorts of adults with FD, but have not been reproduced in dyspeptic children. Neuroimaging studies conducted in adults with FD support the presence of abnormal CNS processing of pain signals as compared to controls and in FD patients with hypersensitivity as compared to FD patients with normal sensation[61,62]. Vandenberghe *et al*[63] postulated that intense stimulation of low threshold multimodal afferent pathways, as opposed to sensitization of nociceptive pathways, occurs in hypersensitive FD adults. Their conclusion is based on studying 48 FD adults (hypersensitive, n = 20) in whom non-pain symptoms were induced at similar distending pressures that resulted in pain. At a peripheral level, hypersensitivity may be induced by a number of factors, including alterations in mediator release (*e.g.*, serotonin) or receptors (*e.g.*, 5-HT or TRPV1), inflammation, or the stress response.

Serotonin (5-HT) is abundant throughout the intestine and is an important neurotransmitter within the brain and the GI tract where it plays a key role in the regulation of motility and sensation. The effects of serotonin are modified by 5-HT receptors and its reuptake controlled by SERT. In adults with FD, plasma levels of 5-HT are decreased in the basal and postprandial states[64]. This has not been studied directly in children with FD; however, gastric 5-HT content and SERT mRNA do not differ between children with FD and controls[65]. Due to its important role in sensation, serotonin (broadly or specific serotonin receptors) represents a potentially important treatment target.

Transient receptor potential (TRP) channels survey the gastrointestinal contents for chemicals ingested, produced within the gastrointestinal tract (including those produced by the microbiome), and/or generated by inflammatory responses[66]. TRP vanilloid type 1 (TRPV1) is a polymodal nociceptor on GI afferent neurons and is the specific sensor for capsaicin. Based on oral capsaicin capsule titration, the majority of adults with FD demonstrate visceral chemosensitivity involving TRPV1 pathways[67-69]. Repeated ingestion of capsaicin in healthy volunteers initially increases symptoms, but after 4 wk decreases symptoms through desensitization of both chemo- and mechanoreceptors[70]. The effects on sensitivity appear to be dependent on length of exposure. In healthy volunteers with 7 d exposure, chemoreceptors remain sensitized while threshold of mechanoreceptors to distention decreases[71]. TRPV1 potentially plays a key role in chemosensation and possibly mechanosensitivity; as such, TRPV1 may represent another therapeutic target.

Inflammation and stress have been implicated in the pathophysiology of visceral hypersensitivity in FD. Consistent with the biopsychosocial model, electromechanical dysfunction may also be influenced by anxiety and the stress response. Anxiety is the most highly implicated psychological contributor to the development and maintenance of FGIDs including FD. Approximately 50% of children and adolescents with FD demonstrate elevated anxiety scores[72]. Anxiety can trigger the stress response which is mediated primarily through the release of corticotrophin releasing hormone (CRH) from the hypothalamus. The stress response results in physiologic effects relevant to FGIDs including inflammation (particularly mast cell activation), sympathetic nervous system activation, altered gastric accommodation, gastric dysmotility, and visceral hypersensitivity. CRH also alters central processing of nociceptive messages. The effects of CRH on hypersensitivity and electromechanical dysfunction may be direct and mediated *via* CRH1 and CRH2 receptors. Downstream effects of CRH-induced mast cell activation and mediator release can stimulate afferent nerves signaling pain, sensitize afferent nerves resulting in visceral hypersensitivity, and alter electromechanical function. In adults with FD, hypersensitivity is associated with mast cell degranulation after balloon distention of the proximal stomach[73].

ELECTROMECHANICAL DYSFUNCTION

Visceral hypersensitivity undoubtedly has a role in dyspeptic symptoms, but it is identified in only a fraction of patients diagnosed clinically with FD. In contrast, disordered accommodation, delayed gastric emptying, gastric

electrical rhythm disturbances, and altered antroduodenal motility are all physiologically relevant and common in FD (Figure 1). As reviewed by Azpiroz *et al*[74], gastric motor function is interdependent on visceral sensation and is a complex function affected by both tonic and induced stimuli. Understanding physiologic abnormalities in specific disorders such as FD can guide effective therapy.

Assessment of electromechanical dysfunction

Motor function of the stomach and duodenum is a coordinated activity meant to prepare food for digestion and initiate passage through the small intestine. The stomach serves as a reservoir for ingested food and functions to grind food and then provide passage to the intestine at a rate appropriate for effective nutrient absorption. In the interdigestive period, gastroduodenal motility is modulated by the migrating motor complex (MMC) which is a multiphase action propagated from the gastric antrum into the small intestine controlled by the enteric nervous system, central nervous system, and intestinal regulatory hormones. Gastroduodenal motility depends on prandial state, food composition, presence and type of inflammation, distal intestinal motor function, and both motor and autonomic neural input. Symptoms related to altered gastroduodenal motor function may include abdominal pain, nausea, vomiting, and early satiety and can occur due to rapid[75] or delayed gastric emptying, or altered proximal stomach accommodation with normal gastric emptying. Gastroduodenal mechanical function can be measured with a variety of tools including scintigraphic or breath gastric emptying study (GES), gastric barostat, antroduodenal manometry (ADM), and electrogastrography (EGG) as well as newer studies including single-photon emission computed tomography (SPECT), and the wireless motility capsule (WMC). Each test measures related but different aspects of physiology including compliance, accommodation, contractility, coordination, and propagation as highlighted below.

Gastric emptying

Pediatric studies have identified abnormal gastric emptying in FD. In a study of 15 FD adolescents using the ^{13}C-*s platensis* breath test, gastric emptying of solids was significantly delayed[38]. Solid-phase delays were similarly identified in 26% of dyspeptic children when evaluated with the ^{13}C-octanoic breath test[37]. Emptying function has also been evaluated in pediatric dypeptics with scintigraphy using 99mTc-sulfur colloid and a standard meal[76]. Although a majority of the 57 patients had normal gastric emptying at 2- and 4-h post meal, abnormalities of rapid (20%) and slow (20%) gastric emptying were observed. Symptoms did not correlate with emptying rates in these children. Another study utilizing scintigraphy demonstrated delayed solid emptying in 47% of patients, but again there was no relationship between emptying and symptom severity[77]. In contrast, Devanarayana *et al*[78] recently used antral ultrasound to correlate gastric emptying after a liquid meal with symptoms in pediatric dyspeptics. Forty-one FD patients had delay in both gastric emptying rate (% change in antral cross sectional area from 1 to 15 min post ingestion) and antral motility index (product of contractile amplitude and frequency) compared to healthy controls. Severity of symptoms correlated negatively with gastric emptying rate (r = -0.35), but not with other measures of motility. Gastric emptying appears to have no relationship to satiety in children[37]. Delays in gastric emptying may also be affected by concurrence of constipation in pediatric dyspepsia[79]. FD patients with constipation had longer gastric emptying times than FD patients without constipation, and treatment with lactulose over 3 mo resolved the difference.

Abnormal gastric emptying by scintigraphic evaluation has been demonstrated in a significant proportion of adults with FD[80-82] although findings may be affected by the modality of measurement as well as meal volume and contents[83]. In adults, there have been no reproducible relationships between impaired emptying and specific symptoms. Some studies have revealed no or only weak associations with symptoms[84-86]. Other studies have reported variable and highly inconsistent associations with nausea, vomiting, postprandial fullness, and bloating with both positive and negative relationships with regard to pain[87-91]. Postprandial fullness and nausea, and severe early satiety have been reported with delayed liquid emptying[88,90].

Gastric accommodation

Gastric accommodation, the ability of the proximal stomach to relax and serve as a reservoir for food, is implicated as a motor abnormality responsible for symptoms in some dyspeptic patients[92]. Impaired accommodation has been associated with early satiety in some but not all studies[84,91,93]. Assessment of accommodation can be conducted with gastric barostat, ultrasound, MRI, and SPECT. Gastric emptying and water-load capacity are certainly affected by accommodation, but neither is a specific measure of fundic relaxation. Impaired accommodation was demonstrated in pediatric RAP patients assessed by 2-dimensional ultrasound[94]. Participants, most of whom had dyspeptic symptoms, had decreased proximal stomach saggital area and increased rate of proximal stomach emptying after a liquid meal when compared to healthy controls. A similar assessment of RAP patients utilized 3-dimensional ultrasound to assess antral relaxation and gastric distribution of ingested liquids[95]. Participants demonstrated decreased postprandial proximal filling (accommodation) and altered liquid distribution favoring the distal stomach despite no difference in gastric emptying rate. Ultrasound evaluation of children with FD also showed increased antral distension after a mixed solid-liquid meal, but without specific evaluation of the proximal stomach[96]. Adolescents with FD also have a lower postprandial gastric volume change than healthy adults when assessed by SPECT[38]. No MRI studies of gastric function in pediatric FD patients have been published.

In adults with FD, decreased gastric accommodation and abnormal gastric volumes are widely demonstrated using barostat[90,97,98], ultrasound[99,100], SPECT[80,101,102], and

MRI[83]. Accommodation defects have been reported in 40% of adults with FD as assessed by barostat and in 47% as assessed by SPECT[93,101]. It is less clear whether symptoms are associated with abnormal accommodation or gastric volumes[91] and whether newer imaging modalities such as MRI will consistently support these findings[103].

Electrogastrography

Electrogastrography (EGG) is a noninvasive method to evaluate gastric myoelectrical activity. It can assess rhythmic gastric slow waves associated with frequency and propagation of contractions, as well as superimposed activity (spike/second) indicative of antral contractility. Cutaneous abdominal electrodes are utilized to obtain raw data, then computer analysis is performed to determine targeted values for comparison. Normative data are considered similar in children, adolescents, and adults[104], but not in neonates or toddlers[105].

Children with FD have abnormal EGG compared to healthy children, indicating underlying myoelectrical dysfunction. Chen *et al*[106] assessed 15 pediatric patients with FD compared to 17 healthy controls using surface electrodes. Children with FD had a lower percentage of slow waves and more time with no rhythmic activity in fasting and fed states. In the postprandial state, frequency of gastric slow waves also increased less in subjects than controls although measures of contractility (power) were similar. In an independent study of 30 children with FD, EGGs were abnormal in 50% and correlated with symptom severity[77].

Electrogastrogram abnormalities in adults with FD are similar to those described in children[42,107]. Patients with abnormal EGG also had higher postprandial pain scores, and patients with a history of vomiting had more frequent fasting bradygastria and fewer normal slow waves. This symptom correlation suggests clinical relevance of EGG abnormalities and is consistent with other data correlating EGG and symptoms in pediatric FD[106,108]. However, the role of EGG abnormalities as a therapeutic target remains to be established.

Antroduodenal manometry

Antroduodenal manometry also demonstrates abnormal motility in children with FD[109]. A study of 34 children and 35 adults with FD found a majority with abnormal motility with a neuropathic pattern observed most commonly[110]. Several studies of antroduodenal motility also demonstrate abnormalities in adults with FD[111,112], but symptoms, intestinal dysmotility, and gastric emptying delays are not clearly correlated[112]. The relationship between motility studies is made even less clear in that a study of 31 adults with FD showed abnormal EGG was not associated with concurrent abnormalities in antroduodenal manometry[113], and available pediatric data supports this concept[114]. The clinical significance of altered antroduodenal motility, particularly as a therapeutic target, is not established.

Wireless motility capsule

The WMC shows promise as a relatively noninvasive, clinically relevant measure of gastrointestinal motility[115]. It is used to study prokinetic medication efficacy[116] and to describe an adult irritable bowel syndrome cohort[117]. Data is not yet available in adult or pediatric dyspeptics, but an initial study suggests the WMC is a sensitive detector of motor abnormalities in pediatric patients with upper gastrointestinal symptoms[118].

Mechanisms of electromechanical dysfunction

The specific cause of electromechanical dysfunction in FD is unclear, but may be related to immune activation[119]. Inflammation is implicated as a contributor in dyspepsia-associated dysmotility[31,120]. However, this effect appears to require specific inflammatory pathways. For example, EGG abnormalities in children and adolescents with FD are independent of chronic gastritis, but associated with antral mast cell and eosinophil density[121,122]. Likewise, in children with FD, increased antral mast cell density is associated with slower gastric emptying[121].

As alluded to previously, the stress response also has effects on electromechanical function. Experimentally induced stress has been shown to increase symptoms and inhibit normal postprandial EGG responses in some, but not all studies[123,124]. Stress is shown to impair accommodation and to decrease gastric emptying[125,126]. The effect on gastric emptying appears to be mediated primarily *via* CRH receptors.

THERAPIES FOR PEDIATRIC FD

Proper identification of functional dyspepsia using symptom based criteria (Rome Ⅲ) is the first step in treatment. Diagnostic and screening tests to evaluate for diseases with similar symptoms are sometimes important, but not necessary for FD diagnosis. Providing a named diagnosis (*i.e.,* FD) and the expectation of treatment success potentially increases the treatment response rate. Importantly, the placebo effect may be particularly strong in children with FGIDs and should be considered when interpreting efficacy of studied interventions[127].

Reassurance and education regarding FGIDs is imperative. Validating that subjective symptoms are real and putting them in the context of the biopsychosocial model aids in directing effective treatment and provides hope for patients and families. Visceral hypersensitivity and electromechanical dysfunction represent potential targets, but patients may be more effectively managed if underlying factors (such as inflammation, anxiety, *etc.*) are considered in the treatment plan. Treating FD, like other FGIDs, in the conceptual framework of the biopsychosocial model necessitates inclusion of both medical and psychological interventions. Effective medical therapy targeted to the specific pathophysiologic mechanism is preferred, but symptom-based therapy may also be use-

ful. Although we will discuss medications in the context of their most likely target, it should be noted that visceral sensation, motor function, and inflammation do not exist in a vacuum; many medications exert an effect on more than one domain of sensation and mechanical function.

Targeting visceral hypersensitivity

Treatment of visceral sensitivity related to distension in FD has focused largely on antidepressant therapy, including tricyclic antidepressants (TCAs), selective serotonin uptake inhibitors (SSRIs), and related medications. Antidepressants may have primary effects on comorbid anxiety/depression that secondarily alter symptom perception, coping skills, arousal thresholds, and/or sleep quality. Alternately, they may affect functional gastrointestinal pain through central nervous system analgesia or a direct effect on gastrointestinal tract sensitivity. Serotonergic neurons have a role in gastrointestinal pain as discussed above, but antinociceptive effects of these medications cannot always be dissociated from their influence on motility and, in some cases, may be integral to effective treatment[128]. For example, TCAs slow gastric emptying and small bowel transit in healthy patients[129,130], but do not affect SPECT-determined gastric accomodation or outcomes of the nutrient drink test, except for post-satiation nausea[129]. Similarly, SSRIs shorten small bowel transit time in healthy patients, but do not clearly decrease gastric sensitivity or compliance[131,132]. Treatment with TCAs, SSRIs, and related medications must be carefully weighed against potential adverse effects, including cardiac dysrhythmias, suicidality, and anticholinergic effects, and monitored to minimize these relatively rare, but potentially life-threatening issues.

Several studies have investigated whether TCAs, SSRIs, and related medications alter visceral sensitivity and overall symptoms in adult FD. Data in healthy adult volunteers demonstrate no change in tolerated gastric volume in the nutrient drink test after a short treatment course with desipramine (TCA) or escitalopram (SSRI)[133]. Although total symptom scores induced by the nutrient drink test were influenced, treatment effects were nullified in multivariate analysis considering age, gender, BMI, and baseline scores. Fluoxetine (SSRI) improved symptom scores in depressed adults with FD[134], but non-depressed subjects had no change in symptom scores and EGG measures were similar across all groups. Sertraline (SSRI) similarly failed to alter global symptoms or quality of life in adults with FD[135]. Finally, a randomized clinical trial (RCT) of venlafaxine, a medication with combined SSRI and selective norepinephrine reuptake inhibition (SNRI), demonstrated significant patient dropout due to medication adverse effects and no differences in symptom scores, health-related quality of life, anxiety, or depression[136]. Taken together, current evidence does not support a strong direct effect of SSRIs or TCAs on visceral sensitivity in adults. The potential role of these medications in treatment of visceral hypersensitivity, as well as gastroduodenal motility, may be further clarified by an international multicenter placebo-controlled RCT currently underway to compare escitalopram to amitriptyline in adults with FD. This trial has completed enrollment and data collection for the primary outcome of global symptom score, and also is assessing solid gastric emptying, liquid nutrient drink test, and SPECT (http://clinicaltrials.gov, NCT00248651).

Limited data exists regarding treatment of pediatric FD with TCAs and SSRIs, and studies typically include a mixed cohort of FGIDs. A double-blind placebo-controlled RCT of amitriptyline (TCA) in 33 pediatric patients with IBS treated for 8 wk demonstrated improvement in QOL and some IBS-associated symptoms[137]. Symptom improvement was limited to very specific symptoms (*i.e.*, right lower quadrant pain) and the reason for such specificity is not clear. Amitriptyline also was studied in 90 pediatric FGID patients in a multicenter double-blinded placebo-controlled RCT[138]. Few patients were diagnosed with FD (8% placebo, 13% amitriptyline), but primary outcome of symptom relief was not different when analyzed by diagnosis. No difference in symptom relief, depression, or functional disability was noted, although anxiety was decreased in subjects receiving treatment. Notably, at least "fair" improvement in pain relief was seen in greater than 2/3 of subjects receiving placebo. A retrospective study of 98 pediatric FGID patients (n = 16 with FD) treated with TCAs found greater than 75% symptom response rate in all FGID subtypes, but limitations include lack of validated outcome measures, blinding, and control subjects[139]. A 12-wk open label study of citalopram (SSRI) in 25 pediatric patients with RAP identified improvement in global symptoms, somatic symptoms, anxiety, and functional impairment[140]. There are no published placebo-controlled RCTs of SSRIs for treatment of pediatric FGIDs in general or FD in particular. Given the questionable efficacy in adults with FD, SSRIs should not be viewed as first-line therapy, if at all, in pediatric FD.

In addition to mechanosensitivity, visceral chemosensitivity may represent a valid therapeutic target. Lipid sensitivity may be addressed through diet modification, but there have not been any studies demonstrating long-term benefit from low fat diets. Acid sensitivity may be addressed more directly through acid reducing medications. Acid-suppressive therapy with histamine-2 receptor antagonists (H2RA) and proton-pump inhibitors (PPI) improve pain in adults with FD[141-143]. PPI therapy may be more effective than H2RA[144], but studies typically have a mixed cohort without control for presence of *H. pylori* infection, gastroesophageal reflux disease (GERD), or both. A randomized, controlled trial in adults found that PPI therapy improved symptoms only in FD patients with concurrent heartburn[145]. Whether the therapeutic benefit is related to acid hypersensitivity is not clear as these medications may be treating a component of acid mucosal injury or co-morbid GERD, or may also improve dyspeptic symptoms related to delayed gastric emptying[146]. Still, acid reduction therapy remains the

most common treatment prescribed empirically by pediatric gastroenterologists for FD in children[147]. In children with abdominal pain, famotidine has demonstrated superiority to placebo in global improvement, and additional benefit is noted in children with FD[148]. In a large pediatric cohort, omeprazole had no benefit over ranitidine or famotidine in the relief of pain, nausea, or vomiting[149]. Although acid suppression appears promising, the specific mechanism of action in FD remains unclear.

Treatment of visceral chemosenstivity in FD also has targeted specific nociceptors including TRPV1. As described earlier, healthy adults ingesting capsaicin achieve desensitization following initial increase in symptoms, and FD adults may have increased chemosensitivity to TRPV1 agonists. A double-blind, placebo-controlled trial of red pepper powder in 30 FD adults demonstrated efficacy in decreasing overall symptoms, epigastric pain, and epigastric fullness within 3 wk[150]. Although some initial discomfort occurred in treatment group patients, only two discontinued the study due to severe pain or burning. Capsaicin or other TRPV1 agents have promise in FD patients with demonstrated chemosensitivity.

Targeting electromechanical dysfunction

Therapies for electromechanical dysfunction in FD can be broken down into those targeting gastric motility/emptying and those targeting gastric accommodation. Therapies to increase gastrointestinal motility and emptying have met with mixed results for FD. A meta-analysis of 1844 adult patients with FD and 1599 controls found that prokinetics were effective in decreasing symptoms[151]. The authors importantly note that most studies of prokinetics assess short-term efficacy only. Interestingly, a separate analysis of studies including measures of symptom improvement and gastric emptying found no correlation between the two, suggesting that alternate effects of prokinetics are responsible for symptom improvement[152].

Prokinetics evaluated in adults include agents primarily targeting 5-HT (5-HT$_3$ antagonists and 5-HT$_4$ agonists), dopamine, and motilin receptors. Cisapride, a 5-HT$_4$ receptor agonist, demonstrated symptom reduction in adults with FD in one meta-analysis, but potential bias and inclusion of specific FD-subtypes may affect applicability of findings[153]. In pediatric patients with dyspepsia it may normalize gastric myoelectric activity[154], but data on clinical effects is not available. Cisapride and newer 5-HT$_4$ receptor agonists regulate intestinal motility through effects on enteric cholinergic neurons, enhancing gastric emptying and accomodation, as well as potentially modulating visceral sensitivity[155,156]. Although cisapride was withdrawn from the United States and European markets due to concern for potentially fatal cardiac arrythmias, it is not clear that these effects are common in otherwise healthy children[157] and the medication can still be used in limited capacity with close supervision. Another serotonergic/anti-dopaminergic compound, levosulpiride, has demonstrated noninferiority to cisapride[158] with safety and efficacy confirmed in an open-label trial of 279 adults with FD[159]. A selective 5-HT$_4$ agonist and 5-HT$_3$ antagonist (mosapride) has shown mixed results in FD symptom improvement[160-162]. Cinitapride, a relatively new 5-HT$_4$ receptor agonist/dopamine-2 receptor antagonist, was demonstrated to relieve symptoms and reduce symptom severity as well as domperidone in a double-blind phase Ⅲ RCT[163]. There is a lack of pediatric data regarding agents targeting 5-HT receptors.

Metoclopramide is a dopamine antagonist with a long history of use in FD as an effective promotility agent that reduces dyspeptic symptoms[164,165], but adverse effects may include irreversible extrapyramidal symptoms. There is evidence that metoclopramide liquid formulation may actually be more effective than the tablet[166]. Domperidone, a dopamine-2 receptor antagonist that does not cross the blood-brain barrier, is shown to improve symptoms in adults with FD[167] though it may be less effective when compared to cisapride[168,169]. Domperidone is currently available for pediatric patients only as an investigational new drug for compassionate use. Itopride, which is anti-dopaminergic and inhibits acetylcholinesterase, did not have promising results in a phase Ⅲ trial in adults[170], but a meta-analysis that included a heterogenous patient population with potential comorbid disease (*i.e.*, *H. pylori*) suggests that it may be effective in symptom reduction[171]. A lack of proven efficacy and significant potential side effects should limit the long-term use of metoclopramide in pediatric FD.

Erythromycin activates antral and small intestinal motilin receptors, and may have differential physiologic effects in children with underlying gastrointestinal disorders, including FD[172]. Erythromycin in adults with FD improved bloating and gastric emptying of liquids and solids, but did not affect meal related symptom severity[173]. The motilin agonist ABT 229 provided no symptom improvement in adults with FD[174]. Another motilin agonist, mitemcinal, showed promise in relieving gastroparesis-associated symptoms in adult diabetics[175]. Efficacy in a subset of those patients with lower body mass index and hemoglobin A1C suggests a role in nondiabetics with upper gastrointestinal symptoms[176]. Motilin receptor agonists are known to decrease gastric accommodation and compliance[177,178] and are susceptible to tachyphylaxis, both factors that may contribute to limited efficacy in FD.

Actiomide is a novel agent that has minimal interaction with serotonin and dopamine receptors. It affects gastrointestinal motility in adult FD, including improving accommodation and gastric emptying[179], through muscarinic receptor inhibition. This, in turn, increases acetylcholine release and inhibits its degradation. Elimination of meal-related symptoms, and improvement in symptom subgroups and quality of life was demonstrated in a phase Ⅲ clinical trial in Japan[180] . Phase Ⅲ trials are currently in preparation in the US and Europe.

Gastric accommodation represents another potential therapeutic target within the broad category of electro-

mechanical dysfunction. Buspirone, a 5HT$_{1a}$ receptor agonist, increased accomodation and decreased symptom severity, postprandial symptoms, and liquid gastric emptying rate, but did not specifically affect gastric sensitivity to distension by barostat in adults with FD[181]. Tandospirone, a partial 5HT$_{1a}$ agonist similar to buspirone, also improved symptom scores in FD adults, but had no effect on early satiety implicating central anxiolytic effects rather than altered gastric accommodation[182]. Sumatriptan is another 5HT$_1$ receptor agonist that alters gastric size in dyspeptics, but specific mechanical effect and association with symptom improvement remains unclear[93,183]. A subset of FD patients also showed improvement in nausea and accommodation when treated with ondansetron, a 5HT$_3$ antagonist, but mechanical and clinical effects were disassociated[184]. Tegaserod, a partial 5HT$_4$ receptor agonist, is shown to enhance gastric accommodation and two large randomized trials showed significant symptom relief compared to placebo[185]. Paroxetine, an SSRI, has been shown to enhance gastric accomodation in healthy volunteers but has not been studied in FD[186].

Cyproheptadine is efficacious in improving symptoms in children with FD[187]. As an antagonist of serotonin, histamine H1, and muscarinic receptors, it is possible that physiologic effects are due to increased gastric accommodation or decreased gastric hypersensitivity to distension. In a retrospective open-label study of 80 children, Rodriguez *et al*[187] showed FD-symptoms significantly improved in 33 (41%) and resolved in 11 (14%) with very good medication tolerance even in nonresponders. It was previously found to be effective in a RCT of children with functional abdominal pain[188].

Complementary therapies such as ginger[189,190], peppermint oil[191], and iberogast[192], may also have a role in the treatment of FD. Ginger enhances gastric emptying in healthy volunteers and adults with FD but had no impact on FD symptoms[193,194]. In healthy volunteers, peppermint oil enhances gastric emptying without effects on sensitivity or accomodation[195,196]. It was effective for irritable bowel syndrome in children, but has not been specifically studied in FD[191]. Iberogast (STW 5), an herbal preparation, improves symptoms in FD, but there is not clear data determining whether effects are directly mediated by acceleration of gastric emptying or an alternate mechanism[192,197].

Non-medication treatments

Gastrointestinal motility can also be influenced by mechanical devices including the gastric electrical stimulator. The device utilizes electrodes implanted into the antrum to deliver high frequency, low amplitude stimulation. Adult studies show the device decreases symptom severity and improves quality of life[198] and findings were recently replicated in pediatric trials[10,199]. The study of 24 pediatric FD patients included those who did not improve with conventional medical therapy and most underwent temporary endoscopic gastric pacemaker placement to assess for symptom improvement prior to implantation of the permanent device[10]. Most patients showed significant gastrointestinal symptom improvement, as well as improved quality of life and global health scores.

Given the interaction between the stress response, visceral hypersensitivity, and electromechanical dysfunction, non-medication treatment of stress and anxiety likely have a role in the management of these patients.. Psychological and relaxation interventions studied in children with FGIDs include cognitive behavioral therapy, gut-directed hypnotherapy[200,201], yoga[202], and biofeedback-assisted relaxation therapy (BART)[203]. Children receiving a standardized course of targeted medication plus BART demonstrated better outcomes including decrease in pain intensity, decrease in pain episode duration, and global pain improvement as compared to children receiving only the medication component.

This gives rise to the hope that treatments addressing multiple, complementary targets within the biopsychosocial model can improve outcomes for children with FD, although further research needs to be done with multiple-component treatments to determine optimal combinations for individual children.

CONCLUSION

FGIDs, including functional dyspepsia, are incompletely understood despite high prevalence and significant impact on patient quality of life and healthcare costs. FGIDs are best approached utilizing a biopsychosocial model in which all relevant factors (biologic, psychologic and social) are identified and targeted in treatment. As mechanisms of disease are further investigated, both in laboratory and clinical models, opportunities arise to target therapies. In addition to inflammation (addressed elsewhere), visceral hypersensitivity and gastrointestinal dysmotility are pathophysiolgic alterations that may respond to directed treatment. Despite limited evidence in children, the role of pharmacologic agents within a broader biopsychosocial treatment context remains promising.

There remains a need for placebo-controlled trials of therapy targeting visceral hypersensitivity and electromechanical dysfunction in children with FD. Likewise, there is a need to better understand the diagnostic and prognostic utility of various tests of upper intestinal sensory and mechanical function including visceral sensitivity, accommodation, and gastric emptying. Application of knowledge from placebo-controlled trials and specific tests of function may improve directed medical therapy for children with FD.

REFERENCES

1 **Hyams JS**, Burke G, Davis PM, Rzepski B, Andrulonis PA. Abdominal pain and irritable bowel syndrome in adolescents: a community-based study. *J Pediatr* 1996; **129**: 220-226 [PMID: 8765619]

2 **Saps M**, Adams P, Bonilla S, Chogle A, Nichols-Vinueza

D. Parental report of abdominal pain and abdominal pain-related functional gastrointestinal disorders from a community survey. *J Pediatr Gastroenterol Nutr* 2012; **55**: 707-710 [PMID: 22744191 DOI: 10.1097/MPG.0b013e3182662401]
3 **Vila M**, Kramer T, Obiols JE, Garralda ME. Abdominal pain in British young people: associations, impairment and health care use. *J Psychosom Res* 2012; **73**: 437-442 [PMID: 23148811 DOI: 10.1016/j.jpsychores.2012.09.009]
4 **Spee LA**, Lisman-Van Leeuwen Y, Benninga MA, Bierma-Zeinstra SM, Berger MY. Prevalence, characteristics, and management of childhood functional abdominal pain in general practice. *Scand J Prim Health Care* 2013; **31**: 197-202 [PMID: 24106821 DOI: 10.3109/02813432.2013.844405]
5 **Dong L**, Dingguo L, Xiaoxing X, Hanming L. An epidemiologic study of irritable bowel syndrome in adolescents and children in China: a school-based study. *Pediatrics* 2005; **116**: e393-e396 [PMID: 16140684 DOI: 10.1542/peds.2004-2764]
6 **Rajindrajith S**, Devanarayana NM. Subtypes and Symptomatology of Irritable Bowel Syndrome in Children and Adolescents: A School-based Survey Using Rome III Criteria. *J Neurogastroenterol Motil* 2012; **18**: 298-304 [PMID: 22837878 DOI: 10.5056/jnm.2012.18.3.298]
7 **Saps M**, Nichols-Vinueza DX, Rosen JM, Velasco-Benítez CA. Prevalence of functional gastrointestinal disorders in Colombian school children. *J Pediatr* 2014; **164**: 542-545.e1 [PMID: 24332822 DOI: 10.1016/j.jpeds.2013.10.088]
8 **Saps M**, Seshadri R, Sztainberg M, Schaffer G, Marshall BM, Di Lorenzo C. A prospective school-based study of abdominal pain and other common somatic complaints in children. *J Pediatr* 2009; **154**: 322-326 [PMID: 19038403 DOI: 10.1016/j.jpeds.2008.09.047]
9 **Dengler-Crish CM**, Horst SN, Walker LS. Somatic complaints in childhood functional abdominal pain are associated with functional gastrointestinal disorders in adolescence and adulthood. *J Pediatr Gastroenterol Nutr* 2011; **52**: 162-165 [PMID: 21150653 DOI: 10.1097/MPG.0b013e3181ec1d2e]
10 **Lu PL**, Teich S, Di Lorenzo C, Skaggs B, Alhajj M, Mousa HM. Improvement of quality of life and symptoms after gastric electrical stimulation in children with functional dyspepsia. *Neurogastroenterol Motil* 2013; **25**: 567-e456 [PMID: 23433238 DOI: 10.1111/nmo.12104]
11 **Van Oudenhove L**, Vandenberghe J, Vos R, Holvoet L, Demyttenaere K, Tack J. Risk factors for impaired health-related quality of life in functional dyspepsia. *Aliment Pharmacol Ther* 2011; **33**: 261-274 [PMID: 21083672 DOI: 10.1111/j.1365-2036.2010.04510.x]
12 **Walker LS**, Sherman AL, Bruehl S, Garber J, Smith CA. Functional abdominal pain patient subtypes in childhood predict functional gastrointestinal disorders with chronic pain and psychiatric comorbidities in adolescence and adulthood. *Pain* 2012; **153**: 1798-1806 [PMID: 22721910 DOI: 10.1016/j.pain.2012.03.026]
13 **Talley NJ**. Functional gastrointestinal disorders as a public health problem. *Neurogastroenterol Motil* 2008; **20** Suppl 1: 121-129 [PMID: 18402649 DOI: 10.1111/j.1365-2982.2008.01097.x]
14 **Dhroove G**, Chogle A, Saps M. A million-dollar work-up for abdominal pain: is it worth it? *J Pediatr Gastroenterol Nutr* 2010; **51**: 579-583 [PMID: 20706149 DOI: 10.1097/MPG.0b013e3181de0639]
15 **Inadomi JM**, Fennerty MB, Bjorkman D. Systematic review: the economic impact of irritable bowel syndrome. *Aliment Pharmacol Ther* 2003; **18**: 671-682 [PMID: 14510740]
16 **APLEY J**, NAISH N. Recurrent abdominal pains: a field survey of 1,000 school children. *Arch Dis Child* 1958; **33**: 165-170 [PMID: 13534750]
17 **Walker LS C-DA,** Rasquin-Weber, A. Questionnaire on Pediatric Gastrointestinal Symptoms, Rome III Version (QPGS-RIII). In: Drossman DA CE, Delvaux M, Spiller RC, Talley NJ, Thompson WG, Whitehead WE, editor. Rome III: The Functional Gastrointestinal Disorders. 3rd ed. McLean, Virginia: Degnon Associates, Inc., 2006: 963-990
18 **Rasquin A**, Di Lorenzo C, Forbes D, Guiraldes E, Hyams JS, Staiano A, Walker LS. Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology* 2006; **130**: 1527-1537 [PMID: 16678566 DOI: 10.1053/j.gastro.2005.08.063]
19 **Tack J**, Talley NJ, Camilleri M, Holtmann G, Hu P, Malagelada JR, Stanghellini V. Functional gastroduodenal disorders. *Gastroenterology* 2006; **130**: 1466-1479 [PMID: 16678560 DOI: 10.1053/j.gastro.2005.11.059]
20 **Schurman JV**, Friesen CA, Danda CE, Andre L, Welchert E, Lavenbarg T, Cocjin JT, Hyman PE. Diagnosing functional abdominal pain with the Rome II criteria: parent, child, and clinician agreement. *J Pediatr Gastroenterol Nutr* 2005; **41**: 291-295 [PMID: 16131983]
21 **Hyams JS**, Davis P, Sylvester FA, Zeiter DK, Justinich CJ, Lerer T. Dyspepsia in children and adolescents: a prospective study. *J Pediatr Gastroenterol Nutr* 2000; **30**: 413-418 [PMID: 10776953]
22 **Corsetti M**, Caenepeel P, Fischler B, Janssens J, Tack J. Impact of coexisting irritable bowel syndrome on symptoms and pathophysiological mechanisms in functional dyspepsia. *Am J Gastroenterol* 2004; **99**: 1152-1159 [PMID: 15180740 DOI: 10.1111/j.1572-0241.2004.30040.x]
23 **Schurman JV**, Singh M, Singh V, Neilan N, Friesen CA. Symptoms and subtypes in pediatric functional dyspepsia: relation to mucosal inflammation and psychological functioning. *J Pediatr Gastroenterol Nutr* 2010; **51**: 298-303 [PMID: 20479684 DOI: 10.1097/MPG.0b013e3181d1363c]
24 **Rippel SW**, Acra S, Correa H, Vaezi M, Di Lorenzo C, Walker LS. Pediatric patients with dyspepsia have chronic symptoms, anxiety, and lower quality of life as adolescents and adults. *Gastroenterology* 2012; **142**: 754-761 [PMID: 22226783 DOI: 10.1053/j.gastro.2011.12.043]
25 **Aro P**, Talley NJ, Agréus L, Johansson SE, Bolling-Sternevald E, Storskrubb T, Ronkainen J. Functional dyspepsia impairs quality of life in the adult population. *Aliment Pharmacol Ther* 2011; **33**: 1215-1224 [PMID: 21443537 DOI: 10.1111/j.1365-2036.2011.04640.x]
26 **Ford AC**, Thabane M, Collins SM, Moayyedi P, Garg AX, Clark WF, Marshall JK. Prevalence of uninvestigated dyspepsia 8 years after a large waterborne outbreak of bacterial dysentery: a cohort study. *Gastroenterology* 2010; **138**: 1727-1736; quiz e12 [PMID: 20117111 DOI: 10.1053/j.gastro.2010.01.043]
27 **Rosen JM**, Adams PN, Saps M. Umbilical hernia repair increases the rate of functional gastrointestinal disorders in children. *J Pediatr* 2013; **163**: 1065-1068 [PMID: 23759426 DOI: 10.1016/j.jpeds.2013.04.042]
28 **Saps M**, Bonilla S. Early life events: infants with pyloric stenosis have a higher risk of developing chronic abdominal pain in childhood. *J Pediatr* 2011; **159**: 551-554.e1 [PMID: 21513946 DOI: 10.1016/j.jpeds.2011.03.018]
29 **Geeraerts B**, Van Oudenhove L, Fischler B, Vandenberghe J, Caenepeel P, Janssens J, Tack J. Influence of abuse history on gastric sensorimotor function in functional dyspepsia. *Neurogastroenterol Motil* 2009; **21**: 33-41 [PMID: 18694440 DOI: 10.1111/j.1365-2982.2008.01178.x]
30 **Klooker TK**, Braak B, Painter RC, de Rooij SR, van Elburg RM, van den Wijngaard RM, Roseboom TJ, Boeckxstaens GE. Exposure to severe wartime conditions in early life is associated with an increased risk of irritable bowel syndrome: a population-based cohort study. *Am J Gastroenterol* 2009; **104**: 2250-2256 [PMID: 19513027 DOI: 10.1038/ajg.2009.282]
31 **Friesen CA**, Schurman JV, Colombo JM, Abdel-Rahman SM. Eosinophils and mast cells as therapeutic targets in pediatric functional dyspepsia. *World J Gastrointest Pharmacol Ther* 2013; **4**: 86-96 [PMID: 24199024 DOI: 10.4292/wjgpt.v4.i4.86]
32 **Feng B**, La JH, Schwartz ES, Gebhart GF. Irritable bowel syndrome: methods, mechanisms, and pathophysiology. Neural and neuro-immune mechanisms of visceral hypersensitivity in irritable bowel syndrome. *Am J Physiol Gastrointest Liver Physiol* 2012; **302**: G1085-G1098 [PMID: 22403791

DOI: 10.1152/ajpgi.00542.2011]
33 **Bouin M**, Lupien F, Riberdy M, Boivin M, Plourde V, Poitras P. Intolerance to visceral distension in functional dyspepsia or irritable bowel syndrome: an organ specific defect or a pan intestinal dysregulation? *Neurogastroenterol Motil* 2004; **16**: 311-314 [PMID: 15198653 DOI: 10.1111/j.1365-2982.2004.00511.x]
34 **Moriarty KJ**, Dawson AM. Functional abdominal pain: further evidence that whole gut is affected. *Br Med J* (Clin Res Ed) 1982; **284**: 1670-1672 [PMID: 6805649]
35 **Trimble KC**, Farouk R, Pryde A, Douglas S, Heading RC. Heightened visceral sensation in functional gastrointestinal disease is not site-specific. Evidence for a generalized disorder of gut sensitivity. *Dig Dis Sci* 1995; **40**: 1607-1613 [PMID: 7648957]
36 **Schurman JV**, Friesen CA, Andre L, Welchert E, Lavenbarg T, Danda CE, Cocjin JT, Hyman PE. Diagnostic utility of the water load test in children with chronic abdominal pain. *J Pediatr Gastroenterol Nutr* 2007; **44**: 51-57 [PMID: 17204953 DOI: 10.1097/01.mpg.0000233189.10695.74]
37 **Hoffman I**, Tack J. Assessment of gastric motor function in childhood functional dyspepsia and obesity. *Neurogastroenterol Motil* 2012; **24**: 108-112, e81 [PMID: 22103293 DOI: 10.1111/j.1365-2982.2011.01813.x]
38 **Chitkara DK**, Camilleri M, Zinsmeister AR, Burton D, El-Youssef M, Freese D, Walker L, Stephens D. Gastric sensory and motor dysfunction in adolescents with functional dyspepsia. *J Pediatr* 2005; **146**: 500-505 [PMID: 15812453 DOI: 10.1016/j.jpeds.2004.11.031]
39 **Anderson JL**, Acra S, Bruehl S, Walker LS. Relation between clinical symptoms and experimental visceral hypersensitivity in pediatric patients with functional abdominal pain. *J Pediatr Gastroenterol Nutr* 2008; **47**: 309-315 [PMID: 18728527 DOI: 10.1097/MPG.0b013e3181653a6f]
40 **Boeckxstaens GE**, Hirsch DP, van den Elzen BD, Heisterkamp SH, Tytgat GN. Impaired drinking capacity in patients with functional dyspepsia: relationship with proximal stomach function. *Gastroenterology* 2001; **121**: 1054-1063 [PMID: 11677196]
41 **Jones MP**, Hoffman S, Shah D, Patel K, Ebert CC. The water load test: observations from healthy controls and patients with functional dyspepsia. *Am J Physiol Gastrointest Liver Physiol* 2003; **284**: G896-G904 [PMID: 12529263 DOI: 10.1152/ajpgi.00361.2002]
42 **Koch KL**, Hong SP, Xu L. Reproducibility of gastric myoelectrical activity and the water load test in patients with dysmotility-like dyspepsia symptoms and in control subjects. *J Clin Gastroenterol* 2000; **31**: 125-129 [PMID: 10993427]
43 **Strid H**, Norström M, Sjöberg J, Simrén M, Svedlund J, Abrahamsson H, Björnsson ES. Impact of sex and psychological factors on the water loading test in functional dyspepsia. *Scand J Gastroenterol* 2001; **36**: 725-730 [PMID: 11444471]
44 **Jones MP**, Roth LM, Crowell MD. Symptom reporting by functional dyspeptics during the water load test. *Am J Gastroenterol* 2005; **100**: 1334-1339 [PMID: 15929766 DOI: 10.1111/j.1572-0241.2005.40802.x]
45 **Chen CL**, Hu CT, Lin HH, Yi CH. Clinical utility of electrogastrography and the water load test in patients with upper gastrointestinal symptoms. *J Smooth Muscle Res* 2006; **42**: 149-157 [PMID: 17159331]
46 **Lee KJ**, Kim JH, Cho SW. Dietary influence on electrogastrography and association of alterations in gastric myoelectrical activity with symptoms in patients with functional dyspepsia. *J Gastroenterol Hepatol* 2006; **21**: 59-64 [PMID: 16706813 DOI: 10.1111/j.1440-1746.2005.04088.x]
47 **Hoffman I**, Vos R, Tack J. Assessment of gastric sensorimotor function in paediatric patients with unexplained dyspeptic symptoms and poor weight gain. *Neurogastroenterol Motil* 2007; **19**: 173-179 [PMID: 17300286 DOI: 10.1111/j.1365-2982.2006.00850.x]
48 **Di Lorenzo C**, Youssef NN, Sigurdsson L, Scharff L, Griffiths J, Wald A. Visceral hyperalgesia in children with functional abdominal pain. *J Pediatr* 2001; **139**: 838-843 [PMID: 11743510 DOI: 10.1067/mpd.2001.118883]
49 **Holtmann G**, Gschossmann J, Neufang-Hüber J, Gerken G, Talley NJ. Differences in gastric mechanosensory function after repeated ramp distensions in non-consulters with dyspepsia and healthy controls. *Gut* 2000; **47**: 332-336 [PMID: 10940267]
50 **Tack J**, Caenepeel P, Fischler B, Piessevaux H, Janssens J. Symptoms associated with hypersensitivity to gastric distention in functional dyspepsia. *Gastroenterology* 2001; **121**: 526-535 [PMID: 11522735]
51 **Farré R**, Vanheel H, Vanuytsel T, Masaoka T, Törnblom H, Simrén M, Van Oudenhove L, Tack JF. In functional dyspepsia, hypersensitivity to postprandial distention correlates with meal-related symptom severity. *Gastroenterology* 2013; **145**: 566-573 [PMID: 23702005 DOI: 10.1053/j.gastro.2013.05.018]
52 **Samsom M**, Verhagen MA, vanBerge Henegouwen GP, Smout AJ. Abnormal clearance of exogenous acid and increased acid sensitivity of the proximal duodenum in dyspeptic patients. *Gastroenterology* 1999; **116**: 515-520 [PMID: 10029608]
53 **Miwa H**, Nakajima K, Yamaguchi K, Fujimoto K, Veldhuyzen VAN Zanten SJ, Kinoshita Y, Adachi K, Kusunoki H, Haruma K. Generation of dyspeptic symptoms by direct acid infusion into the stomach of healthy Japanese subjects. *Aliment Pharmacol Ther* 2007; **26**: 257-264 [PMID: 17593071 DOI: 10.1111/j.1365-2036.2007.03367.x]
54 **Schwartz MP**, Samsom M, Smout AJ. Human duodenal motor activity in response to acid and different nutrients. *Dig Dis Sci* 2001; **46**: 1472-1481 [PMID: 11478499]
55 **Ishii M**, Manabe N, Kusunoki H, Kamada T, Sato M, Imamura H, Shiotani A, Hata J, Haruma K. Real-time evaluation of dyspeptic symptoms and gastric motility induced by duodenal acidification using noninvasive transnasal endoscopy. *J Gastroenterol* 2008; **43**: 935-941 [PMID: 19107337 DOI: 10.1007/s00535-008-2303-5]
56 **di Stefano M**, Vos R, Vanuytsel T, Janssens J, Tack J. Prolonged duodenal acid perfusion and dyspeptic symptom occurrence in healthy volunteers. *Neurogastroenterol Motil* 2009; **21**: 712-e40 [PMID: 19236580 DOI: 10.1111/j.1365-2982.2009.01274.x]
57 **Feinle C**, Meier O, Otto B, D'Amato M, Fried M. Role of duodenal lipid and cholecystokinin A receptors in the pathophysiology of functional dyspepsia. *Gut* 2001; **48**: 347-355 [PMID: 11171824]
58 **Fried M**, Feinle C. The role of fat and cholecystokinin in functional dyspepsia. *Gut* 2002; **51** Suppl 1: i54-i57 [PMID: 12077066]
59 **Christianson JA**, Gebhart GF. Assessment of colon sensitivity by luminal distension in mice. *Nat Protoc* 2007; **2**: 2624-2631 [PMID: 17948005 DOI: 10.1038/nprot.2007.392]
60 **Miranda A**, Mickle A, Medda B, Zhang Z, Phillips RJ, Tipnis N, Powley TL, Shaker R, Sengupta JN. Altered mechanosensitive properties of vagal afferent fibers innervating the stomach following gastric surgery in rats. *Neuroscience* 2009; **162**: 1299-1306 [PMID: 19477237 DOI: 10.1016/j.neuroscience.2009.05.042]
61 **Zeng F**, Qin W, Liang F, Liu J, Tang Y, Liu X, Yuan K, Yu S, Song W, Liu M, Lan L, Gao X, Liu Y, Tian J. Abnormal resting brain activity in patients with functional dyspepsia is related to symptom severity. *Gastroenterology* 2011; **141**: 499-506 [PMID: 21684280 DOI: 10.1053/j.gastro.2011.05.003]
62 **Van Oudenhove L**, Vandenberghe J, Dupont P, Geeraerts B, Vos R, Dirix S, Bormans G, Vanderghinste D, Van Laere K, Demyttenaere K, Fischler B, Tack J. Abnormal regional brain activity during rest and (anticipated) gastric distension in

functional dyspepsia and the role of anxiety: a H(2)(15)O-PET study. *Am J Gastroenterol* 2010; **105**: 913-924 [PMID: 20160711 DOI: 10.1038/ajg.2010.39]
63 **Vandenberghe J**, Vos R, Persoons P, Demyttenaere K, Janssens J, Tack J. Dyspeptic patients with visceral hypersensitivity: sensitisation of pain specific or multimodal pathways? *Gut* 2005; **54**: 914-919 [PMID: 15951533 DOI: 10.1136/gut.2004.052605]
64 **Cheung CK**, Lee YY, Chan Y, Cheong PK, Law WT, Lee SF, Sung JJ, Chan FK, Wu JC. Decreased Basal and postprandial plasma serotonin levels in patients with functional dyspepsia. *Clin Gastroenterol Hepatol* 2013; **11**: 1125-1129 [PMID: 23591288 DOI: 10.1016/j.cgh.2013.03.026]
65 **Faure C**, Patey N, Gauthier C, Brooks EM, Mawe GM. Serotonin signaling is altered in irritable bowel syndrome with diarrhea but not in functional dyspepsia in pediatric age patients. *Gastroenterology* 2010; **139**: 249-258 [PMID: 20303355 DOI: 10.1053/j.gastro.2010.03.032]
66 **Holzer P**. Transient receptor potential (TRP) channels as drug targets for diseases of the digestive system. *Pharmacol Ther* 2011; **131**: 142-170 [PMID: 21420431 DOI: 10.1016/j.pharmthera.2011.03.006]
67 **Li X**, Cao Y, Wong RK, Ho KY, Wilder-Smith CH. Visceral and somatic sensory function in functional dyspepsia. *Neurogastroenterol Motil* 2013; **25**: 246-253, e165 [PMID: 23171089 DOI: 10.1111/nmo.12044]
68 **Führer M**, Vogelsang H, Hammer J. A placebo-controlled trial of an oral capsaicin load in patients with functional dyspepsia. *Neurogastroenterol Motil* 2011; **23**: 918-e397 [PMID: 21883698 DOI: 10.1111/j.1365-2982.2011.01766.x]
69 **Hammer J**, Führer M, Pipal L, Matiasek J. Hypersensitivity for capsaicin in patients with functional dyspepsia. *Neurogastroenterol Motil* 2008; **20**: 125-133 [PMID: 17931342 DOI: 10.1111/j.1365-2982.2007.00997.x]
70 **Führer M**, Hammer J. Effect of repeated, long term capsaicin ingestion on intestinal chemo- and mechanosensation in healthy volunteers. *Neurogastroenterol Motil* 2009; **21**: 521-527, e7 [PMID: 19126186 DOI: 10.1111/j.1365-2982.2008.01227.x]
71 **Hammer J**. Effect of repeated capsaicin ingestion on intestinal chemosensation and mechanosensation. *Aliment Pharmacol Ther* 2006; **24**: 679-686 [PMID: 16907900 DOI: 10.1111/j.1365-2036.2006.03022.x]
72 **Schurman JV**, Danda CE, Friesen CA, Hyman PE, Simon SD, Cocjin JT. Variations in psychological profile among children with recurrent abdominal pain. *J Clin Psychol Med Settings* 2008; **15**: 241-251 [PMID: 19104969 DOI: 10.1007/s10880-008-9120-0]
73 **Hou XH**, Zhu LR, Li QX, Chen JDZ. Alterations in mast cells and 5-HT positive cells in gastric mucosa in functional dyspepsia patients with hypersensitivity. *Neurogastroenterol Motil* 2001; **13**: 398-399
74 **Azpiroz F**, Feinle-Bisset C, Grundy D, Tack J. Gastric sensitivity and reflexes: basic mechanisms underlying clinical problems. *J Gastroenterol* 2014; **49**: 206-218 [PMID: 24306100 DOI: 10.1007/s00535-013-0917-8]
75 **Kusano M**, Zai H, Shimoyama Y, Hosaka H, Kuribayashi S, Kawamura O, Mori M. Rapid gastric emptying, rather than delayed gastric emptying, might provoke functional dyspepsia. *J Gastroenterol Hepatol* 2011; **26** Suppl 3: 75-78 [PMID: 21443715 DOI: 10.1111/j.1440-1746.2011.06627.x]
76 **Chitkara DK**, Delgado-Aros S, Bredenoord AJ, Cremonini F, El-Youssef M, Freese D, Camilleri M. Functional dyspepsia, upper gastrointestinal symptoms, and transit in children. *J Pediatr* 2003; **143**: 609-613 [PMID: 14615731 DOI: 10.1067/S0022-3476(03)00504-3]
77 **Friesen CA**, Lin Z, Hyman PE, Andre L, Welchert E, Schurman JV, Cocjin JT, Burchell N, Pulliam S, Moore A, Lavenbarg T, McCallum RW. Electrogastrography in pediatric functional dyspepsia: relationship to gastric emptying and symptom severity. *J Pediatr Gastroenterol Nutr* 2006; **42**: 265-269 [PMID: 16540794 DOI: 10.1097/01.mpg.0000189367.99416.5e]
78 **Devanarayana NM**, Rajindrajith S, Perera MS, Nishanthanie SW, Benninga MA. Gastric emptying and antral motility parameters in children with functional dyspepsia: association with symptom severity. *J Gastroenterol Hepatol* 2013; **28**: 1161-1166 [PMID: 23517336 DOI: 10.1111/jgh.12205]
79 **Boccia G**, Buonavolontà R, Coccorullo P, Manguso F, Fuiano L, Staiano A. Dyspeptic symptoms in children: the result of a constipation-induced cologastric brake? *Clin Gastroenterol Hepatol* 2008; **6**: 556-560 [PMID: 18378497 DOI: 10.1016/j.cgh.2008.01.001]
80 **Delgado-Aros S**, Camilleri M, Cremonini F, Ferber I, Stephens D, Burton DD. Contributions of gastric volumes and gastric emptying to meal size and postmeal symptoms in functional dyspepsia. *Gastroenterology* 2004; **127**: 1685-1694 [PMID: 15578506]
81 **Troncon LE**, Herculano JR, Savoldelli RD, Moraes ER, Secaf M, Oliveira RB. Relationships between intragastric food maldistribution, disturbances of antral contractility, and symptoms in functional dyspepsia. *Dig Dis Sci* 2006; **51**: 517-526 [PMID: 16614961 DOI: 10.1007/s10620-006-3164-5]
82 **Waldron B**, Cullen PT, Kumar R, Smith D, Jankowski J, Hopwood D, Sutton D, Kennedy N, Campbell FC. Evidence for hypomotility in non-ulcer dyspepsia: a prospective multifactorial study. *Gut* 1991; **32**: 246-251 [PMID: 2013418]
83 **Fruehauf H**, Steingoetter A, Fox MR, Kwiatek MA, Boesiger P, Schwizer W, Fried M, Thumshirn M, Goetze O. Characterization of gastric volume responses and liquid emptying in functional dyspepsia and health by MRI or barostat and simultaneous C-acetate breath test. *Neurogastroenterol Motil* 2009; **21**: 697-e37 [PMID: 19368659 DOI: 10.1111/j.1365-2982.2009.01267.x]
84 **van Lelyveld N**, Schipper M, Samsom M. Lack of relationship between chronic upper abdominal symptoms and gastric function in functional dyspepsia. *Dig Dis Sci* 2008; **53**: 1223-1230 [PMID: 17932769 DOI: 10.1007/s10620-007-0012-1]
85 **Talley NJ**, Locke GR, Lahr BD, Zinsmeister AR, Tougas G, Ligozio G, Rojavin MA, Tack J. Functional dyspepsia, delayed gastric emptying, and impaired quality of life. *Gut* 2006; **55**: 933-939 [PMID: 16322108 DOI: 10.1136/gut.2005.078634]
86 **Talley NJ**, Verlinden M, Jones M. Can symptoms discriminate among those with delayed or normal gastric emptying in dysmotility-like dyspepsia? *Am J Gastroenterol* 2001; **96**: 1422-1428 [PMID: 11374677 DOI: 10.1111/j.1572-0241.2001.03683.x]
87 **Pallotta N**, Pezzotti P, Calabrese E, Baccini F, Corazziari E. Relationship between gastrointestinal and extra-gastrointestinal symptoms and delayed gastric emptying in functional dyspeptic patients. *World J Gastroenterol* 2005; **11**: 4375-4381 [PMID: 16038037]
88 **Sarnelli G**, Caenepeel P, Geypens B, Janssens J, Tack J. Symptoms associated with impaired gastric emptying of solids and liquids in functional dyspepsia. *Am J Gastroenterol* 2003; **98**: 783-788 [PMID: 12738456 DOI: 10.1111/j.1572-0241.2003.07389.x]
89 **Stanghellini V**, Tosetti C, Paternico A, Barbara G, Morselli-Labate AM, Monetti N, Marengo M, Corinaldesi R. Risk indicators of delayed gastric emptying of solids in patients with functional dyspepsia. *Gastroenterology* 1996; **110**: 1036-1042 [PMID: 8612991]
90 **Bisschops R**, Karamanolis G, Arts J, Caenepeel P, Verbeke K, Janssens J, Tack J. Relationship between symptoms and ingestion of a meal in functional dyspepsia. *Gut* 2008; **57**: 1495-1503 [PMID: 18519430 DOI: 10.1136/gut.2007.137125]
91 **Kindt S**, Dubois D, Van Oudenhove L, Caenepeel P, Arts J, Bisschops R, Tack J. Relationship between symptom pattern, assessed by the PAGI-SYM questionnaire, and gastric sensorimotor dysfunction in functional dyspepsia. *Neurogastroenterol Motil* 2009; **21**: 1183-e105 [PMID: 19663903 DOI:

10.1111/j.1365-2982.2009.01374.x]
92 **Bisschops R**, Tack J. Dysaccommodation of the stomach: therapeutic nirvana? *Neurogastroenterol Motil* 2007; **19**: 85-93 [PMID: 17244162 DOI: 10.1111/j.1365-2982.2006.00863.x]
93 **Tack J**, Piessevaux H, Coulie B, Caenepeel P, Janssens J. Role of impaired gastric accommodation to a meal in functional dyspepsia. *Gastroenterology* 1998; **115**: 1346-1352 [PMID: 9834261]
94 **Olafsdottir E**, Gilja OH, Aslaksen A, Berstad A, Fluge G. Impaired accommodation of the proximal stomach in children with recurrent abdominal pain. *J Pediatr Gastroenterol Nutr* 2000; **30**: 157-163 [PMID: 10697134]
95 **Olafsdottir E**, Gilja OH, Tefera S, Fluge G, Berstad A. Intragastric maldistribution of a liquid meal in children with recurrent abdominal pain assessed by three-dimensional ultrasonography. *Scand J Gastroenterol* 2003; **38**: 819-825 [PMID: 12940433]
96 **Cucchiara S**, Minella R, Iorio R, Emiliano M, Az-Zeqeh N, Vallone G, Bali MA, Alfieri E, Scoppa A. Real-time ultrasound reveals gastric motor abnormalities in children investigated for dyspeptic symptoms. *J Pediatr Gastroenterol Nutr* 1995; **21**: 446-453 [PMID: 8583298]
97 **Karamanolis G**, Caenepeel P, Arts J, Tack J. Association of the predominant symptom with clinical characteristics and pathophysiological mechanisms in functional dyspepsia. *Gastroenterology* 2006; **130**: 296-303 [PMID: 16472585 DOI: 10.1053/j.gastro.2005.10.019]
98 **Lunding JA**, Tefera S, Bayati A, Gilja OH, Mattsson H, Hausken T, Berstad A. Pressure-induced gastric accommodation studied with a new distension paradigm. Abnormally low accommodation rate in patients with functional dyspepsia. *Scand J Gastroenterol* 2006; **41**: 544-552 [PMID: 16638696 DOI: 10.1080/00365520500353723]
99 **Gilja OH**, Hausken T, Wilhelmsen I, Berstad A. Impaired accommodation of proximal stomach to a meal in functional dyspepsia. *Dig Dis Sci* 1996; **41**: 689-696 [PMID: 8674389]
100 **Hata T**, Kato M, Kudo T, Nishida M, Nishida U, Imai A, Yoshida T, Hirota J, Kamada G, Ono S, Nakagawa M, Nakagawa S, Shimizu Y, Takeda H, Asaka M. Comparison of gastric relaxation and sensory functions between functional dyspepsia and healthy subjects using novel drinking-ultrasonography test. *Digestion* 2013; **87**: 34-39 [PMID: 23343967 DOI: 10.1159/000343935]
101 **Bredenoord AJ**, Chial HJ, Camilleri M, Mullan BP, Murray JA. Gastric accommodation and emptying in evaluation of patients with upper gastrointestinal symptoms. *Clin Gastroenterol Hepatol* 2003; **1**: 264-272 [PMID: 15017667]
102 **van den Elzen BD**, Bennink RJ, Holman R, Tytgat GN, Boeckxstaens GE. Impaired drinking capacity in patients with functional dyspepsia: intragastric distribution and distal stomach volume. *Neurogastroenterol Motil* 2007; **19**: 968-976 [PMID: 17973641 DOI: 10.1111/j.1365-2982.2007.00971.x]
103 **Bharucha AE**, Manduca A, Lake DS, Fidler J, Edwards P, Grimm RC, Zinsmeister AR, Riederer SJ. Gastric motor disturbances in patients with idiopathic rapid gastric emptying. *Neurogastroenterol Motil* 2011; **23**: 617-e252 [PMID: 21470342 DOI: 10.1111/j.1365-2982.2011.01710.x]
104 **Friesen CA**, Lin Z, Schurman JV, Andre L, McCallum RW. An evaluation of adult electrogastrography criteria in healthy children. *Dig Dis Sci* 2006; **51**: 1824-1828 [PMID: 16957992 DOI: 10.1007/s10620-006-9323-x]
105 **Chen JD**, Co E, Liang J, Pan J, Sutphen J, Torres-Pinedo RB, Orr WC. Patterns of gastric myoelectrical activity in human subjects of different ages. *Am J Physiol* 1997; **272**: G1022-G1027 [PMID: 9176209]
106 **Chen JD**, Lin X, Zhang M, Torres-Pinedo RB, Orr WC. Gastric myoelectrical activity in healthy children and children with functional dyspepsia. *Dig Dis Sci* 1998; **43**: 2384-2391 [PMID: 9824123]
107 **Sha W**, Pasricha PJ, Chen JD. Rhythmic and spatial abnormalities of gastric slow waves in patients with functional dyspepsia. *J Clin Gastroenterol* 2009; **43**: 123-129 [PMID: 18719512 DOI: 10.1097/MCG.0b013e318157187a]
108 **Riezzo G**, Chiloiro M, Guerra V, Borrelli O, Salvia G, Cucchiara S. Comparison of gastric electrical activity and gastric emptying in healthy and dyspeptic children. *Dig Dis Sci* 2000; **45**: 517-524 [PMID: 10749327]
109 **Cucchiara S**, Bortolotti M, Colombo C, Boccieri A, De Stefano M, Vitiello G, Pagano A, Ronchi A, Auricchio S. Abnormalities of gastrointestinal motility in children with nonulcer dyspepsia and in children with gastroesophageal reflux disease. *Dig Dis Sci* 1991; **36**: 1066-1073 [PMID: 1864198]
110 **Di Lorenzo C**, Hyman PE, Flores AF, Kashyap P, Tomomasa T, Lo S, Snape WJ. Antroduodenal manometry in children and adults with severe non-ulcer dyspepsia. *Scand J Gastroenterol* 1994; **29**: 799-806 [PMID: 7824859]
111 **Jebbink HJ**, vanBerge-Henegouwen GP, Akkermans LM, Smout AJ. Small intestinal motor abnormalities in patients with functional dyspepsia demonstrated by ambulatory manometry. *Gut* 1996; **38**: 694-700 [PMID: 8707114]
112 **Wilmer A**, Van Cutsem E, Andrioli A, Tack J, Coremans G, Janssens J. Ambulatory gastrojejunal manometry in severe motility-like dyspepsia: lack of correlation between dysmotility, symptoms, and gastric emptying. *Gut* 1998; **42**: 235-242 [PMID: 9536949]
113 **Sha W**, Pasricha PJ, Chen JD. Correlations among electrogastrogram, gastric dysmotility, and duodenal dysmotility in patients with functional dyspepsia. *J Clin Gastroenterol* 2009; **43**: 716-722 [PMID: 19247205 DOI: 10.1097/MCG.0b013e31818b8ed9]
114 **Di Lorenzo C**, Reddy SN, Flores AF, Hyman PE. Is electrogastrography a substitute for manometric studies in children with functional gastrointestinal disorders? *Dig Dis Sci* 1997; **42**: 2310-2316 [PMID: 9398811]
115 **Rao SS**, Mysore K, Attaluri A, Valestin J. Diagnostic utility of wireless motility capsule in gastrointestinal dysmotility. *J Clin Gastroenterol* 2011; **45**: 684-690 [PMID: 21135705 DOI: 10.1097/MCG.0b013e3181ff0122]
116 **Rozov-Ung I**, Mreyoud A, Moore J, Wilding GE, Khawam E, Lackner JM, Semler JR, Sitrin MD. Detection of drug effects on gastric emptying and contractility using a wireless motility capsule. *BMC Gastroenterol* 2014; **14**: 2 [PMID: 24383478 DOI: 10.1186/1471-230X-14-2]
117 **DuPont AW**, Jiang ZD, Harold SA, Snyder N, Galler GW, Garcia-Torres F, DuPont HL. Motility abnormalities in irritable bowel syndrome. *Digestion* 2014; **89**: 119-123 [PMID: 24503633 DOI: 10.1159/000356314]
118 **Green AD**, Belkind-Gerson J, Surjanhata BC, Mousa H, Kuo B, Di Lorenzo C. Wireless motility capsule test in children with upper gastrointestinal symptoms. *J Pediatr* 2013; **162**: 1181-1187 [PMID: 23290514 DOI: 10.1016/j.jpeds.2012.11.040]
119 **Liebregts T**, Adam B, Bredack C, Gururatsakul M, Pilkington KR, Brierley SM, Blackshaw LA, Gerken G, Talley NJ, Holtmann G. Small bowel homing T cells are associated with symptoms and delayed gastric emptying in functional dyspepsia. *Am J Gastroenterol* 2011; **106**: 1089-1098 [PMID: 21245834 DOI: 10.1038/ajg.2010.512]
120 **Schäppi MG**, Borrelli O, Knafelz D, Williams S, Smith VV, Milla PJ, Lindley KJ. Mast cell-nerve interactions in children with functional dyspepsia. *J Pediatr Gastroenterol Nutr* 2008; **47**: 472-480 [PMID: 18852640 DOI: 10.1097/MPG.0b013e318186008e]
121 **Friesen CA**, Lin Z, Singh M, Singh V, Schurman JV, Burchell N, Cocjin JT, McCallum RW. Antral inflammatory cells, gastric emptying, and electrogastrography in pediatric functional dyspepsia. *Dig Dis Sci* 2008; **53**: 2634-2640 [PMID: 18320315 DOI: 10.1007/s10620-008-0207-0]
122 **Friesen CA**, Lin Z, Garola R, Andre L, Burchell N, Moore A,

Roberts CC, McCallum RW. Chronic gastritis is not associated with gastric dysrhythmia or delayed solid emptying in children with dyspepsia. *Dig Dis Sci* 2005; **50**: 1012-1018 [PMID: 15986846]

123 **Yin J**, Levanon D, Chen JD. Inhibitory effects of stress on postprandial gastric myoelectrical activity and vagal tone in healthy subjects. *Neurogastroenterol Motil* 2004; **16**: 737-744 [PMID: 15601423 DOI: 10.1111/j.1365-2982.2004.00544.x]

124 **De Giorgi F**, Sarnelli G, Cirillo C, Savino IG, Turco F, Nardone G, Rocco A, Cuomo R. Increased severity of dyspeptic symptoms related to mental stress is associated with sympathetic hyperactivity and enhanced endocrine response in patients with postprandial distress syndrome. *Neurogastroenterol Motil* 2013; **25**: 31-8.e2-31-8.e3 [PMID: 22908903 DOI: 10.1111/nmo.12004]

125 **van den Elzen BD**, Boeckxstaens GE. Review article: a critical view on impaired accommodation as therapeutic target for functional dyspepsia. *Aliment Pharmacol Ther* 2006; **23**: 1499-1510 [PMID: 16696798 DOI: 10.1111/j.1365-2036.2006.02930.x]

126 **Lee HS**, An YS, Kang J, Yoo JH, Lee KJ. Effect of acute auditory stress on gastric motor responses to a meal in healthy volunteers. *J Gastroenterol Hepatol* 2013; **28**: 1699-1704 [PMID: 23800263 DOI: 10.1111/jgh.12309]

127 **Benninga MA**, Mayer EA. The power of placebo in pediatric functional gastrointestinal disease. *Gastroenterology* 2009; **137**: 1207-1210 [PMID: 19717127 DOI: 10.1053/j.gastro.2009.08.023]

128 **Grover M**, Camilleri M. Effects on gastrointestinal functions and symptoms of serotonergic psychoactive agents used in functional gastrointestinal diseases. *J Gastroenterol* 2013; **48**: 177-181 [PMID: 23254779 DOI: 10.1007/s00535-012-0726-5]

129 **Bouras EP**, Talley NJ, Camilleri M, Burton DD, Heckman MG, Crook JE, Richelson E. Effects of amitriptyline on gastric sensorimotor function and postprandial symptoms in healthy individuals: a randomized, double-blind, placebo-controlled trial. *Am J Gastroenterol* 2008; **103**: 2043-2050 [PMID: 18803000]

130 **Gorard DA**, Libby GW, Farthing MJ. Effect of a tricyclic antidepressant on small intestinal motility in health and diarrhea-predominant irritable bowel syndrome. *Dig Dis Sci* 1995; **40**: 86-95 [PMID: 7821126]

131 **Gorard DA**, Libby GW, Farthing MJ. 5-Hydroxytryptamine and human small intestinal motility: effect of inhibiting 5-hydroxytryptamine reuptake. *Gut* 1994; **35**: 496-500 [PMID: 8174987]

132 **Ladabaum U**, Glidden D. Effect of the selective serotonin reuptake inhibitor sertraline on gastric sensitivity and compliance in healthy humans. *Neurogastroenterol Motil* 2002; **14**: 395-402 [PMID: 12213107]

133 **Talley NJ**, Camilleri M, Chitkara DK, Bouras E, Locke GR, Burton D, Rucker MJ, Thapa P, Zinsmeister AR. Effects of desipramine and escitalopram on postprandial symptoms induced by the nutrient drink test in healthy volunteers: a randomized, double-blind, placebo-controlled study. *Digestion* 2005; **72**: 97-103 [PMID: 16172545 DOI: 10.1159/000088363]

134 **Wu CY**, Chou LT, Chen HP, Chang CS, Wong PG, Chen GH. Effect of fluoxetine on symptoms and gastric dysrhythmia in patients with functional dyspepsia. *Hepatogastroenterology* 2003; **50**: 278-283 [PMID: 12630041]

135 **Tan VP**, Cheung TK, Wong WM, Pang R, Wong BC. Treatment of functional dyspepsia with sertraline: a double-blind randomized placebo-controlled pilot study. *World J Gastroenterol* 2012; **18**: 6127-6133 [PMID: 23155342 DOI: 10.3748/wjg.v18.i42.6127]

136 **van Kerkhoven LA**, Laheij RJ, Aparicio N, De Boer WA, Van den Hazel S, Tan AC, Witteman BJ, Jansen JB. Effect of the antidepressant venlafaxine in functional dyspepsia: a randomized, double-blind, placebo-controlled trial. *Clin Gastroenterol Hepatol* 2008; **6**: 746-752; quiz 718 [PMID: 18424191 DOI: 10.1016/j.cgh.2008.02.051]

137 **Bahar RJ**, Collins BS, Steinmetz B, Ament ME. Double-blind placebo-controlled trial of amitriptyline for the treatment of irritable bowel syndrome in adolescents. *J Pediatr* 2008; **152**: 685-689 [PMID: 18410774 DOI: 10.1016/j.jpeds.2007.10.012]

138 **Saps M**, Youssef N, Miranda A, Nurko S, Hyman P, Cocjin J, Di Lorenzo C. Multicenter, randomized, placebo-controlled trial of amitriptyline in children with functional gastrointestinal disorders. *Gastroenterology* 2009; **137**: 1261-1269 [PMID: 19596010 DOI: 10.1053/j.gastro.2009.06.060]

139 **Teitelbaum JE**, Arora R. Long-term efficacy of low-dose tricyclic antidepressants for children with functional gastrointestinal disorders. *J Pediatr Gastroenterol Nutr* 2011; **53**: 260-264 [PMID: 21865971 DOI: 10.1097/MPG.0b013e318217df7c]

140 **Campo JV**, Perel J, Lucas A, Bridge J, Ehmann M, Kalas C, Monk K, Axelson D, Birmaher B, Ryan N, Di Lorenzo C, Brent DA. Citalopram treatment of pediatric recurrent abdominal pain and comorbid internalizing disorders: an exploratory study. *J Am Acad Child Adolesc Psychiatry* 2004; **43**: 1234-1242 [PMID: 15381890 DOI: 10.1097/01.chi.0000136563.31709.b0]

141 **Redstone HA**, Barrowman N, Veldhuyzen Van Zanten SJ. H2-receptor antagonists in the treatment of functional (nonulcer) dyspepsia: a meta-analysis of randomized controlled clinical trials. *Aliment Pharmacol Ther* 2001; **15**: 1291-1299 [PMID: 11552898]

142 **Moayyedi P**, Delaney BC, Vakil N, Forman D, Talley NJ. The efficacy of proton pump inhibitors in nonulcer dyspepsia: a systematic review and economic analysis. *Gastroenterology* 2004; **127**: 1329-1337 [PMID: 15521002]

143 **Meineche-Schmidt V**, Christensen E, Bytzer P. Randomised clinical trial: identification of responders to short-term treatment with esomeprazole for dyspepsia in primary care - a randomised, placebo-controlled study. *Aliment Pharmacol Ther* 2011; **33**: 41-49 [PMID: 21083590 DOI: 10.1111/j.1365-2036.2010.04501.x]

144 **Jones RH**, Baxter G. Lansoprazole 30 mg daily versus ranitidine 150 mg b.d. in the treatment of acid-related dyspepsia in general practice. *Aliment Pharmacol Ther* 1997; **11**: 541-546 [PMID: 9218080]

145 **Peura DA**, Kovacs TO, Metz DC, Siepman N, Pilmer BL, Talley NJ. Lansoprazole in the treatment of functional dyspepsia: two double-blind, randomized, placebo-controlled trials. *Am J Med* 2004; **116**: 740-748 [PMID: 15144910 DOI: 10.1016/j.amjmed.2004.01.008]

146 **Futagami S**, Shimpuku M, Song JM, Kodaka Y, Yamawaki H, Nagoya H, Shindo T, Kawagoe T, Horie A, Gudis K, Iwakiri K, Sakamoto C. Nizatidine improves clinical symptoms and gastric emptying in patients with functional dyspepsia accompanied by impaired gastric emptying. *Digestion* 2012; **86**: 114-121 [PMID: 22846371 DOI: 10.1159/000339111]

147 **Schurman JV**, Hunter HL, Friesen CA. Conceptualization and treatment of chronic abdominal pain in pediatric gastroenterology practice. *J Pediatr Gastroenterol Nutr* 2010; **50**: 32-37 [PMID: 19915496 DOI: 10.1097/MPG.0b013e3181ae3610]

148 **See MC**, Birnbaum AH, Schechter CB, Goldenberg MM, Benkov KJ. Double-blind, placebo-controlled trial of famotidine in children with abdominal pain and dyspepsia: global and quantitative assessment. *Dig Dis Sci* 2001; **46**: 985-992 [PMID: 11341669]

149 **Dehghani SM**, Imanieh MH, Oboodi R, Haghighat M. The comparative study of the effectiveness of cimetidine, ranitidine, famotidine, and omeprazole in treatment of children with dyspepsia. *ISRN Pediatr* 2011; **2011**: 219287 [PMID: 22389770 DOI: 10.5402/2011/219287]

150 **Bortolotti M**, Coccia G, Grossi G, Miglioli M. The treatment of functional dyspepsia with red pepper. *Aliment Pharmacol Ther* 2002; **16**: 1075-1082 [PMID: 12030948]

151 **Hiyama T**, Yoshihara M, Matsuo K, Kusunoki H, Kamada T, Ito M, Tanaka S, Nishi N, Chayama K, Haruma K. Meta-

analysis of the effects of prokinetic agents in patients with functional dyspepsia. *J Gastroenterol Hepatol* 2007; **22**: 304-310 [PMID: 17295758 DOI: 10.1111/j.1440-1746.2006.04493.x]

152 **Janssen P**, Harris MS, Jones M, Masaoka T, Farré R, Törnblom H, Van Oudenhove L, Simrén M, Tack J. The relation between symptom improvement and gastric emptying in the treatment of diabetic and idiopathic gastroparesis. *Am J Gastroenterol* 2013; **108**: 1382-1391 [PMID: 24005344 DOI: 10.1038/ajg.2013.118]

153 **Moayyedi P**, Soo S, Deeks J, Delaney B, Innes M, Forman D. Pharmacological interventions for non-ulcer dyspepsia. *Cochrane Database Syst Rev* 2006; **(4)**: CD001960 [PMID: 17054151 DOI: 10.1002/14651858.CD001960.pub3]

154 **Riezzo G**, Cucchiara S, Chiloiro M, Minella R, Guerra V, Giorgio I. Gastric emptying and myoelectrical activity in children with nonulcer dyspepsia. Effect of cisapride. *Dig Dis Sci* 1995; **40**: 1428-1434 [PMID: 7628264]

155 **Bharucha AE**, Camilleri M, Haydock S, Ferber I, Burton D, Cooper S, Tompson D, Fitzpatrick K, Higgins R, Zinsmeister AR. Effects of a serotonin 5-HT(4) receptor antagonist SB-207266 on gastrointestinal motor and sensory function in humans. *Gut* 2000; **47**: 667-674 [PMID: 11034583]

156 **Bouras EP**, Camilleri M, Burton DD, Thomforde G, McKinzie S, Zinsmeister AR. Prucalopride accelerates gastrointestinal and colonic transit in patients with constipation without a rectal evacuation disorder. *Gastroenterology* 2001; **120**: 354-360 [PMID: 11159875]

157 **Levy J**, Hayes C, Kern J, Harris J, Flores A, Hyams J, Murray R, Tolia V. Does cisapride influence cardiac rhythm? Results of a United States multicenter, double-blind, placebo-controlled pediatric study. *J Pediatr Gastroenterol Nutr* 2001; **32**: 458-463 [PMID: 11396814]

158 **Mearin F**, Rodrigo L, Pérez-Mota A, Balboa A, Jiménez I, Sebastián JJ, Patón C. Levosulpiride and cisapride in the treatment of dysmotility-like functional dyspepsia: a randomized, double-masked trial. *Clin Gastroenterol Hepatol* 2004; **2**: 301-308 [PMID: 15067624]

159 **Lozano R**, Concha MP, Montealegre A, de Leon L, Villalba JO, Esteban HL, Cromeyer M, García JR, Brossa A, Lluberes G, Sandí EI, Quirós HB. Effectiveness and safety of levosulpiride in the treatment of dysmotility-like functional dyspepsia. *Ther Clin Risk Manag* 2007; **3**: 149-155 [PMID: 18360622]

160 **Hallerbäck BI**, Bommelaer G, Bredberg E, Campbell M, Hellblom M, Lauritsen K, Wienbeck M, Holmgren LL. Dose finding study of mosapride in functional dyspepsia: a placebo-controlled, randomized study. *Aliment Pharmacol Ther* 2002; **16**: 959-967 [PMID: 11966505]

161 **Kinoshita Y**, Hashimoto T, Kawamura A, Yuki M, Amano K, Sato H, Adachi K, Sato S, Oshima N, Takashima T, Kitajima N, Abe K, Suetsugu H. Effects of famotidine, mosapride and tandospirone for treatment of functional dyspepsia. *Aliment Pharmacol Ther* 2005; **21** Suppl 2: 37-41 [PMID: 15943845 DOI: 10.1111/j.1365-2036.2005.02472.x]

162 **Otaka M**, Jin M, Odashima M, Matsuhashi T, Wada I, Horikawa Y, Komatsu K, Ohba R, Oyake J, Hatakeyama N, Watanabe S. New strategy of therapy for functional dyspepsia using famotidine, mosapride and amitriptyline. *Aliment Pharmacol Ther* 2005; **21** Suppl 2: 42-46 [PMID: 15943846 DOI: 10.1111/j.1365-2036.2005.02473.x]

163 **Du Y**, Su T, Song X, Gao J, Zou D, Zuo C, Xie W, Wang B, Zhang Z, Xu J, Tian D, Luo H, Zhang Z, Wang S, Chen J, Guo J, Gong L, Ding Y, Li Z. Efficacy and safety of cinitapride in the treatment of mild to moderate postprandial distress syndrome-predominant functional dyspepsia. *J Clin Gastroenterol* 2014; **48**: 328-335 [PMID: 24440931 DOI: 10.1097/MCG.0000000000000033]

164 **Albibi R**, McCallum RW. Metoclopramide: pharmacology and clinical application. *Ann Intern Med* 1983; **98**: 86-95 [PMID: 6336644]

165 **Fumagalli I**, Hammer B. Cisapride versus metoclopramide in the treatment of functional dyspepsia. A double-blind comparative trial. *Scand J Gastroenterol* 1994; **29**: 33-37 [PMID: 8128175]

166 **Banani SJ**, Lankarani KB, Taghavi A, Bagheri MH, Sefidbakht S, Geramizadeh B. Comparison of metoclopramide oral tablets and solution in treatment of dysmotility-like dyspepsia. *Am J Health Syst Pharm* 2008; **65**: 1057-1061 [PMID: 18499880 DOI: 10.2146/ajhp070381]

167 **Veldhuyzen van Zanten SJ**, Jones MJ, Verlinden M, Talley NJ. Efficacy of cisapride and domperidone in functional (nonulcer) dyspepsia: a meta-analysis. *Am J Gastroenterol* 2001; **96**: 689-696 [PMID: 11280535 DOI: 10.1111/j.1572-0241.2001.03521.x]

168 **Halter F**, Staub P, Hammer B, Guyot J, Miazza BM. Study with two prokinetics in functional dyspepsia and GORD: domperidone vs. cisapride. *J Physiol Pharmacol* 1997; **48**: 185-192 [PMID: 9223023]

169 **Van Outryve M**, De Nutte N, Van Eeghem P, Gooris JP. Efficacy of cisapride in functional dyspepsia resistant to domperidone or metoclopramide: a double-blind, placebo-controlled study. *Scand J Gastroenterol Suppl* 1993; **195**: 47-52; discussion 52-53 [PMID: 8516658]

170 **Talley NJ**, Tack J, Ptak T, Gupta R, Giguère M. Itopride in functional dyspepsia: results of two phase III multicentre, randomised, double-blind, placebo-controlled trials. *Gut* 2008; **57**: 740-746 [PMID: 17965059 DOI: 10.1136/gut.2007.132449]

171 **Huang X**, Lv B, Zhang S, Fan YH, Meng LN. Itopride therapy for functional dyspepsia: a meta-analysis. *World J Gastroenterol* 2012; **18**: 7371-7377 [PMID: 23326147 DOI: 10.3748/wjg.v18.i48.7371]

172 **Cucchiara S**, Minella R, Scoppa A, Emiliano M, Calabrese F, Az-Zeqeh N, Rea B, Salvia G. Antroduodenal motor effects of intravenous erythromycin in children with abnormalities of gastrointestinal motility. *J Pediatr Gastroenterol Nutr* 1997; **24**: 411-418 [PMID: 9144124]

173 **Arts J**, Caenepeel P, Verbeke K, Tack J. Influence of erythromycin on gastric emptying and meal related symptoms in functional dyspepsia with delayed gastric emptying. *Gut* 2005; **54**: 455-460 [PMID: 15753526 DOI: 10.1136/gut.2003.035279]

174 **Talley NJ**, Verlinden M, Snape W, Beker JA, Ducrotte P, Dettmer A, Brinkhoff H, Eaker E, Ohning G, Miner PB, Mathias JR, Fumagalli I, Staessen D, Mack RJ. Failure of a motilin receptor agonist (ABT-229) to relieve the symptoms of functional dyspepsia in patients with and without delayed gastric emptying: a randomized double-blind placebo-controlled trial. *Aliment Pharmacol Ther* 2000; **14**: 1653-1661 [PMID: 11121915]

175 **McCallum RW**, Cynshi O. Efficacy of mitemcinal, a motilin agonist, on gastrointestinal symptoms in patients with symptoms suggesting diabetic gastropathy: a randomized, multicenter, placebo-controlled trial. *Aliment Pharmacol Ther* 2007; **26**: 107-116 [PMID: 17555427 DOI: 10.1111/j.1365-2036.2007.03346.x]

176 **Takanashi H**, Cynshi O. Motilides: a long and winding road: lessons from mitemcinal (GM-611) on diabetic gastroparesis. *Regul Pept* 2009; **155**: 18-23 [PMID: 19345243 DOI: 10.1016/j.regpep.2009.03.011]

177 **Kamerling IM**, Van Haarst AD, Burggraaf J, Schoemaker RC, Biemond I, Heinzerling H, Jones R, Cohen AF, Masclee AA. Motilin effects on the proximal stomach in patients with functional dyspepsia and healthy volunteers. *Am J Physiol Gastrointest Liver Physiol* 2003; **284**: G776-G781 [PMID: 12519743 DOI: 10.1152/ajpgi.00456.2002]

178 **Cuomo R**, Vandaele P, Coulie B, Peeters T, Depoortere I, Janssens J, Tack J. Influence of motilin on gastric fundus tone and on meal-induced satiety in man: role of cholinergic pathways. *Am J Gastroenterol* 2006; **101**: 804-811 [PMID: 16635226 DOI: 10.1111/j.1572-0241.2005.00339.x]

179 **Kusunoki H**, Haruma K, Manabe N, Imamura H, Kamada T, Shiotani A, Hata J, Sugioka H, Saito Y, Kato H, Tack J. Therapeutic efficacy of acotiamide in patients with functional dyspepsia based on enhanced postprandial gastric accommodation and emptying: randomized controlled study evaluation by real-time ultrasonography. *Neurogastroenterol Motil* 2012; **24**: 540-545, 540-545 [PMID: 22385472 DOI: 10.1111/j.1365-2982.2012.01897.x]

180 **Matsueda K**, Hongo M, Tack J, Saito Y, Kato H. A placebo-controlled trial of acotiamide for meal-related symptoms of functional dyspepsia. *Gut* 2012; **61**: 821-828 [PMID: 22157329 DOI: 10.1136/gutjnl-2011-301454]

181 **Tack J**, Janssen P, Masaoka T, Farré R, Van Oudenhove L. Efficacy of buspirone, a fundus-relaxing drug, in patients with functional dyspepsia. *Clin Gastroenterol Hepatol* 2012; **10**: 1239-1245 [PMID: 22813445 DOI: 10.1016/j.cgh.2012.06.036]

182 **Miwa H**, Nagahara A, Tominaga K, Yokoyama T, Sawada Y, Inoue K, Ashida K, Fukuchi T, Hojo M, Yamashita H, Tomita T, Hori K, Oshima T. Efficacy of the 5-HT1A agonist tandospirone citrate in improving symptoms of patients with functional dyspepsia: a randomized controlled trial. *Am J Gastroenterol* 2009; **104**: 2779-2787 [PMID: 19638966 DOI: 10.1038/ajg.2009.427]

183 **Malatesta MG**, Fascetti E, Ciccaglione AF, Cappello G, Grossi L, Ferri A, Marzio L. 5-HT1-receptor agonist sumatriptan modifies gastric size after 500 ml of water in dyspeptic patients and normal subjects. *Dig Dis Sci* 2002; **47**: 2591-2595 [PMID: 12452400]

184 **Marzio L**, Cappello G, Grossi L, Manzoli L. Effect of the 5-HT3 receptor antagonist, ondansetron, on gastric size in dyspeptic patients with impaired gastric accommodation. *Dig Liver Dis* 2008; **40**: 188-193 [PMID: 18242155 DOI: 10.1016/j.dld.2007.11.013]

185 **Vakil N**, Laine L, Talley NJ, Zakko SF, Tack J, Chey WD, Kralstein J, Earnest DL, Ligozio G, Cohard-Radice M. Tegaserod treatment for dysmotility-like functional dyspepsia: results of two randomized, controlled trials. *Am J Gastroenterol* 2008; **103**: 1906-1919 [PMID: 18616658 DOI: 10.1111/j.1572-0241.2008.01953.x]

186 **Tack J**, Broekaert D, Coulie B, Fischler B, Janssens J. Influence of the selective serotonin re-uptake inhibitor, paroxetine, on gastric sensorimotor function in humans. *Aliment Pharmacol Ther* 2003; **17**: 603-608 [PMID: 12622770]

187 **Rodriguez L**, Diaz J, Nurko S. Safety and efficacy of cyproheptadine for treating dyspeptic symptoms in children. *J Pediatr* 2013; **163**: 261-267 [PMID: 23419589 DOI: 10.1016/j.jpeds.2012.12.096]

188 **Sadeghian M**, Farahmand F, Fallahi GH, Abbasi A. Cyproheptadine for the treatment of functional abdominal pain in childhood: a double-blinded randomized placebo-controlled trial. *Minerva Pediatr* 2008; **60**: 1367-1374 [PMID: 18971897]

189 **Ghayur MN**, Gilani AH. Pharmacological basis for the medicinal use of ginger in gastrointestinal disorders. *Dig Dis Sci* 2005; **50**: 1889-1897 [PMID: 16187193 DOI: 10.1007/s10620-005-2957-2]

190 **Palatty PL**, Haniadka R, Valder B, Arora R, Baliga MS. Ginger in the prevention of nausea and vomiting: a review. *Crit Rev Food Sci Nutr* 2013; **53**: 659-669 [PMID: 23638927 DOI: 10.1080/10408398.2011.553751]

191 **Kline RM**, Kline JJ, Di Palma J GJ. Enteric-coated, pH-dependent peppermint oil capsules for the treatment of irritable bowel syndrome in children. *J Pediatr* 2001; **138**: 125-128 [PMID: 11148527]

192 **Braden B**, Caspary W, Börner N, Vinson B, Schneider AR. Clinical effects of STW 5 (Iberogast) are not based on acceleration of gastric emptying in patients with functional dyspepsia and gastroparesis. *Neurogastroenterol Motil* 2009; **21**: 632-638, e25 [PMID: 19220753 DOI: 10.1111/j.1365-2982.2008.01249.x]

193 **Wu KL**, Rayner CK, Chuah SK, Changchien CS, Lu SN, Chiu YC, Chiu KW, Lee CM. Effects of ginger on gastric emptying and motility in healthy humans. *Eur J Gastroenterol Hepatol* 2008; **20**: 436-440 [PMID: 18403946 DOI: 10.1097/MEG.0b013e3282f4b224]

194 **Hu ML**, Rayner CK, Wu KL, Chuah SK, Tai WC, Chou YP, Chiu YC, Chiu KW, Hu TH. Effect of ginger on gastric motility and symptoms of functional dyspepsia. *World J Gastroenterol* 2011; **17**: 105-110 [PMID: 21218090 DOI: 10.3748/wjg.v17.i1.105]

195 **Inamori M**, Akiyama T, Akimoto K, Fujita K, Takahashi H, Yoneda M, Abe Y, Kubota K, Saito S, Ueno N, Nakajima A. Early effects of peppermint oil on gastric emptying: a crossover study using a continuous real-time 13C breath test (BreathID system). *J Gastroenterol* 2007; **42**: 539-542 [PMID: 17653649 DOI: 10.1007/s00535-007-2067-3]

196 **Papathanasopoulos A**, Rotondo A, Janssen P, Boesmans W, Farré R, Vanden Berghe P, Tack J. Effect of acute peppermint oil administration on gastric sensorimotor function and nutrient tolerance in health. *Neurogastroenterol Motil* 2013; **25**: e263-e271 [PMID: 23489975 DOI: 10.1111/nmo.12102]

197 **von Arnim U**, Peitz U, Vinson B, Gundermann KJ, Malfertheiner P. STW 5, a phytopharmacon for patients with functional dyspepsia: results of a multicenter, placebo-controlled double-blind study. *Am J Gastroenterol* 2007; **102**: 1268-1275 [PMID: 17531013 DOI: 10.1111/j.1572-0241.2006.01183.x]

198 **O'Grady G**, Egbuji JU, Du P, Cheng LK, Pullan AJ, Windsor JA. High-frequency gastric electrical stimulation for the treatment of gastroparesis: a meta-analysis. *World J Surg* 2009; **33**: 1693-1701 [PMID: 19506941 DOI: 10.1007/s00268-009-0096-1]

199 **Teich S**, Mousa HM, Punati J, Di Lorenzo C. Efficacy of permanent gastric electrical stimulation for the treatment of gastroparesis and functional dyspepsia in children and adolescents. *J Pediatr Surg* 2013; **48**: 178-183 [PMID: 23331812 DOI: 10.1016/j.jpedsurg.2012.10.038]

200 **Vlieger AM**, Rutten JM, Govers AM, Frankenhuis C, Benninga MA. Long-term follow-up of gut-directed hypnotherapy vs. standard care in children with functional abdominal pain or irritable bowel syndrome. *Am J Gastroenterol* 2012; **107**: 627-631 [PMID: 22310221 DOI: 10.1038/ajg.2011.487]

201 **van Tilburg MA**, Chitkara DK, Palsson OS, Turner M, Blois-Martin N, Ulshen M, Whitehead WE. Audio-recorded guided imagery treatment reduces functional abdominal pain in children: a pilot study. *Pediatrics* 2009; **124**: e890-e897 [PMID: 19822590 DOI: 10.1542/peds.2009-0028]

202 **Kuttner L**, Chambers CT, Hardial J, Israel DM, Jacobson K, Evans K. A randomized trial of yoga for adolescents with irritable bowel syndrome. *Pain Res Manag* 2006; **11**: 217-223 [PMID: 17149454]

203 **Schurman JV**, Wu YP, Grayson P, Friesen CA. A pilot study to assess the efficacy of biofeedback-assisted relaxation training as an adjunct treatment for pediatric functional dyspepsia associated with duodenal eosinophilia. *J Pediatr Psychol* 2010; **35**: 837-847 [PMID: 20185416 DOI: 10.1093/jpepsy/jsq010]

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REVIEW

Approach to *Helicobacter pylori* infection in geriatric population

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Abstract

The prevalence of *Helicobacter pylori* (*H. pylori*) infection and its complications increase with age. The majority of infected individuals remain asymptomatic throughout the life but 10%-20% develops peptic ulcer disease and 1% gastric malignancies. The incidence of ulcers and their complications are more common in the older population resulting in higher hospitalization and mortality rates. The increased use of medications causing gastric mucosal damage and the decreased secretion of protective prostaglandins in elderly are major factors increasing gastric mucosal sensitivity to the destructive effects of *H. pylori*. Due to higher prevalence of gastrointestinal (GI) malignancies, upper GI endoscopy is mostly preferred in elderly for the diagnosis of infection. Therefore, "endoscopy and treat" strategy may be more appropriate instead of "test and treat" strategy for dyspeptic patients in older age. Urea breath test and stool antigen test can be used for control of eradication, except for special cases requiring follow-up with endoscopy. The indications for treatment and suggested eradication regimens are similar with other age groups; however, the eradication failure may be a more significant problem due to high antibiotic resistance and low compliance rate in elderly. Multidrug usage and drug interactions should always be considered before starting the treatment. This paper reviews briefly the epidemiology, diagnosis, disease manifestations, and treatment options of *H. pylori* in the geriatric population.

Key words: *Helicobacter pylori*; Epidemiology; Diagnosis; Treatment; Eradication; Elderly; Geriatrics; Geriatric population

Core tip: *Helicobacter pylori* (*H. pylori*) infection is more common in the older population and may cause significant complications with severe morbidity and mortality. There are similarities but also differences in the diagnosis and treatment of infection in elderly population than non-elderly. Health care providers to the geriatric population should take into consideration these nuances in the management of *H. pylori* infection in the older patients.

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INTRODUCTION

The discovery of *Helicobacter pylori (H. pylori)* by Marshall and Warren in 1983 resulted in a breakthrough in the understanding and management of gastric diseases. Currently, it is well known that *H. pylori* infection causes chronic gastritis that may progress into peptic ulcer

disease (PUD), gastric adenocarcinoma, and mucosa-associated lymphoid tissue lymphoma (MALToma)[1-3]. The ability of this bacterium to persist and establish a low-grade inflammatory state might induce an immunologic response that may influence the occurrence and progression of local and systemic diseases[4]. Indeed, *H. pylori,* now one of the best models for the investigation of infectious diseases, have been widely studied to the extent of finding its associations with extragastric disorders[5,6]. Despite the extensive knowledge on the virulence factors and immune manipulation mechanisms of *H. pylori*, there has been little success developing a vaccination for this organism[7]. Instead, eradication therapy is used for prevention and treatment. Recently, the eradication rates through the standard proton pump inhibitor (PPI)-based triple therapy has declined to unsatisfactory levels of 80% or less, possibly due to antibiotic resistance, poor compliance, and rapid metabolisms of PPI[8-10]. Therefore, several novel treatment regimens are emerging[11]. The frequency of *H. pylori* infection, its manifestations, and eradication options are variable and depend on many factors including age. In this review, we discuss the different aspects of *H. pylori* infection and its eradication in elderly.

H. PYLORI INFECTION IN GERIATRICS

Epidemiology

H. pylori infection becomes rarer in recent years especially in young and middle-aged populations due to improvements in the quality of healthcare and effective treatment options[12]. However, the rate of *H. pylori* infection and its complications are still increasing with age worldwide. Epidemiologic studies report higher prevalence of *H. pylori* infection in elderly with a ratio of over 70% in patients with gastrointestinal diseases and approximately 60% in asymptomatic patients[13,14]. Although the majority of the infected patients remain asymptomatic throughout the life, about 10%-20% of the patients will develop PUD, and 1% will develop gastric cancer and MALToma in addition to the possible extragastric complications[15,16]. Particularly elderly patients suffer from more serious complications resulting in higher hospitalization and mortality rates[17,18]. This difference in the geriatric population can be illustrated by several factors. Firstly, in an older patient, the presentation of *H. pylori* infection may be subtle or atypical, which may delay the diagnosis. With advanced age, the increased presence of concomitant diseases and multidrug therapy, especially medications causing gastric mucosal damage and bleeding (*e.g.,* nonsteroidal anti-inflammatory drugs (NSAID), bisphosphonates, antiplatelet drugs, warfarin), can lead to increased and severe complications of *H. pylori* infection[19]. In particular, NSAID and *H. pylori* are independently the two most important causes of peptic ulcer in adult population[20]. A meta-analysis showed that the peptic ulcer risk in *H. pylori* infected NSAID takers was 61 times more compared to *H. pylori* negative individuals not taking NSAID[21]. In parallel to this study, *H. pylori* infection in elderly NSAID users is also associated with a significantly increased ulcer risk, which should be a concern considering the common use of NSAID in elderly population[20]. Despite the unclear and rather complex synergy between *H. pylori* infection and NSAID, it is well known that both deteriorate mucosal defense mechanisms considerably. Besides, the decreased secretion of protective prostaglandins, as well as gastric acid (possibly due to fundal atrophic gastritis) with increased age can destruct the mucosal barrier[22,23]. Clinical studies performed in the United States have shown that the percentage of *H. pylori* screening in hospitalized elderly patients having PUD is only 40%-56%, with a 50%-73% treatment rate after a positive test result[24]. These results indicate that even if the clinical characteristics and epidemiologic distribution of *H. pylori* infection in the elderly have been extensively reported, the medical attention for the *H. pylori* infection in this population remains low.

Diagnosis

H. pylori infection can be diagnosed by noninvasive or invasive methods. The selection of the appropriate test may vary with the clinical setting[2,25,26]. Noninvasive tests include ^{13}C-urea breath test (UBT), stool antigen test (SAT), and serology. The UBT is a readily available test with an accuracy rate of > 97.9% in elderly patients regardless of the cognitive function, comorbidity, and co-treatment status[27-29]. The SAT is reported to have a sensitivity of 76%-81% and specificity of 80%-93% in hospitalized elderly patients[30,31], although these numbers may have been presumably improved with the recent advances in the SAT method. Currently, the laboratory SAT format (ELISA) with monoclonal antibodies is recommended rather than the rapid in-office test due to the significant difference in the accuracy[26]. Both UBT and SAT can be used for infection follow-up after eradication therapy because of their ability to detect active infection[26]. The serology test is a widely used and inexpensive test, but its diagnostic accuracy is variable[32] and only validated IgG tests should be used[26]. Positive serology may indicate a past infection, and thus it cannot be used for infection follow-up after eradication[33,34]. In elderly patients with immunodeficiency or protein malnutrition, false negative serology results may occur due to lack of antibody response[29,35]. However, serology is helpful in patients with low bacterial load (*e.g.*, use of antimicrobial and antisecretorial agents, bleeding, presence of malignant lesions, *etc.*) and therefore remains the only test that is not affected by local changes in the stomach. Also, for all invasive and noninvasive tests except for serology, discontinuation of PPI use for two weeks prior to testing is necessary[26].

Invasive techniques requiring an endoscopy are usually preferred in elderly patients due to the higher prevalence of gastrointestinal malignancies, as well as for their superiority in analyzing the severity of gastritis and detecting premalignant lesions[36,37]. *H. pylori* can be detected through histological examination or by indirect assess-

ment of the biopsy specimen with urease test, culture, or polymerase chain reaction (PCR) analysis[38,39]. The urease test provides inexpensive and rapid detection, however it has lower sensitivity in patients aged 60 years and older[38]. Cultures can assess the susceptibility of the strain to antimicrobial agents, which is important for the management of the infection[40]. Nonetheless, false negative results might be obtained with cultures due to frequent antibiotic use in elderly. PCR detection of *H. pylori* infection offers sensitive and accurate results rapidly and it is increasingly becoming popular. PCR assays allow simultaneous detection, quantification, genotyping, and virulence factor identification, as well as determination of antibiotic resistant and cancer susceptible strains of *H. pylori*[39,41]. Despite the common statement of histopathology being the "gold standard" for diagnosis of *H. Pylori* infection, its accuracy depends on sampling locations and presence of atrophic gastritis[42]. In addition, the frequent antibiotic and PPI use, as well as active and recent bleeding may alter the sensitivity. Therefore, discontinuation of PPIs two weeks prior to endoscopy, and specimen collection from both the body and antrum are recommended[42]. In particular, it has been recently reported that in patients with extensive gastric atrophy, the corpus greater curvature is the optimum biopsy site for histopathologic evaluation[43].

Although current guidelines recommend a general "test and treat" strategy for the uninvestigated dyspepsia[26], in populations with higher gastric cancer risk like elderly patients, "endoscope and treat" strategy is preferred especially considering the lower acurracy of the noninvasive tests in the elderly[44,45]. In addition, *H. pylori* infection in elderly might be asymptomatic or present with other symptoms than dyspepsia. For example, the inflammation caused by chronic *H. pylori* infection may result in atrophic gastritis and subsequently vitamin B12 deficiency[46]. Therefore, a complete work-up for *H. pylori* is not only limited to diagnostic tests for detecting the infection, but also includes the complications and comorbidities of the disease.

EFFECTS OF ERADICATION THERAPY ON *H. PYLORI* ASSOCIATED DISEASE MANIFESTATIONS

Peptic ulcer disease and associated bleeding

H. pylori infection and NSAID/aspirin use have independent and additive effects on the higher prevalence of PUD and ulcer bleeding in the elderly[47,48]. *H. pylori* positive NSAID users have an almost two fold increased risk of peptic ulcer bleeding compared to NSAID users without *H. pylori*[49]. Taken together with the increased likelihood of bleeding associated with NSAID use in elderly (approximately 7 times more frequent than young adults)[20], the concomitant presence of NSAID use and *H. pylori* infection in elderly should raise a potential concern for PUD and associated bleeding.

The eradication of *H. pylori* in elderly patients with PUD heals ulcers in over 95% of patients[50], improves symptoms in over 85% of patients[51], and dramatically lowers the recurrence rate from 41.6% to 2.2%[52]. For prevention of both duodenal ulcer recurrence (RR = 0.19) and gastric ulcer recurrence (RR = 0.31) *H. pylori* eradication is superior to no treatment[53].

It is well established that the eradication of *H. pylori* prior to use of NSAID/aspirin is beneficial in prevention of PUD and associated bleeding[54]. However, the influence of *H. pylori* eradication in NSAID/aspirin users is controversial. Based on multiple studies in this regard, the most recent Maastricht IV/ Florence Consensus Report[26] have slightly different recommendations for long term NSAID and low dose aspirin users. For NSAID users it is recommended to have continued PPI treatment in addition to *H. pylori* eradication. For low dose aspirin users, *H. pylori* test should be performed if there is a history of PUD. After eradication in these patients, the incidence of gastric bleeding remains low even without gastroprotective agents[26].

Functional dyspepsia and gastritis

Patients with dyspepsia and *H. pylori* infection are reported to have functional dyspepsia (FD) rather than PUD, although the eradication benefit is less evident in FD in comparison to PUD[26]. However, the long-term relief of dyspepsia has been shown in one of 12 patients with *H. pylori* and functional dyspepsia after *H. pylori* eradication, which is better than any other treatment[55].

Prolonged *H. pylori* infection is a well-recognized cause of different phenotypes of gastritis based on the topography of the colonization and inflammation in the stomach, including mild pangastritis, corpus, and antrum predominant gastritis, each with different clinical outcomes[2,26]. The antrum predominant gastritis, the most common form of *H. pylori* mediated gastritis, is usually associated with a normal to high secretion of gastric acid and an increased risk of duodenal ulcer disease[2,56]. On the other hand, the corpus predominant gastritis is usually associated with hypochlorhydria and results in an increased risk of developing gastric atrophy, intestinal metaplasia, and ultimately gastric carcinoma[2,48,57]. As the name implies, the patients with mild pangastritis do not have clinically significant disease. It needs to be noted that the different phenotypes are not completely separate entities, and antrum predominant gastritis may progress into the other types[2,56]. Regarding the effects of advancing age on gastritis, it has been shown that gastric acid secretion decreases with age only in *H. pylori* positive subjects[22]. This influence is probably due to the increasing prevalence of fundic atrophic gastritis in elderly[58]. Evidence suggests that eradication of *H. pylori* infection results in significant decrease in the activity of gastritis in elderly[59].

Gastric malignancies

H. pylori eradication may prevent gastric cancer[60]; however, its effects depend on the histological stage and gastric

localization. The progression of the premalignant lesions can be prevented with the eradication[61], whereas if intestinal metaplasia is established the eradication does not completely prevent the gastric cancer, although it might slow the progression[62,63]. A meta-analysis has shown that the eradication significantly improves corpus atrophy, but not antrum, and not intestinal metaplasia[64]. Therefore, the early diagnosis with endoscopy and treatment are important in elderly patients. For low grade MALTomas, *H. pylori* eradication is the first line treatment but the patients need to be followed up after the treatment in case the lymphoma fails to respond to the eradication[65].

Extragastric diseases

H. pylori has been associated not only with diseases of the gastrointestinal tract but also with extragastric diseases most of which are commonly seen in elderly population[6]. However, the causal or therapeutic links are stronger in some extragastric diseases than the others. The eradication is indicated in patients with unexplained iron deficiency anemia, idiopathic thrombocytopenic purpura, and vitamin B12 deficiency with significantly clear evidence[66-70].

Multiple studies reported higher prevalence of *H. pylori* infection in patients with type 2 diabetes mellitus (DM), with one study analyzing the individuals older than 60 year old[6,71]. Some groups even propose an association between *H. pylori* infection and the metabolic syndrome, supported by the synergistic effect of *H. pylori* infection and higher body mass index (BMI) in increasing the level of glycosylated hemoglobin[72], the significant association of *H. pylori* seropositivity with both DM and insulin use, as well as the independent association of *H. pylori* positivity with microalbuminuria[73]. On the other hand, there are some other groups contesting these associations with opposite findings[74,75]. Therefore, for obesity and DM the evidence is unclear and further studies are warranted.

Some epidemiologic studies suggest the association of *H. pylori* infection and neurologic diseases such as stroke, Parkinson's and Alzheimer's diseases[6,76-78], as well as ischemic heart disease[79]. Nonetheless, the evidence is equivocal for *H. pylori* eradication and improvement of these diseases[26]. Lastly, the bioavailability of thyroxine and Capitalize L-dopa improves with *H. pylori* eradication, although there is no verification of direct clinical benefit to the patients[80,81].

ERADICATION THERAPY

The triple therapy of PPI, clarithromycin, and amoxicillin (or metronidazole) has been the standard for *H. pylori* eradication since 1997 when the first Maastricht conference report was published[82]. However, multiple studies have reported suboptimal efficacy of this regimen with cure rates of less than the initial aim of 80%[8-10,83-87]. The decrease in efficacy might be associated with increased resistance to clarithromycin, high bacterial load, strain types, high gastric acidity, and low compliance[26,88]. Among these factors, the clarithromycin resistance has been identified as the major contributor to the eradication failure. To improve the efficacy, different combinations of currently available antibiotics have been assessed[26,89,90]. Triple therapy with PPI, amoxicillin, and metronidazole has been proposed as an alternative to the standard therapy with cure rates of 82%-94%[91-94]. Sequential therapy including a 5-d period with PPI-amoxicillin, followed by a 5-d period with PPI, clarithromycin, metronidazole (or tinidazole) is another regimen that has been studied in different countries. A recent systematic review of 22 trials revealed that the sequential therapy is more effective than standard triple therapies, confirming that the sequential administration of drugs is a successful therapeutic intervention for *H. pylori* eradication. Whether the use of the modified sequential therapy with longer duration of sequential regimens is actually more advantageous than that of 10-d sequential therapy requires further studies[95,96]. Non-bismuth quadruple therapy, also called "concomitant therapy", has been offered as a more convenient regimen for the patient, which involves all three antibiotics to be taken simultaneously together with a PPI for a period of 10-14 d. A recent meta-analysis from 19 studies (2070 patients) on concomitant therapy revealed a mean of 88% cure rate, superior to standard triple therapy, with a safe and well-tolerated profile[97].

The rate of the clarithromycin resistance is variable in different regions, with a threshold of 15%-20% prevalence to classify low or high clarithromycin resistance[26]. The clarithromycin resistance determines the approach to *H. pylori* eradication. In regions with low resistance, the standard triple therapy including clarithromycin is still recommended as first line regimen[26]. Different ways of improving the effectiveness of PPI-clarithromycin-containing regimens have been proposed including increasing the dosage and timing. Significant evidence from multiple studies suggests that high-dose PPIs increase in the cure rates up to 10% in comparison with standard doses[98]. Extension of PPI-clarithromycin-containing triple therapies from 7-d to 10-14 d has been shown to increase the eradication rate by about 5% without significant difference in the rate of side effects[99,100]. Bismuth-containing quadruple therapy may be either the first line regimen in a low clarithromycin resistance region or the second line therapy if PPI-clarithromycin containing triple therapy fails. An alternative second line treatment in this population is levofloxacin-containing triple therapy. After two treatment failures, third line treatment should be guided by antimicrobial susceptibility testing[26].

In regions with high clarithromycin resistance, bismuth-containing quadruple treatment has been suggested as the first line regimen[26]. This regimen achieved a significantly better eradication rate compared to standard triple therapy (82% *vs* 62%) in a population with high clarithromycin resistance[101]. If the bismuth-containing quadruple therapy is not available, sequential treatment or a non-bismuth quadruple therapy is may be administered. Similar to the low clarithromycin resistance regions, if the first line treatment fails in a high resistance region, it may be followed by levofloxacin-containing triple therapy as

the second line, and antibiotic susceptibility guided treatment as the third line therapy[26].

In the light of above-mentioned guidelines for *H. pylori* eradication, there are several issues to be emphasized in elderly population. Firstly, antibiotic resistance is particularly important in elderly due to increased prevalence of drug consumption and lower compliance potential in this population[102,103]. The health care providers should be especially cautious about the emerging levofloxacin resistance primarily in patients with chronic infectious bronchopneumopathy as they may have already received fluoroquinolones[26]. Structured patient counseling and follow-up might improve the patient compliance and efficacy of the therapy[104] and therefore, assist preventing antibiotic resistance. Secondly, the drug interaction is of significant importance in elderly population in whom polypharmacy is a common occurrence. Although the choice of PPI in *H. pylori* eradication does not affect the treatment success when used in standard doses[87], different PPIs might have different drug interactions. Omeprazole is the PPI that is most likely to have drug interactions particularly with cardiovascular drugs and clopidogrel, both of which commonly used in elderly. On the other hand, pantoprazole is the least likely PPI to interact with clopidogrel[105]. Similarly, frequently used antibiotics for eradication such as clarithromycin, amoxicillin, metronidazole, and tetracycline may also have important drug interactions with commonly used medications in elderly[106]. Although it is not easy to determine the effects of a particular drug's interaction in the large number of variables, cardiovascular drugs such as statins, antiarrhythmic drugs, and warfarin are among the well-established drugs which may interact with these antibiotics[106]. If the risk of interaction outweighs the benefit, the eradication treatment should be avoided or suspended. In addition, some co-morbidities in the elderly might require additional modification in the treatment plan. For example, while metronidazole can be used without dosage alteration in patients with renal failure, amoxicillin and clarithromycin require dose adjustment in patients with creatinine clearance less than 30 mL/min. These antibiotics may cause transient and mild elevation in the liver enzymes, but severe hepatotoxicity is unusual particularly in short term usage. Dosage adjustments for PPIs are not necessary in elderly patients or those with renal failure or mild hepatic impairment[106].

Last but not least, as the complications of *H. pylori* infection are increased with age, the proper follow-up testing needs to be conducted after eradication therapy to prevent further progression of the disease. While patients with gastric ulcer or gastric MALToma, or severe gastritis should be evaluated by endoscopy after therapy, the remaining situations may be followed-up with noninvasive methods (UBT or laboratory-based validated monoclonal SAT)[26,106].

CONCLUSION

H. pylori infection is a prevalent health problem in the older patients due to multiple factors increasing the potential damage of bacteria to gastric mucosa. The comorbidities and multidrug therapy can lead to increased and severe complications of *H. pylori* infection. The invasive tests using upper GI endoscopy should be preferred for the diagnosis of infection. The therapeutic approach suggested by the Maastricht IV Consensus Report is also suitable for older patients; however, the eradication failure may be a more significant problem due to high antibiotic resistance and low compliance rate. The expectation from eradication therapy in these patients should meet the therapeutic goals and therefore, the health care providers should take into account the specific characteristics of geriatric population.

REFERENCES

1 **Marshall BJ**. Helicobacter pylori. *Am J Gastroenterol* 1994; **89**: S116-S128 [PMID: 8048402]
2 **Suerbaum S**, Michetti P. Helicobacter pylori infection. *N Engl J Med* 2002; **347**: 1175-1186 [PMID: 12374879 DOI: 10.1056/NEJMra020542]
3 **Uemura N**, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, Taniyama K, Sasaki N, Schlemper RJ. Helicobacter pylori infection and the development of gastric cancer. *N Engl J Med* 2001; **345**: 784-789 [PMID: 11556297 DOI: 10.1056/NEJMoa001999]
4 **Gasbarrini A**, Franceschi F, Cammarota G, Pola P, Gasbarrini G. Vascular and immunological disorders associated with Helicobacter pylori infection. *Ital J Gastroenterol Hepatol* 1998; **30**: 115-118 [PMID: 9615278]
5 **Franceschi F**, Gasbarrini A. Helicobacter pylori and extragastric diseases. *Best Pract Res Clin Gastroenterol* 2007; **21**: 325-334 [PMID: 17382280 DOI: 10.1016/j.bpg.2006.10.003]
6 **Roubaud Baudron C**, Franceschi F, Salles N, Gasbarrini A. Extragastric diseases and Helicobacter pylori. *Helicobacter* 2013; **18** Suppl 1: 44-51 [PMID: 24011245 DOI: 10.1111/hel.12077]
7 **Salama NR**, Hartung ML, Müller A. Life in the human stomach: persistence strategies of the bacterial pathogen Helicobacter pylori. *Nat Rev Microbiol* 2013; **11**: 385-399 [PMID: 23652324 DOI: 10.1038/nrmicro3016]
8 **Chuah SK**, Tsay FW, Hsu PI, Wu DC. A new look at anti-Helicobacter pylori therapy. *World J Gastroenterol* 2011; **17**: 3971-3975 [PMID: 22046084 DOI: 10.3748/wjg.v17.i35.3971]
9 **Graham DY**, Shiotani A. New concepts of resistance in the treatment of Helicobacter pylori infections. *Nat Clin Pract Gastroenterol Hepatol* 2008; **5**: 321-331 [PMID: 18446147 DOI: 10.1038/ncpgasthep1138]
10 **Kadayifci A**, Buyukhatipoglu H, Cemil Savas M, Simsek I. Eradication of Helicobacter pylori with triple therapy: an epidemiologic analysis of trends in Turkey over 10 years. *Clin Ther* 2006; **28**: 1960-1966 [PMID: 17213016 DOI: 10.1016/j.clinthera.2006.11.011]
11 **Hsu PI**, Peng NJ. H. pylori Eradication Therapy. *Gastroenterol Res Pract* 2013; **2013**: 935635 [PMID: 23476640 DOI: 10.1155/2013/935635]
12 **Peleteiro B,** Bastos A, Ferro A, Lunet N. Prevalence of Helicobacter pylori Infection Worldwide: A Systematic Review of Studies with National Coverage. *Dig Dis Sci* 2014 Feb 22; Epub ahead of print [PMID: 24563236 DOI: 10.1007/s10620-014-3063-0]
13 **Pilotto A**. Aging and the gastrointestinal tract. *Ital J Gastroenterol Hepatol* 1999; **31**: 137-153 [PMID: 10363200]
14 **Pilotto A**, Franceschi M, Valerio G, Di Mario F, Leandro G. Helicobacter pylori infection in elderly patients with peptic

ulcer. *Age Ageing* 1999; **28**: 412-414 [PMID: 10459798]
15 **Lee YC**, Liou JM, Wu MS, Wu CY, Lin JT. Eradication of helicobacter pylori to prevent gastroduodenal diseases: hitting more than one bird with the same stone. *Therap Adv Gastroenterol* 2008; **1**: 111-120 [PMID: 21180520 DOI: 10.1177/1756283X08094880]
16 **Banić M**, Franceschi F, Babić Z, Gasbarrini A. Extragastric manifestations of Helicobacter pylori infection. *Helicobacter* 2012; **17** Suppl 1: 49-55 [PMID: 22958156 DOI: 10.1111/j.1523-5378.2012.00983.x]
17 **Nagini S**. Carcinoma of the stomach: A review of epidemiology, pathogenesis, molecular genetics and chemoprevention. *World J Gastrointest Oncol* 2012; **4**: 156-169 [PMID: 22844547 DOI: 10.4251/wjgo.v4.i7.156]
18 **Wu MS**, Chen CJ, Lin JT. Host-environment interactions: their impact on progression from gastric inflammation to carcinogenesis and on development of new approaches to prevent and treat gastric cancer. *Cancer Epidemiol Biomarkers Prev* 2005; **14**: 1878-1882 [PMID: 16103430 DOI: 10.1158/1055-9965.EPI-04-0792]
19 **Franceschi M**, Di Mario F, Leandro G, Maggi S, Pilotto A. Acid-related disorders in the elderly. *Best Pract Res Clin Gastroenterol* 2009; **23**: 839-848 [PMID: 19942162 DOI: 10.1016/j.bpg.2009.10.004]
20 **Davidovic M**, Svorcan P, Milanovic P, Antovic A, Milosevic D. Specifics of Helicobacter pylori infection/NSAID effects in the elderly. *Rom J Gastroenterol* 2005; **14**: 253-258 [PMID: 16200236]
21 **Huang JQ**, Sridhar S, Hunt RH. Role of Helicobacter pylori infection and non-steroidal anti-inflammatory drugs in peptic-ulcer disease: a meta-analysis. *Lancet* 2002; **359**: 14-22 [PMID: 11809181 DOI: 10.1016/S0140-6736(02)07273-2]
22 **Haruma K**, Kamada T, Kawaguchi H, Okamoto S, Yoshihara M, Sumii K, Inoue M, Kishimoto S, Kajiyama G, Miyoshi A. Effect of age and Helicobacter pylori infection on gastric acid secretion. *J Gastroenterol Hepatol* 2000; **15**: 277-283 [PMID: 10764028]
23 **Pilotto A**, Salles N. Helicobacter pylori infection in geriatrics. *Helicobacter* 2002; **7** Suppl 1: 56-62 [PMID: 12197911]
24 **Ofman JJ**, Etchason J, Alexander W, Stevens BR, Herrin J, Cangialose C, Ballard DJ, Bratzler D, Elward KS, FitzGerald D, Culpepper-Morgan J, Marshall B. The quality of care for Medicare patients with peptic ulcer disease. *Am J Gastroenterol* 2000; **95**: 106-113 [PMID: 10638567 DOI: 10.1111/j.1572-0241.2000.01514.x]
25 **Gisbert JP**, Pajares JM. Stool antigen test for the diagnosis of Helicobacter pylori infection: a systematic review. *Helicobacter* 2004; **9**: 347-368 [PMID: 15270750 DOI: 10.1111/j.1083-4389.2004.00235.x]
26 **Malfertheiner P**, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F, Gensini GF, Gisbert JP, Graham DY, Rokkas T, El-Omar EM, Kuipers EJ. Management of Helicobacter pylori infection--the Maastricht IV/ Florence Consensus Report. *Gut* 2012; **61**: 646-664 [PMID: 22491499 DOI: 10.1136/gutjnl-2012-302084]
27 **Gisbert JP**, Pajares JM. Review article: 13C-urea breath test in the diagnosis of Helicobacter pylori infection -- a critical review. *Aliment Pharmacol Ther* 2004; **20**: 1001-1017 [PMID: 15569102 DOI: 10.1111/j.1365-2036.2004.02203.x]
28 **Pilotto A**, Franceschi M, Leandro G, Rassu M, Zagari RM, Bozzola L, Furlan F, Bazzoli F, Di Mario F, Valerio G. Noninvasive diagnosis of Helicobacter pylori infection in older subjects: comparison of the 13C-urea breath test with serology. *J Gerontol A Biol Sci Med Sci* 2000; **55**: M163-M167 [PMID: 10795730]
29 **Salles-Montaudon N**, Dertheil S, Broutet N, Gras N, Monteiro L, De Mascarel A, Megraud F, Emeriau JP. Detecting Helicobacter pylori infection in hospitalized frail older patients: the challenge. *J Am Geriatr Soc* 2002; **50**: 1674-1680 [PMID: 12366621]
30 **Vaira D**, Ricci C, Menegatti M, Gatta L, Berardi S, Tampieri A, Miglioli M. Stool test for Helicobacter pylori. *Am J Gastroenterol* 2001; **96**: 1935-1938 [PMID: 11419857 DOI: 10.1111/j.1572-0241.2001.03901.x]
31 **Inelmen EM**, Gasparini G, Sergi G, Enzi G. Evaluation of Helicobacter pylori with a stool antigen assay in frail, elderly patients. *Scand J Gastroenterol* 2005; **40**: 794-799 [PMID: 16109654 DOI: 10.1080/00365520510015638]
32 **Feldman RA**, Deeks JJ, Evans SJ. Multi-laboratory comparison of eight commercially available Helicobacter pylori serology kits. Helicobacter pylori Serology Study Group. *Eur J Clin Microbiol Infect Dis* 1995; **14**: 428-433 [PMID: 7556232]
33 **Laheij RJ**, Straatman H, Jansen JB, Verbeek AL. Evaluation of commercially available Helicobacter pylori serology kits: a review. *J Clin Microbiol* 1998; **36**: 2803-2809 [PMID: 9738024]
34 **Kosunen TU**, Seppälä K, Sarna S, Sipponen P. Diagnostic value of decreasing IgG, IgA, and IgM antibody titres after eradication of Helicobacter pylori. *Lancet* 1992; **339**: 893-895 [PMID: 1348298]
35 **Burns EA**. Effects of aging on immune function. *J Nutr Health Aging* 2004; **8**: 9-18 [PMID: 14730363]
36 **Tytgat GN**. Role of endoscopy and biopsy in the work up of dyspepsia. *Gut* 2002; **50** Suppl 4: iv13-iv16 [PMID: 11953339]
37 **Liou JM**, Lin JT, Wang HP, Huang SP, Lee YC, Shun CT, Lin MT, Wu MS. The optimal age threshold for screening upper endoscopy for uninvestigated dyspepsia in Taiwan, an area with a higher prevalence of gastric cancer in young adults. *Gastrointest Endosc* 2005; **61**: 819-825 [PMID: 15933682]
38 **Abdalla AM,** Sordillo EM, Hanzely Z, Perez-Perez GI, Blaser MJ, Holt PR, Moss SF. Insensitivity of the CLOtest for H. pylori, Especially in the Elderly. *Gastroenterology* 1998; **115**: 243b-2244 [PMID: 9649489]
39 **Oleastro M**, Ménard A, Santos A, Lamouliatte H, Monteiro L, Barthélémy P, Mégraud F. Real-time PCR assay for rapid and accurate detection of point mutations conferring resistance to clarithromycin in Helicobacter pylori. *J Clin Microbiol* 2003; **41**: 397-402 [PMID: 12517879]
40 **Mégraud F**. Advantages and disadvantages of current diagnostic tests for the detection of Helicobacter pylori. *Scand J Gastroenterol Suppl* 1996; **215**: 57-62 [PMID: 8722384]
41 **Ferreira RM**, Machado JC, Letley D, Atherton JC, Pardo ML, Gonzalez CA, Carneiro F, Figueiredo C. A novel method for genotyping the Helicobacter pylori vacA intermediate region directly in gastric biopsy specimens. *J Clin Microbiol* 2012; **50**: 3983-3989 [PMID: 23035185 DOI: 10.1128/JCM.02087-12]
42 **El-Zimaity H**, Serra S, Szentgyorgyi E, Vajpeyi R, Samani A. Gastric biopsies: the gap between evidence-based medicine and daily practice in the management of gastric Helicobacter pylori infection. *Can J Gastroenterol* 2013; **27**: e25-e30 [PMID: 24106732]
43 **Lee JH**, Park YS, Choi KS, Kim do H, Choi KD, Song HJ, Lee GH, Jang SJ, Jung HY, Kim JH. Optimal biopsy site for Helicobacter pylori detection during endoscopic mucosectomy in patients with extensive gastric atrophy. *Helicobacter* 2012; **17**: 405-410 [PMID: 23066901 DOI: 10.1111/j.1523-5378.2012.00972.x]
44 **Ikenberry SO**, Harrison ME, Lichtenstein D, Dominitz JA, Anderson MA, Jagannath SB, Banerjee S, Cash BD, Fanelli RD, Gan SI, Shen B, Van Guilder T, Lee KK, Baron TH. The role of endoscopy in dyspepsia. *Gastrointest Endosc* 2007; **66**: 1071-1075 [PMID: 18028927 DOI: 10.1016/j.gie.2007.07.007]
45 **Niv Y**, Niv G, Koren R. 13C-urea breath test for diagnosis of Helicobacter pylori infection in the elderly. *Dig Dis Sci* 2004; **49**: 1840-1844 [PMID: 15628714]
46 **Sande N**, Nikulin M, Nilsson I, Wadström T, Laxén F, Härkönen M, Suovaniemi O, Sipponen P. Increased risk of developing atrophic gastritis in patients infected with CagA+ Helicobacter pylori. *Scand J Gastroenterol* 2001; **36**:

928-933 [PMID: 11521982]
47 **Pilotto A**. Aging and upper gastrointestinal disorders. *Best Pract Res Clin Gastroenterol* 2004; **18** Suppl: 73-81 [PMID: 15588798 DOI: 10.1016/j.bpg.2004.06.015]
48 **Lochhead P**, El-Omar EM. Helicobacter pylori infection and gastric cancer. *Best Pract Res Clin Gastroenterol* 2007; **21**: 281-297 [PMID: 17382277 DOI: 10.1016/j.bpg.2007.02.002]
49 **Aalykke C**, Lauritsen JM, Hallas J, Reinholdt S, Krogfelt K, Lauritsen K. Helicobacter pylori and risk of ulcer bleeding among users of nonsteroidal anti-inflammatory drugs: a case-control study. *Gastroenterology* 1999; **116**: 1305-1309 [PMID: 10348813]
50 **Murakami M**, Saita H, Takahashi Y, Kusaka S, Asagoe K, Dekigai H, Matsumoto M, Seki M, Mizuno M, Maeda S. Therapeutic effects of lansoprazole on peptic ulcers in elderly patients. *J Clin Gastroenterol* 1995; **20** Suppl 2: S79-S82 [PMID: 7594348]
51 **Pilotto A**, Franceschi M, Leandro G, Bozzola L, Fortunato A, Rassu M, Meli S, Soffiati G, Scagnelli M, Di Mario F, Valerio G. Efficacy of 7 day lansoprazole-based triple therapy for Helicobacter pylori infection in elderly patients. *J Gastroenterol Hepatol* 1999; **14**: 468-475 [PMID: 10355512]
52 **Pilotto A**, Franceschi M, Di Mario F, Leandro G, Bozzola L, Valerio G. The long-term clinical outcome of elderly patients with Helicobacter pylori-associated peptic ulcer disease. *Gerontology* 1998; **44**: 153-158 [PMID: 9592687]
53 **Ford AC**, Delaney BC, Forman D, Moayyedi P. Eradication therapy in Helicobacter pylori positive peptic ulcer disease: systematic review and economic analysis. *Am J Gastroenterol* 2004; **99**: 1833-1855 [PMID: 15330927 DOI: 10.1111/j.1572-0241.2004.40014.x]
54 **Chan FK**, To KF, Wu JC, Yung MY, Leung WK, Kwok T, Hui Y, Chan HL, Chan CS, Hui E, Woo J, Sung JJ. Eradication of Helicobacter pylori and risk of peptic ulcers in patients starting long-term treatment with non-steroidal anti-inflammatory drugs: a randomised trial. *Lancet* 2002; **359**: 9-13 [PMID: 11809180]
55 **Moayyedi P**, Deeks J, Talley NJ, Delaney B, Forman D. An update of the Cochrane systematic review of Helicobacter pylori eradication therapy in nonulcer dyspepsia: resolving the discrepancy between systematic reviews. *Am J Gastroenterol* 2003; **98**: 2621-2626 [PMID: 14687807 DOI: 10.1111/j.1572-0241.2003.08724.x]
56 **Parsonnet J**, Hansen S, Rodriguez L, Gelb AB, Warnke RA, Jellum E, Orentreich N, Vogelman JH, Friedman GD. Helicobacter pylori infection and gastric lymphoma. *N Engl J Med* 1994; **330**: 1267-1271 [PMID: 8145781 DOI: 10.1056/NEJM199405053301803]
57 **Dixon MF**, Pathology of Gastritis and Peptic Ulceration. In: Mobley HLT, Mendz GL, Hazell SL, editors. Helicobacter pylori: Physiology and Genetics. Washington (DC): ASM Press, 2001
58 **Katelaris PH**, Seow F, Lin BP, Napoli J, Ngu MC, Jones DB. Effect of age, Helicobacter pylori infection, and gastritis with atrophy on serum gastrin and gastric acid secretion in healthy men. *Gut* 1993; **34**: 1032-1037 [PMID: 8174948]
59 **Pilotto A**, Di Mario F, Franceschi M, Leandro G, Soffiati G, Scagnelli M, Bozzola L, Valerio G. Cure of Helicobacter pylori infection in the elderly: effects of eradication on gastritis and serological markers. *Aliment Pharmacol Ther* 1996; **10**: 1021-1027 [PMID: 8971305]
60 **Malfertheiner P**, Sipponen P, Naumann M, Moayyedi P, Mégraud F, Xiao SD, Sugano K, Nyrén O. Helicobacter pylori eradication has the potential to prevent gastric cancer: a state-of-the-art critique. *Am J Gastroenterol* 2005; **100**: 2100-2115 [PMID: 16128957 DOI: 10.1111/j.1572-0241.2005.41688.x]
61 **Correa P**, Fontham ET, Bravo JC, Bravo LE, Ruiz B, Zarama G, Realpe JL, Malcom GT, Li D, Johnson WD, Mera R. Chemoprevention of gastric dysplasia: randomized trial of antioxidant supplements and anti-helicobacter pylori therapy. *J Natl Cancer Inst* 2000; **92**: 1881-1888 [PMID: 11106679]
62 **Leung WK**, Lin SR, Ching JY, To KF, Ng EK, Chan FK, Lau JY, Sung JJ. Factors predicting progression of gastric intestinal metaplasia: results of a randomised trial on Helicobacter pylori eradication. *Gut* 2004; **53**: 1244-1249 [PMID: 15306578 DOI: 10.1136/gut.2003.034629]
63 **Wong BC**, Lam SK, Wong WM, Chen JS, Zheng TT, Feng RE, Lai KC, Hu WH, Yuen ST, Leung SY, Fong DY, Ho J, Ching CK, Chen JS. Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. *JAMA* 2004; **291**: 187-194 [PMID: 14722144 DOI: 10.1001/jama.291.2.187]
64 **Wang J**, Xu L, Shi R, Huang X, Li SW, Huang Z, Zhang G. Gastric atrophy and intestinal metaplasia before and after Helicobacter pylori eradication: a meta-analysis. *Digestion* 2011; **83**: 253-260 [PMID: 21282951 DOI: 10.1159/000280318]
65 **Ruskoné-Fourmestraux A**, Fischbach W, Aleman BM, Boot H, Du MQ, Megraud F, Montalban C, Raderer M, Savio A, Wotherspoon A. EGILS consensus report. Gastric extranodal marginal zone B-cell lymphoma of MALT. *Gut* 2011; **60**: 747-758 [PMID: 21317175 DOI: 10.1136/gut.2010.224949]
66 **Qu XH**, Huang XL, Xiong P, Zhu CY, Huang YL, Lu LG, Sun X, Rong L, Zhong L, Sun DY, Lin H, Cai MC, Chen ZW, Hu B, Wu LM, Jiang YB, Yan WL. Does Helicobacter pylori infection play a role in iron deficiency anemia? A meta-analysis. *World J Gastroenterol* 2010; **16**: 886-896 [PMID: 20143469]
67 **Muhsen K**, Cohen D. Helicobacter pylori infection and iron stores: a systematic review and meta-analysis. *Helicobacter* 2008; **13**: 323-340 [PMID: 19250507 DOI: 10.1111/j.1523-5378.2008.00617.x]
68 **Pellicano R**, Franceschi F, Saracco G, Fagoonee S, Roccarina D, Gasbarrini A. Helicobacters and extragastric diseases. *Helicobacter* 2009; **14** Suppl 1: 58-68 [PMID: 19712170 DOI: 10.1111/j.1523-5378.2009.00699.x]
69 **Arnold DM**, Bernotas A, Nazi I, Stasi R, Kuwana M, Liu Y, Kelton JG, Crowther MA. Platelet count response to H. pylori treatment in patients with immune thrombocytopenic purpura with and without H. pylori infection: a systematic review. *Haematologica* 2009; **94**: 850-856 [PMID: 19483158 DOI: 10.3324/haematol.2008.005348]
70 **George JN**. Definition, diagnosis and treatment of immune thrombocytopenic purpura. *Haematologica* 2009; **94**: 759-762 [PMID: 19483153 DOI: 10.3324/haematol.2009.007674]
71 **Jeon CY**, Haan MN, Cheng C, Clayton ER, Mayeda ER, Miller JW, Aiello AE. Helicobacter pylori infection is associated with an increased rate of diabetes. *Diabetes Care* 2012; **35**: 520-525 [PMID: 22279028 DOI: 10.2337/dc11-1043]
72 **Hsieh MC**, Lee TC, Cheng SM, Tu ST, Yen MH, Tseng CH. The influence of type 2 diabetes and glucose-lowering therapies on cancer risk in the Taiwanese. *Exp Diabetes Res* 2012; **2012**: 413782 [PMID: 22719752 DOI: 10.1155/2012/413782]
73 **Chung GE**, Heo NJ, Park MJ, Chung SJ, Kang HY, Kang SJ. Helicobacter pylori seropositivity in diabetic patients is associated with microalbuminuria. *World J Gastroenterol* 2013; **19**: 97-102 [PMID: 23326169 DOI: 10.3748/wjg.v19.i1.97]
74 **Akanuma M**, Yanai A, Sakamoto K, Hirata Y, Yamaji Y, Kawazu S, Maeda S. Influence of Helicobacter pylori eradication on the management of type 2 diabetes. *Hepatogastroenterology* 2012; **59**: 641-645 [PMID: 22328266 DOI: 10.5754/hge11960]
75 **Oluyemi A**, Anomneze E, Smith S, Fasanmade O. Prevalence of a marker of active helicobacter pylori infection among patients with type 2 diabetes mellitus in Lagos, Nigeria. *BMC Res Notes* 2012; **5**: 284 [PMID: 22686510 DOI: 10.1186/1756-0500-5-284]
76 **Weller C**, Charlett A, Oxlade NL, Dobbs SM, Dobbs RJ, Peterson DW, Bjarnason IT. Role of chronic infection and inflammation in the gastrointestinal tract in the etiology and pathogenesis of idiopathic parkinsonism. Part 3: pre-

dicted probability and gradients of severity of idiopathic parkinsonism based on H. pylori antibody profile. *Helicobacter* 2005; **10**: 288-297 [PMID: 16104944 DOI: 10.1111/j.1523-5378.2005.00329.x]

77 **Charlett A**, Dobbs RJ, Dobbs SM, Weller C, Ibrahim MA, Dew T, Sherwood R, Oxlade NL, Plant JM, Bowthorpe J, Lawson AJ, Curry A, Peterson DW, Bjarnason IT. Blood profile holds clues to role of infection in a premonitory state for idiopathic parkinsonism and of gastrointestinal infection in established disease. *Gut Pathog* 2009; **1**: 20 [PMID: 19941660 DOI: 10.1186/1757-4749-1-20]

78 **Kountouras J**, Boziki M, Gavalas E, Zavos C, Grigoriadis N, Deretzi G, Tzilves D, Katsinelos P, Tsolaki M, Chatzopoulos D, Venizelos I. Eradication of Helicobacter pylori may be beneficial in the management of Alzheimer's disease. *J Neurol* 2009; **256**: 758-767 [PMID: 19240960 DOI: 10.1007/s00415-009-5011-z]

79 **Franceschi F**, Navarese EP, Mollo R, Giupponi B, De Marco G, Merra G, Gasbarrini G, Silveri NG. [Helicobacter pylori and atherosclerosis. A review of the literature]. *Recenti Prog Med* 2009; **100**: 91-96 [PMID: 19350802]

80 **Bugdaci MS**, Zuhur SS, Sokmen M, Toksoy B, Bayraktar B, Altuntas Y. The role of Helicobacter pylori in patients with hypothyroidism in whom could not be achieved normal thyrotropin levels despite treatment with high doses of thyroxine. *Helicobacter* 2011; **16**: 124-130 [PMID: 21435090 DOI: 10.1111/j.1523-5378.2011.00830.x]

81 **Pierantozzi M**, Pietroiusti A, Brusa L, Galati S, Stefani A, Lunardi G, Fedele E, Sancesario G, Bernardi G, Bergamaschi A, Magrini A, Stanzione P, Galante A. Helicobacter pylori eradication and l-dopa absorption in patients with PD and motor fluctuations. *Neurology* 2006; **66**: 1824-1829 [PMID: 16801644 DOI: 10.1212/01.wnl.0000221672.01272.ba]

82 Current European concepts in the management of Helicobacter pylori infection. The Maastricht Consensus Report. European Helicobacter Pylori Study Group. *Gut* 1997; **41**: 8-13 [PMID: 9274464]

83 **Cosme A**, Montes M, Martos M, Gil I, Mendarte U, Salicio Y, Piñeiro L, Recasens MT, Ibarra B, Sarasqueta C, Bujanda L. Usefulness of antimicrobial susceptibility in the eradication of Helicobacter pylori. *Clin Microbiol Infect* 2013; **19**: 379-383 [PMID: 22512623 DOI: 10.1111/j.1469-0691.2012.03844.x]

84 **Javid G**, Zargar SA, Bhat K, Khan BA, Yatoo GN, Gulzar GM, Shah AH, Sodhi JS, Khan MA, Shoukat A, Saif RU. Efficacy and safety of sequential therapy versus standard triple therapy in Helicobacter pylori eradication in Kashmir India: a randomized comparative trial. *Indian J Gastroenterol* 2013; **32**: 190-194 [PMID: 23515980 DOI: 10.1007/s12664-013-0304-7]

85 **González-Huezo MS**, Rojas-Sánchez A, Rosales-Solís AA, Miranda-Cordero RM, Hinojosa-Ruiz A, Mejía-García E, Cruz-González EG. [Helicobacter pylori eradication frequency with the conventional triple therapy in adult patients at the Centro Médico Issemym]. *Rev Gastroenterol Mex* 2012; **77**: 114-118 [PMID: 22921101 DOI: 10.1016/j.rgmx.2012.05.001]

86 **Georgopoulos S**, Papastergiou V, Xirouchakis E, Laoudi F, Lisgos P, Spiliadi C, Papantoniou N, Karatapanis S. Non-bismuth quadruple "concomitant" therapy versus standard triple therapy, both of the duration of 10 days, for first-line H. pylori eradication: a randomized trial. *J Clin Gastroenterol* 2013; **47**: 228-232 [PMID: 22858517 DOI: 10.1097/MCG.0b013e31826015b0]

87 **Uygun A**, Kadayifçi A, Yeşilova Z, Savaş MC, Ateş Y, Karslioğlu Y, Ciğerim M, Bağci S, Dağalp K. Recent success of pantoprazole -or lansoprazole- based clarithromycin plus amoxicillin treatment in the eradication of Helicobacter pylori. *Turk J Gastroenterol* 2004; **15**: 219-224 [PMID: 16249974]

88 **Kadayifçi A**. What is the best first choice treatment option for Helicobacter pylori? *Turk J Gastroenterol* 2007; **18**: 1-4 [PMID: 17450487]

89 **Kadayifci A**, Uygun A, Polat Z, Kantarcioğlu M, Kılcıler G, Başer O, Ozcan A, Emer O. Comparison of bismuth-containing quadruple and concomitant therapies as a first-line treatment option for Helicobacter pylori. *Turk J Gastroenterol* 2012; **23**: 8-13 [PMID: 22505373]

90 **Polat Z**, Kadayifci A, Kantarcioglu M, Ozcan A, Emer O, Uygun A. Comparison of levofloxacin-containing sequential and standard triple therapies for the eradication of Helicobacter pylori. *Eur J Intern Med* 2012; **23**: 165-168 [PMID: 22284248 DOI: 10.1016/j.ejim.2011.02.011]

91 **Sánchez-Delgado J**, García-Iglesias P, Castro-Fernández M, Bory F, Barenys M, Bujanda L, Lisozain J, Calvo MM, Torra S, Gisbert JP, Calvet X. High-dose, ten-day esomeprazole, amoxicillin and metronidazole triple therapy achieves high Helicobacter pylori eradication rates. *Aliment Pharmacol Ther* 2012; **36**: 190-196 [PMID: 22591220 DOI: 10.1111/j.1365-2036.2012.05137.x]

92 **Nishizawa T**, Suzuki H, Suzuki M, Takahashi M, Hibi T. Proton pump inhibitor-amoxicillin-clarithromycin versus proton pump inhibitor-amoxicillin-metronidazole as first-line Helicobacter pylori eradication therapy. *J Clin Biochem Nutr* 2012; **51**: 114-116 [PMID: 22962528 DOI: 10.3164/jcbn.D-11-00029R1]

93 **Sugizaki K**, Sakata Y, Arai T, Furuhata Y, Iinuma N, Suzuki H. A multicenter prospective observational study of triple therapy with rabeprazole, amoxicillin and metronidazole for Helicobacter pylori in Japan. *Intern Med* 2012; **51**: 3103-3108 [PMID: 23154713]

94 **Uygun A**, Ates Y, Erdil A, Kadayifci A, Cetin C, Gulsen M, Karaeren N, Dagalp K. Efficacy of omeprazole plus two antimicrobials for the eradication of Helicobacter pylori in a Turkish population. *Clin Ther* 1999; **21**: 1539-1548 [PMID: 10509849]

95 **Zullo A**, De Francesco V, Hassan C, Ridola L, Repici A, Bruzzese V, Vaira D. Modified sequential therapy regimens for Helicobacter pylori eradication: a systematic review. *Dig Liver Dis* 2013; **45**: 18-22 [PMID: 23022424 DOI: 10.1016/j.dld.2012.08.025]

96 **Kadayifci A**, Uygun A, Kilciler G, Kantarcioglu M, Kara M, Ozcan A, Emer O. Low efficacy of clarithromycin including sequential regimens for Helicobacter pylori infection. *Helicobacter* 2012; **17**: 121-126 [PMID: 22404442 DOI: 10.1111/j.1523-5378.2011.00924.x]

97 **Gisbert JP**, Calvet X. Update on non-bismuth quadruple (concomitant) therapy for eradication of Helicobacter pylori. *Clin Exp Gastroenterol* 2012; **5**: 23-34 [PMID: 22457599 DOI: 10.2147/CEG.S25419]

98 **Villoria A**. [Acid-related diseases: are higher doses of proton pump inhibitors more effective in the treatment of Helicobacter pylori infection?]. *Gastroenterol Hepatol* 2008; **31**: 546-547 [PMID: 18928760]

99 **Calvet X**, García N, López T, Gisbert JP, Gené E, Roque M. A meta-analysis of short versus long therapy with a proton pump inhibitor, clarithromycin and either metronidazole or amoxycillin for treating Helicobacter pylori infection. *Aliment Pharmacol Ther* 2000; **14**: 603-609 [PMID: 10792124]

100 **Ford A**, Moayyedi P. How can the current strategies for Helicobacter pylori eradication therapy be improved? *Can J Gastroenterol* 2003; **17** Suppl B: 36B-40B [PMID: 12845349]

101 **Uygun A**, Kadayifci A, Safali M, Ilgan S, Bagci S. The efficacy of bismuth containing quadruple therapy as a first-line treatment option for Helicobacter pylori. *J Dig Dis* 2007; **8**: 211-215 [PMID: 17970879 DOI: 10.1111/j.1751-2980.2007.00308.x]

102 **Pilotto A**, Di Mario F, Franceschi M. Treatment of Helicobacter pylori infection in elderly subjects. *Age Ageing* 2000; **29**: 103-109 [PMID: 10791443]

103 **Pilotto A**, Malfertheiner P. Review article: an approach to Helicobacter pylori infection in the elderly. *Aliment Pharmacol Ther* 2002; **16**: 683-691 [PMID: 11929385]

104 **Al-Eidan FA**, McElnay JC, Scott MG, McConnell JB. Management of Helicobacter pylori eradication--the influence

of structured counselling and follow-up. *Br J Clin Pharmacol* 2002; **53**: 163-171 [PMID: 11851640]
105 **Norgard NB**, Mathews KD, Wall GC. Drug-drug interaction between clopidogrel and the proton pump inhibitors. *Ann Pharmacother* 2009; **43**: 1266-1274 [PMID: 19470853 DOI: 10.1345/aph.1M051]
106 **Hines LE**, Murphy JE. Potentially harmful drug-drug interactions in the elderly: a review. *Am J Geriatr Pharmacother* 2011; **9**: 364-377 [PMID: 22078863 DOI: 10.1016/j.amjopharm.2011.10.004]

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REVIEW

Pharmacological therapy of feed intolerance in the critically ills

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Abstract

Feed intolerance in the setting of critical illness is associated with higher morbidity and mortality, and thus requires promptly and effective treatment. Prokinetic agents are currently considered as the first-line therapy given issues relating to parenteral nutrition and post-pyloric placement. Currently, the agents of choice are erythromycin and metoclopramide, either alone or in combination, which are highly effective with relatively low incidence of cardiac, hemodynamic or neurological adverse effects. Diarrhea, however, can occur in up to 49% of patients who are treated with the dual prokinetic therapy, which is not associated with Clostridium difficile infection and settled soon after the cessation of the drugs. Hence, the use of prokinetic therapy over a long period or for prophylactic purpose must be avoided, and the indication for ongoing use of the drug(s) must be reviewed frequently. Second line therapy, such as total parenteral nutrition and post-pyloric feeding, must be considered once adverse effects relating the prokinetic therapy develop.

Key words: Adverse effects; Critical illness; Enteral feeding; Feed intolerance; Prokinetic therapy

Core tip: Feed intolerance during critical illness must be promptly recognized and treated due to the associated morbidity and mortality. The current first line treatment for feed intolerance is prokinetic therapy with erythromycin and metoclopramide (alone or in combination), which are highly effective and free of significant adverse effects. Although diarrhoea occurs commonly after combination prokinetic therapy, it is not associated with Clostridium difficile colitis and settled shortly after stopping the treatment. The use of prokinetic therapy over a long period or for prophylactic purpose, therefore, must be avoided and the indication for ongoing use of the drug(s) should be frequently reviewed.

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INTRODUCTION

Enteral nutrition is preferred method of nutritional support during critical illness given its major benefit in preserving intestinal mucosal barrier function, cheap and has significantly fewer infective complications as compared to total parenteral nutrition[1-6]. Unfortunately, gastrointestinal motility is frequently impaired in these patients and consequently, naso-gastric (NG) feeding cannot be tolerated in approximately 50% patients[1-3] due vomiting, feed reflux or regurgitation, pulmonary aspiration[3-5]. Not only these feeding complications are associated with higher morbidity and mortality[4-6], they also prevent adequate delivery of nutrition to meet the daily caloric requirement of these patients. Thus, it is important that feed intolerance is promptly identified and treated.

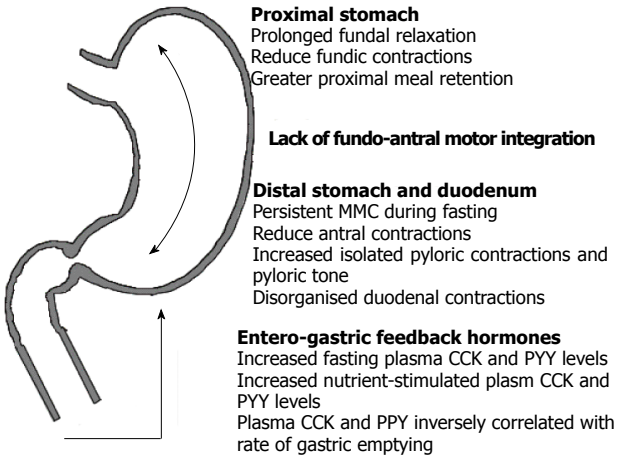

Figure 1 Gastric motor abnormalities reported during critical illness. CCK: Cholecystokinin; PYY: peptide YY.

Prokinetic agents are currently considered as the first-line therapy for feed intolerance given issues relating to parenteral nutrition and post-pyloric feeding[7-9]. In addition to the technical difficulties related to the placement of post-pyloric feeding tube, the morbidity and mortality benefits of post-pyloric feeding have not been demonstrated in these patients, especially in those who do not have impaired gastric emptying, and thus, routine use of post pyloric feeding is not recommended[10-12]. Even in feed-intolerant patients who failed to response to prokinetic therapy[13], evidence to support post-pyloric feeding in these patients is also lacking. Although total parenteral nutrition offers an alternative approach to deliver nutrition to these patients, it is associated with a higher rate of infective and hyperglycemic complication morbidity, necessitate the need for meticulous care of intravenous lines and blood glucose managment. This review aims to provide an overview of the current pharmacological approach to treat feed intolerance and gastrointestinal dysmotility during critical illness.

UPPER GASTROINTESTINAL DYSMOTILITY AND FEED INTOLERANCE DURING CRITICAL ILLNESS

Gastric emptying (GE) is commonly impaired during critical illness with up to 50% of mechanically ventilated patients have delayed GE[14-19]. Furthermore, antro-pyloro-duodenal as well as intestinal motilities during both fasting and fed stage are also frequently impaired in these patients[2,20], characterized by (1) an absence gastric phase Ⅲ motility and a loss of antro-pyloro-duodenal integration during the fasting state[21]; and (2) a delayed fundal relaxation, a reduced antral motility[20,22], an increased isolated pyloric activity[20] and a disrupted motor integration between the proximal and distal stomach[23] during feeding (Figure 1). Compared to healthy subjects, proximal gastric relaxation is more prolonged in critically ill patients and is associated with a greater suppression of fundic wave activity in response to intestinal nutrient infusion[24,25]. There is also a marked reduction in number of antral pressure waves and antral motility index but an increase in the isolated pyloric pressure waves and pyloric tone during a gastric meal[20,23]. The organisation of the duodenal contractions in these patients is also markedly abnormal with approximately 50% of these contractions being propagated in a retrograde manner[20,23]. Furthermore, the motor integration between the proximal and distal stomach, which is important for meal distribution and emptying, is also disrupted and leads to increased retention of the meal in the proximal stomach[23].

The mechanisms underlying gastrointestinal motility dysfunction during critical illness remain uncertain. Overall, the prolonged fundal relaxation, reduced antral activity and increased pyloric activity in response to a nutrient meal is consistent with enhanced motor feedback responses to the entero-gastric reflex. In keeping with this notion, the gastric motor disturbances in critically ill patients are associated with enhanced increases plasma cholecystokinin (CCK) and peptide YY (PYY) concentrations (gut hormones that mediate the entero-gastric motor feedback responses) during both fasting and in response to intestinal nutrients[26-28]. Together with the known adverse effects of CCK and PPY on gastric emptying, reciprocal relationship between the rate of gastric emptying and plasma concentrations of CCK and PYY suggests a potential role of these hormones in the pathogenesis of impaired gastric empyting during critical illness[26].

Other potential contributors that have been implicated in the pathogenesis of upper gastrointestinal motor dysfunction during critical illness are: admission diagnosis, severity of the critical illness, pre-existing morbidities, recent abdominal surgery, shock, electrolyte abnormalities, hyperglycaemia, age, gender, and drugs including those that used for sedation (benzodiazepines), analgesia (opioids) and maintaining blood pressure (catecholamines)[29-31].

Current pharmacological therapy of feed intolerance

Given the impaired gastric emptying is the main cause of feed intolerance, the main aim of the current available drug therapy for feed intolerance is to improve gastric emptying.

Dopamine agonists: Metoclopramide and domperidone are the dopamine agonists that have been used to treat feed intolerance in critical care for a long time. In contrast to metoclopramide, domperidone is a peripherally acting dopamine antagonist, which avoids the central nervous side effects and thus, has little extra-pyramidal adverse effects. Whilst these agents have been reported to improve gastric emptying in these patients, its efficacy in improving feed intolerance remains controversial[7-9]. The effect of metoclopramide on the gastric residual volume (GRV) was not observed after an enterally administered 10 mg dose, and not after the third dose, a modest reduction in GRV was detected[7-9]. Recently, metoclopramide [10 mg *qid iv*] has been

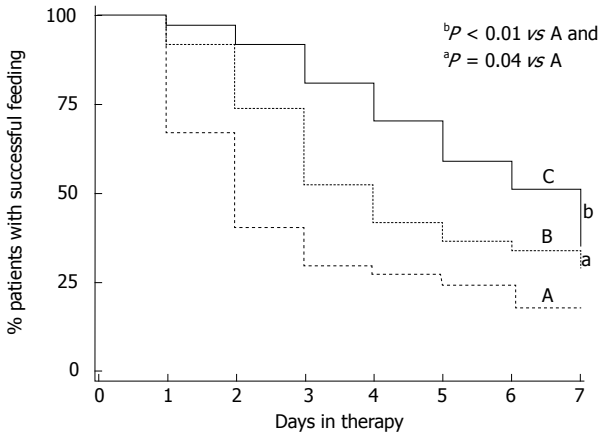

Figure 2 Efficacy of metoclopramide (A), erythromycin (B) and combined erythromycin and metoclopramide (C) in the treatment of feed intolerance of critical illness over 7-d period.

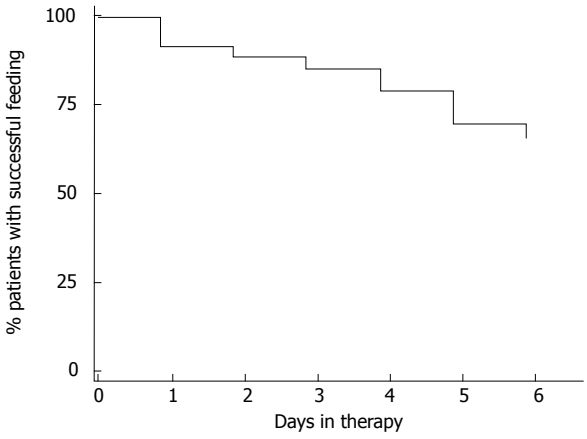

Figure 3 Efficacy of rescue combined metoclopramide and erythromycin in critically ill patients who failed to response to either erythromycin or metoclopramide in the treatment of feed intolerance.

shown to improve feed intolerance during critical illness but its therapeutic efficacy declines progressive over the 7 d (from 85% in the first days of therapy to less than 35% after 7 d of treatment, Figure 2)[32]. Metoclopramide, however, is not effective[33] and, in fact, contraindicated[34] in patients with brain injury, as it can raise intracranial pressure further.

Motilin agonists: Erythromycin is the only available motilin agonist uses in clinical practice. Given at a low dosage, ranging between 3 to 7 mg/kg per day, erythromycin has been shown to increase both gastric emptying and improve feed intolerance in critically ill patients[7-9]. Whilst enterally administered metoclopramide and cisapride have been shown to have a more rapid onset of action than erythromycin, the overall effect of these agents on GRV in these patients is similar to that of erythromycin[7-9]. In a recent randomized, double-blind trial, low dose erythromycin (200 mg *bid iv*) was found to be more efficacious than metoclopramide in improving feed intolerance in these patients[32]. The major issue with both agents, however, is the rapid development of tachyphylaxis, leading to a marked reduction in efficacy after a week of therapy (approximately 30% at day 7)[32] (Figure 2). For patients who failed to respond to either agent, the use of rescue combination therapy (*i.e.*, erythromycin and metoclopramide) was highly effective and minimized the development of tachyphylaxis[32] (Figure 3).

The role of combination prokinetic therapy as the first line therapy for feed intolerance has also been evaluated in a double-blind randomized study[35]. The use of first-line combination therapy to treat feed intolerance was significantly more effective than erythromycin alone, allowing a significantly greater amount of feed to be given to the patients during treatment. First-line combination therapy was also associated with a lesser degree of drug tachyphylaxis and up to 60% of patients remained responsive at day 7 of treatment[35] (Figure 2). Major adverse effects were not observed in either mono- or dual-therapy groups during both studies[32,35], supporting the use of low dose erythromycin, particularly in combination with metoclopramide, in the management of feed intolerance during critical illness. Despites these data, routine use of erythromycin for feed intolerance has not been universally recommended amongst the Intensive Care Physicians due the major concern of promoting bacterial resistance development with the widespread use of low dose erythromycin[36,37].

Serotonin (5-Hydroxytryptamine) receptor agonists: Serotonin is a monoamine neurotransmitter that acts on a variety of receptor types in the gastrointestinal tract, and has been shown to stimulates peristalsis[37]. This property leads to the use of this pharmacological agent as a prokinetic drug. Cisapride is the most well known agent in this class, and has dual stimulatory effects on the 5-Hydroxytryptamine (5-HT$_4$) serotonin receptors and the parasympathetic nervous system, leading to increases in both 5-HT$_4$ and acetylcholine in the enteric nervous system. The use of cisapride has been shown to associate with improved gastric emptying in critically ill patients as well as reduced the occurrence of feed intolerance[38-42]. Due to case reports of cisapride induced lethal cardiac toxicity[43], however, the drug has been withdrawn and is not available for clinical use.

Tegaserod is another serotonin (partial) agonist that have been trialed in critically ill patients. Similar to cisapride, although tegaserod improved gastric motility and accelerated gastric emptying[44], the drug was withdrawn in 2007 due to cardiovascular adverse effects. Together, evidence indicated that this class of drug is not an ideal prokinetic agent due to the associated cardiovascular side effects, and it use in critically ill patients is not recommended.

Novel prokinetic agents

Opiate receptor antagonists: The use of this class of drug bases on the fact that opiate reduces both gastric and intestinal motility, leading to an increase in feed intolerance during critical illness. Although the regular use of nasogastric naloxone (an opioid antagonist) has been shown

to reduce GRV and incidence of ventilation associated pneumonia (VAP) in critically ill patients who were receiving *iv* fentanyl, it had not impact on the time to wean from mechanical ventilation or the time to discharge from ICU[45]. Thus, the use of naloxone (8 mg *qid* nasogastric) has not been routinely adopted in clinical practice given its lack of easy administration and increases expense.

Recent data on mu (μ) receptor antagonists are, however, more promising. Unlike naxolone, these peripherial mu-opioid receptor antagonists do not antagonise the analgesic effects of analgesia and induce withdraw effects[46]. Alvimopan, a peripheral μ-opioid receptor antagonist, has been shown to counteract the inhibitory effect of opiate on small bowel motility[47] and significant reduce both the time to bowel recovery and time to discharge from hospital in patients with abdominal surgery[48]. The efficacy of alvimopan in the management of feed intolerance during critical illness, however, has not been formally assessed and warranted further evaluation.

CCK receptor antagonists: Compared to healthy subjects, critically ill patients have increased plasma fasting and nutrient-stimulated CCK concentration, which is further elevated in those who have delayed gastric emptying[49] or feed intolerance[50]. Given CCK plays a major role in the negative feedback inhibition of gastric emptying in response to meal, the higher plasma concentrations of CCK in critically ill patients are thought to potentially contribute to the gastric dysmotility and feed intolerance. In health, the use of loxiglumide has been found to associate with enhanced lower oesophageal sphincter function and gastric emptying. Given these findings, the use of CCK receptor antagonist may have a potential role in the management of impaired gastric emptying and feed intolerance during critical illness. Unfortunately, such study has not been conducted.

Ghrelin agonist: Ghrelin, a motilin related peptide, has a number of actions on the gastrointestinal tract, including stimulation of appetite[51] and gastrokinetic effects[52]. Physiologically, ghrelin induces phase Ⅲ gastric contractions and increases the resting tone of the fundus[53]. Based on these actions, the use of ghrelin analogue has been shown to improved gastric motility and the rate of gastric emptying in diabetic patients with gastroparesis[54]. Unfortunately, in addition to the prokinetic property, ghrelin also has anabolic effects by induce releases of growth hormones. Given the use of growth hormone has been reported to associate with increased mortality in the critically ill[55], the potential clinical use of exogenous ghrelin as a prokinetic agent has been cautious, and thus, has not been further evaluation in this patient group.

ADVERSE EFFECTS OF PROKINETIC THERAPY

Cardiovascular side effects

The potentially fatal ventricular arrhythmia relating to prolongation of the QT interval, *torsades de pointes,* has always been a major concern with the use of currently available prokinetics[56], as all agents have been shown to block the human ether-a-go-go-related gene currents which is important in mediation of cardiac rhythm[57,58]. Compared to metoclopramide and erythromycin, cisapride and domperidone are approximately 100 times more potent in the inhibition of human ether-a-go-go-related gene currents and, thus, carry the highest risk of inducing cardiac arrthymia[57,58]. The risk of arrhythmia, however, can be potentiated by a number of patient-related factors such as known history of cardiac arrhythmia, structural heart disease, poor left ventricular function and electrolyte disturbances[59]. In addition, it is important to recognize a number of drug interactions that can increase the risk of cardiac arrhythmia, which is particularly relevant in critical ill setting as poly-pharmacy is common. Concurrent administration of erythromycin and drugs that metabolized by CYP3A4 isoenzyme, such as antifungal and anti-arrhythmic drugs, calcium channel blockers, haloperidol and pimozide can increase the risk of adverse cardiac events and should be avoided[59]. It is important to recognize, however, that these concerns related to the cardiac adverse effects are extrapolated from reports or studies performed in non-critically ill patients. Thus far, there has been report of cardiac toxicities or arrhythmias with the use of metoclopramide or erythromycin in clinical studies that involved adults or pre-term infants during critical illness[31,34,60-62].

Another potential cardiovascular side effect of erythromycin is hypotension. In healthy volunteers, a reduction in systolic blood pressure by 10 mmHg has been observed after a single dose of erythromycin[63]. Such haemodynamic effects of erythromycin may be more relevant in critically ill patients given their cardiovascular function is already compromised. Our study[62], however, failed to demonstrate any impact of low dose erythromycin on blood pressure and heart rate, reassuring that erythromycin is safe to be used a prokinetic during critical illness.

Neurological side effects

In non-critical illness setting, long-term use of metoclopramide can be associated with somnolence, nervousness, extra-pyramidal dyskinesis, galactorrhea and menstrual disorders in up to 20% of patients[64,65], especially the elderly females. These side effects are difficult to detect, and thus, not reported during critical illness as the patients are paralyzed for mechanical ventilation. However, the use of metoclopramide is contraindicated in head injury patients as it is not effective[32] and more importantly, can increase intra-cranial pressure[33]. Similarly, in patients with a known history of myasthenia gravis, erythromycin can precipitate myasthenia crisis[66] and should be avoided in these patients.

Gastrointestinal side effects

Up to 25% patients with enteral feeding have watery di-

arrhoea[67,68] and the majority of cases are not related to infection. The aetiology is likely to be multi-factorial and can relate to increased gastrointestinal transit[69], reduced intestinal absorption[70], disturbed carbohydrate fermentation from altered bowel flora[67], and the hyper-osmolar effects of enteral feeds[67,68], leading to osmotic diarrhoea in most patients. Consequently, diarrhoea is more frequently observed in patients who receive enteral feeding at a high rate (*e.g.*, greater than 50 mL/h)[71], which improves when the rate of enteral feeding is reduced[67,68]. Recently, in a study of 180 critically ill patients who had feed intolerance, 40% patients developed diarrhoea after 10 d after commencement of prokinetic therapy (erythromycin and/or metoclopramide), and was most prevalent in those who received combination therapy [49% *vs* 30% (erythromycin) *vs* 32% (metoclopramide)][61]. The diarrhea lasted for a mean duration of 3.6 ± 1.2 d and directly correlated with the amount of feeds delivered[61]. More importantly, none of the patients with diarrhoea had *Clostridium difficile* infection and the diarrhoea resolved quickly with the cessation of prokinetic therapy[61].

ISSUES RELATED TO THE DEVELOPMENT OF BACTERIAL RESISTANCE

Given the prokinetic dose of erythromycin is low and in the "sublethal" concentrations of antibiotic effects, the widespread use of this medication as a prokinetic has been cautioned[35,36] as it can exert selective pressure on bacteria and can lead to the development of bacterial resistance[72], particularly in the setting of critical illness. The concerns, however, remain hypothetical as there are no data in the current literature to support this hypothesis with the short-term use of low-dose erythromycin[73]. In order to overcome this issue, a number of motilin derivatives that have no antibiotic property have been developed. Unfortunately, the prokinetic effects of these new agents are less durable, and are most likely due to the rapid development of drug tachyphylaxis[74-76].

TREATMENT ALGORITHM FOR FEED INTOLERANCE DURING CRITICAL ILLNESS

In addition to pharmacotherapy, there are a number of factors in the general management of the ICU patient which can help to prevent gut dysmotility and avoid its sequelae. These include patient posture, which should be at least 30º head up to reduce aspiration and nosocomial pneumonia in the setting of absent gastro-esophageal pressure[77,78]. Reduction in the dosage of opiates[30,45] and catecholamines to minimal tolerated levels and avoidance of the use of dopamine[79] will also reduce exogenous causes of delayed gastric emptying. If analgesia is required, short-acting agents like fentanyl or remifentanil are preferred and the uses of morphine should be minimised. Hyperglycemia may contribute to slow gastric emptying and blood glucose should be controlled. Prolonged fasting may affect gastrointestinal motility in healthy subjects[80], but early initiation of feeding has not been shown to affect subsequent gastric emptying or gastrointestinal hormones[81] but does improve subsequent nutrient absorption[82].

If feed intolerance develops despite the above preventive measures, prokinetic therapy should be commenced in patients who have no contraindications. Available data indicate that the combination of low dose erythromycin (200 mg *bid iv*) and metoclopramide (10 mg *qid iv*) is the most effective treatment with the lowest risk of developing drug tachyphylaxis. In Units which are concerned about the risk of bacterial resistance or Clostridium difficile infection, metoclopramide can be used the first line therapy and if this agent fails, rescue combination therapy with erythromycin should be adopted. In all cases, prokinetic treatment can be ceased after 7 d of therapy if successful feeding has been achieved or as soon as diarrhoea becomes a problem. In cases where prokinetic therapy fails, particularly with the combination use of erythromycin and metoclopramide, post-pyloric delivery of enteral feed to overcome impair gastric emptying should be considered. If this approach also fails or is not available, parenteral nutrition support with good glycemic care can be adopted.

CONCLUSION

Feed intolerance is common amongst the critically ill patients and, if not treated promptly, can lead to increased morbidity and mortality. Currently, treatment with prokinetics is considered as the first line therapy given the related technical difficulty of post-pyloric placement and the potential infective morbidities of parenteral nutrition. Metoclopramide and erythromycin are the two agents that have been shown to improve feed intolerance in these patients with a relatively good safety profile. Available data suggest that the agents should be used in combination to achieve the highest efficacy with a least incidence of tachyphylaxis. The major but hypothetical concern with the widespread use of low dose erythromycin as a prokinetic in clinical practice, however, is the development of bacterial resistance. Further development and evaluation of novel prokinetic agents, therefore, are warranted to overcome problems relating to drug tachyphylaxis and development of bacterial resistance.

REFERENCES

1 **De Beaux M**, Fraser R, Finnis M, De Keulenaer B, Liberalli D, Satanek M. Enteral nutrition in the critically ill: a prospective survey in an Australian intensive care unit. *Anaesth Intensive Care* 2001; **29**: 619-622 [PMID: 11771607]
2 **Dive A**, Moulart M, Jonard P, Jamart J, Mahieu P. Gastroduodenal motility in mechanically ventilated critically ill patients: a manometric study. *Crit Care Med* 1994; **22**: 441-447 [PMID: 8124995 DOI: 10.1097/00003246-199403000-00014]
3 **Mutlu GM**, Mutlu EA, Factor P. GI complications in patients receiving mechanical ventilation. *Chest* 2001; **119**:

1222-1241 [PMID: 11296191 DOI: 10.1378/chest.119.4.1222]
4 **Mullen JL**, Buzby GP, Matthews DC, Smale BF, Rosato EF. Reduction of operative morbidity and mortality by combined preoperative and postoperative nutritional support. *Ann Surg* 1980; **192**: 604-613 [PMID: 6776917 DOI: 10.1097/00000658-198019250-00004]
5 **Heyland D**, Cook DJ, Winder B, Brylowski L, Van deMark H, Guyatt G. Enteral nutrition in the critically ill patient: a prospective survey. *Crit Care Med* 1995; **23**: 1055-1060 [PMID: 7774216 DOI: 10.1097/00003246-199506000-00010]
6 **Dempsey DT**, Mullen JL, Buzby GP. The link between nutritional status and clinical outcome: can nutritional intervention modify it? *Am J Clin Nutr* 1988; **47**: 352-356 [PMID: 3124596]
7 **Stroud M**, Duncan H, Nightingale J. Guidelines for enteral feeding in adult hospital patients. *Gut* 2003; **52** Suppl 7: vii1-vii12 [PMID: 14612488 DOI: 10.1136/gut.52.suppl_7.vii1]
8 **Tisherman SA**, Marik PE, Ochoa J. Promoting enteral feeding 101. *Crit Care Med* 2002; **30**: 1653-1654 [PMID: 12130996 DOI: 10.1097/00003246-200207000-00044]
9 **MacLaren R**. Intolerance to intragastric enteral nutrition in critically ill patients: complications and management. *Pharmacotherapy* 2000; **20**: 1486-1498 [PMID: 11130221 DOI: 10.1592/phco.20.19.1486.34853]
10 **Heyland DK**, Drover JW, Dhaliwal R, Greenwood J. Optimizing the benefits and minimizing the risks of enteral nutrition in the critically ill: role of small bowel feeding. *JPEN J Parenter Enteral Nutr* 2002; **26**: S51-S55; discussion S51-S55 [PMID: 12405623]
11 **Ho K,** Dobb G, Webb AR. A comparison of early gastric and post pyloric feeding in critically ill patients- a meta-analysis. *Intensive Care Med* 2006; **32**: 639-649 [DOI: 10.1007/s00134-006-0128-3]
12 **Marik PE**, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. *Crit Care Med* 2001; **29**: 2264-2270 [PMID: 11801821 DOI: 10.1097/00003246-200112000-00005]
13 **Davies AR**, Bellomo R. Establishment of enteral nutrition: prokinetic agents and small bowel feeding tubes. *Curr Opin Crit Care* 2004; **10**: 156-161 [PMID: 15075727 DOI: 10.1097/00075198-200404000-00013]
14 **Montejo JC**. Enteral nutrition-related gastrointestinal complications in critically ill patients: a multicenter study. The Nutritional and Metabolic Working Group of the Spanish Society of Intensive Care Medicine and Coronary Units. *Crit Care Med* 1999; **27**: 1447-1453 [PMID: 10470748 DOI: 10.1097/00003246-199908000-00006]
15 **Spapen HD**, Duinslaeger L, Diltoer M, Gillet R, Bossuyt A, Huyghens LP. Gastric emptying in critically ill patients is accelerated by adding cisapride to a standard enteral feeding protocol: results of a prospective, randomized, controlled trial. *Crit Care Med* 1995; **23**: 481-485 [PMID: 7874898 DOI: 10.1097/00003246-199503000-00011]
16 **Ritz MA**, Fraser R, Edwards N, Di Matteo AC, Chapman M, Butler R, Cmielewski P, Tournadre JP, Davidson G, Dent J. Delayed gastric emptying in ventilated critically ill patients: measurement by 13 C-octanoic acid breath test. *Crit Care Med* 2001; **29**: 1744-1749 [PMID: 11546976 DOI: 10.1097/00003246-200109000-00015]
17 **Heyland DK**, Tougas G, King D, Cook DJ. Impaired gastric emptying in mechanically ventilated, critically ill patients. *Intensive Care Med* 1996; **22**: 1339-1344 [PMID: 8986483 DOI: 10.1007/BF01709548]
18 **Kao CH**, ChangLai SP, Chieng PU, Yen TC. Gastric emptying in head-injured patients. *Am J Gastroenterol* 1998; **93**: 1108-1112 [PMID: 9672339 DOI: 10.1111/j.1572-0241.1998.00338.x]
19 **Chapman M,** Fraser, R, Bartholomeusz, F, Creed, S, Russo, A, Jones,K , Bellon,M , Chatterton, B , Horowitz, M. Gastric Emptying in the Critically Ill: Relationship between Scintigraphic and Carbon Breath Test Measurement. *Gastroenterology* 2004; **126**: A488
20 **Chapman M**, Fraser R, Vozzo R, Bryant L, Tam W, Nguyen N, Zacharakis B, Butler R, Davidson G, Horowitz M. Antropyloro-duodenal motor responses to gastric and duodenal nutrient in critically ill patients. *Gut* 2005; **54**: 1384-1390 [PMID: 15923669 DOI: 10.1136/gut.2005.065672]
21 **Dive A**, Miesse C, Jamart J, Evrard P, Gonzalez M, Installe E. Duodenal motor response to continuous enteral feeding is impaired in mechanically ventilated critically ill patients. *Clin Nutr* 1994; **13**: 302-306 [PMID: 16843403 DOI: 10.1016/0261-5614(94)90053-1]
22 **Nguyen NQ**, Fraser RJ, Bryant LK, Chapman M, Holloway RH. Diminished functional association between proximal and distal gastric motility in critically ill patients. *Intensive Care Med* 2008; **34**: 1246-1255 [PMID: 18297265 DOI: 10.1007/s00134-008-1036-5]
23 **Nguyen NQ**, Fraser RJ, Bryant LK, Chapman M, Holloway RH. Proximal gastric motility in critically ill patients with type 2 diabetes mellitus. *World J Gastroenterol* 2007; **13**: 270-275 [PMID: 17226907 DOI: 10.3748/wjg.v13.i2.270]
24 **Nguyen NQ**, Fraser RJ, Chapman M, Bryant LK, Holloway RH, Vozzo R, Feinle-Bisset C. Proximal gastric response to small intestinal nutrients is abnormal in mechanically ventilated critically ill patients. *World J Gastroenterol* 2006; **12**: 4383-4388 [PMID: 16865782]
25 **Nguyen NQ**, Fraser RJ, Bryant LK, Chapman MJ, Wishart J, Holloway RH, Butler R, Horowitz M. The relationship between gastric emptying, plasma cholecystokinin, and peptide YY in critically ill patients. *Crit Care* 2007; **11**: R132 [PMID: 18154642 DOI: 10.1186/cc6205]
26 **Nguyen NQ**, Fraser RJ, Chapman M, Bryant LK, Wishart J, Holloway RH, Horowitz M. Fasting and nutrient-stimulated plasma peptide-YY levels are elevated in critical illness and associated with feed intolerance: an observational, controlled study. *Crit Care* 2006; **10**: R175 [PMID: 17173662 DOI: 10.1186/cc5127]
27 **Nguyen NQ**, Fraser RJ, Chapman MJ, Bryant LK, Holloway RH, Vozzo R, Wishart J, Feinle-Bisset C, Horowitz M. Feed intolerance in critical illness is associated with increased basal and nutrient-stimulated plasma cholecystokinin concentrations. *Crit Care Med* 2007; **35**: 82-88 [PMID: 17095943 DOI: 10.1097/01.CCM.0000250317.10791.6C]
28 **Ritz MA**, Fraser R, Tam W, Dent J. Impacts and patterns of disturbed gastrointestinal function in critically ill patients. *Am J Gastroenterol* 2000; **95**: 3044-3052 [PMID: 11095317 DOI: 10.1111/j.1572-0241.2000.03176.x]
29 **Nguyen NQ**, Ng MP, Chapman M, Fraser RJ, Holloway RH. The impact of admission diagnosis on gastric emptying in critically ill patients. *Crit Care* 2007; **11**: R16 [PMID: 17288616 DOI: 10.1186/cc5685]
30 **Nguyen NQ**, Chapman MJ, Fraser RJ, Bryant LK, Burgstad C, Ching K, Bellon M, Holloway RH. The effects of sedation on gastric emptying and intra-gastric meal distribution in critical illness. *Intensive Care Med* 2008; **34**: 454-460 [PMID: 18060542 DOI: 10.1007/s00134-007-0942-2]
31 **Nguyen NQ**, Chapman MJ, Fraser RJ, Bryant LK, Holloway RH. Erythromycin is more effective than metoclopramide in the treatment of feed intolerance in critical illness. *Crit Care Med* 2007; **35**: 483-489 [PMID: 17205032 DOI: 10.1097/01.CCM.0000253410.36492.E9]
32 **Marino LV**, Kiratu EM, French S, Nathoo N. To determine the effect of metoclopramide on gastric emptying in severe head injuries: a prospective, randomized, controlled clinical trial. *Br J Neurosurg* 2003; **17**: 24-28 [PMID: 12779198 DOI: 10.3109/02688690309177968]
33 **Deehan S**, Dobb GJ. Metoclopramide-induced raised intracranial pressure after head injury. *J Neurosurg Anesthesiol* 2002; **14**: 157-160 [PMID: 11907399]
34 **Nguyen NQ**, Chapman M, Fraser RJ, Bryant LK, Burgstad C, Holloway RH. Prokinetic therapy for feed intoler-

ance in critical illness: one drug or two? *Crit Care Med* 2007; **35**: 2561-2567 [PMID: 17828038 DOI: 10.1097/01.CCM.0000286397.04815.B1]
35 **Hawkyard CV**, Koerner RJ. The use of erythromycin as a gastrointestinal prokinetic agent in adult critical care: benefits versus risks. *J Antimicrob Chemother* 2007; **59**: 347-358 [PMID: 17289772]
36 **Singh NK**. Erythromycin as a prokinetic: is the overall benefit corroborated? *Crit Care Med* 2007; **35**: 1446; author reply 1446-1447 [PMID: 17446761]
37 **Tonini M**, Pace F. Drugs acting on serotonin receptors for the treatment of functional GI disorders. *Dig Dis* 2006; **24**: 59-69 [PMID: 16699264]
38 **Goldhill DR**, Toner CC, Tarling MM, Baxter K, Withington PS, Whelpton R. Double-blind, randomized study of the effect of cisapride on gastric emptying in critically ill patients. *Crit Care Med* 1997; **25**: 447-451 [PMID: 9118661 DOI: 10.1097/00003246-199703000-00013]
39 **Heyland DK**, Tougas G, Cook DJ, Guyatt GH. Cisapride improves gastric emptying in mechanically ventilated, critically ill patients. A randomized, double-blind trial. *Am J Respir Crit Care Med* 1996; **154**: 1678-1683 [PMID: 8970354]
40 **MacLaren R**, Kuhl DA, Gervasio JM, Brown RO, Dickerson RN, Livingston TN, Swift K, Headley S, Kudsk KA, Lima JJ. Sequential single doses of cisapride, erythromycin, and metoclopramide in critically ill patients intolerant to enteral nutrition: a randomized, placebo-controlled, crossover study. *Crit Care Med* 2000; **28**: 438-444 [PMID: 10708180 DOI: 10.1097/00003246-200002000-00025]
41 **MacLaren R**, Patrick WD, Hall RI, Rocker GM, Whelan GJ, Lima JJ. Comparison of cisapride and metoclopramide for facilitating gastric emptying and improving tolerance to intragastric enteral nutrition in critically III, mechanically ventilated adults. *Clin Ther* 2001; **23**: 1855-1866 [PMID: 11768837 DOI: 10.1016/S0149-2918(00)89081-5]
42 **Reddy PS**, Deorari AK, Bal CS, Paul VK, Singh M. A double-blind placebo-controlled study on prophylactic use of cisapride on feed intolerance and gastric emptying in preterm neonates. *Indian Pediatr* 2000; **37**: 837-844 [PMID: 10951632]
43 **Walker A,** Szneke P, Weatherby L. The risk of serious cardiac arrhythmias among cisapride users in the United Kingdom and Canada. *Am J Med* 1999; **107**: 356-362 [DOI: 10.1016/S0002-9343(99)00241-7]
44 **Banh HL**, MacLean C, Topp T, Hall R. The use of tegaserod in critically ill patients with impaired gastric motility. *Clin Pharmacol Ther* 2005; **77**: 583-586 [PMID: 15961989 DOI: 10.1016/j.clpt.2005.02.002]
45 **Meissner W**, Dohrn B, Reinhart K. Enteral naloxone reduces gastric tube reflux and frequency of pneumonia in critical care patients during opioid analgesia. *Crit Care Med* 2003; **31**: 776-780 [PMID: 12626983 DOI: 10.1097/01.CCM.0000053652.80849.9F]
46 **Paulson DM**, Kennedy DT, Donovick RA, Carpenter RL, Cherubini M, Techner L, Du W, Ma Y, Schmidt WK, Wallin B, Jackson D. Alvimopan: an oral, peripherally acting, mu-opioid receptor antagonist for the treatment of opioid-induced bowel dysfunction--a 21-day treatment-randomized clinical trial. *J Pain* 2005; **6**: 184-192 [PMID: 15772912 DOI: 10.1016/j.jpain.2004.12.001]
47 **Gonenne J**, Camilleri M, Ferber I, Burton D, Baxter K, Keyashian K, Foss J, Wallin B, Du W, Zinsmeister AR. Effect of alvimopan and codeine on gastrointestinal transit: a randomized controlled study. *Clin Gastroenterol Hepatol* 2005; **3**: 784-791 [PMID: 16234007 DOI: 10.1016/S1542-3565(05)00434-9]
48 **Taguchi A**, Sharma N, Saleem RM, Sessler DI, Carpenter RL, Seyedsadr M, Kurz A. Selective postoperative inhibition of gastrointestinal opioid receptors. *N Engl J Med* 2001; **345**: 935-940 [PMID: 11575284 DOI: 10.1056/NEJMoa010564]
49 **Debas HT**, Farooq O, Grossman MI. Inhibition of gastric emptying is a physiological action of cholecystokinin. *Gastroenterology* 1975; **68**: 1211-1217 [PMID: 1126597]
50 **Nguyen NQ,** Chapman, M, Fraser, R, Bryant L, Holloway, RH, Vozzo, R, Wishart, J, Feinle-Bisset, C, Horowitz, M Elevated cholecystokinin levels and feed intolerance in critical illness. *Critical Care Medicine* 2007; **35**: 82-88 [DOI: 10.1186/cc4561 PMCid: PMC1794491]
51 **Peeters TL**. Ghrelin: a new player in the control of gastrointestinal functions. *Gut* 2005; **54**: 1638-1649 [PMID: 16227363 DOI: 10.1136/gut.2004.062604]
52 **Nagaya N**, Kojima M, Uematsu M, Yamagishi M, Hosoda H, Oya H, Hayashi Y, Kangawa K. Hemodynamic and hormonal effects of human ghrelin in healthy volunteers. *Am J Physiol Regul Integr Comp Physiol* 2001; **280**: R1483-R1487 [PMID: 11294772]
53 **Tack J**, Depoortere I, Bisschops R, Delporte C, Coulie B, Meulemans A, Janssens J, Peeters T. Influence of ghrelin on interdigestive gastrointestinal motility in humans. *Gut* 2006; **55**: 327-333 [PMID: 16216827 DOI: 10.1136/gut.2004.060426]
54 **Murray CD**, Martin NM, Patterson M, Taylor SA, Ghatei MA, Kamm MA, Johnston C, Bloom SR, Emmanuel AV. Ghrelin enhances gastric emptying in diabetic gastroparesis: a double blind, placebo controlled, crossover study. *Gut* 2005; **54**: 1693-1698 [PMID: 16085693 DOI: 10.1136/gut.2005.069088]
55 **Takala J**, Ruokonen E, Webster NR, Nielsen MS, Zandstra DF, Vundelinckx G, Hinds CJ. Increased mortality associated with growth hormone treatment in critically ill adults. *N Engl J Med* 1999; **341**: 785-792 [PMID: 10477776 DOI: 10.1056/NEJM199909093411102]
56 **Tonini M**, De Ponti F, Di Nucci A, Crema F. Review article: cardiac adverse effects of gastrointestinal prokinetics. *Aliment Pharmacol Ther* 1999; **13**: 1585-1591 [PMID: 10594392 DOI: 10.1046/j.1365-2036.1999.00655.x]
57 **Gallacher DJ**, Van de Water A, van der Linde H, Hermans AN, Lu HR, Towart R, Volders PG. In vivo mechanisms precipitating torsades de pointes in a canine model of drug-induced long-QT1 syndrome. *Cardiovasc Res* 2007; **76**: 247-256 [PMID: 17669388 DOI: 10.1016/j.cardiores.2007.06.019]
58 **Lu HR**, Vlaminckx E, Van de Water A, Rohrbacher J, Hermans A, Gallacher DJ. In-vitro experimental models for the risk assessment of antibiotic-induced QT prolongation. *Eur J Pharmacol* 2007; **577**: 222-232 [PMID: 18074444 DOI: 10.1016/j.ejphar.2007.07.070]
59 **Roden DM**. Drug-induced prolongation of the QT interval. *N Engl J Med* 2004; **350**: 1013-1022 [PMID: 14999113 DOI: 10.1056/NEJMra032426]
60 **Ng E**, Shah VS. Erythromycin for the prevention and treatment of feeding intolerance in preterm infants. *Cochrane Database Syst Rev* 2008; **(3)**: CD001815 [PMID: 18646077 DOI: 10.1002/14651858.CD001815.pub2]
61 **Nguyen NQ**, Ching K, Fraser RJ, Chapman MJ, Holloway RH. Risk of Clostridium difficile diarrhoea in critically ill patients treated with erythromycin-based prokinetic therapy for feed intolerance. *Intensive Care Med* 2008; **34**: 169-173 [PMID: 17701160 DOI: 10.1007/s00134-007-0834-5]
62 **Nguyen NQ,** Mangoni AA, Fraser RJ, Chapman M, Bryant L, Burgstad C, Holloway RH. Prokinetic therapy with erythromycin has no significant impact on blood pressure and heart rate in critically ill patients. *Br J Clin Pharmacol* 2007; **63**: 498-500 [DOI: 10.1111/j.1365-2125.2006.02772.x]
63 **Mangoni AA**, Close JC, Rodriguez S, Sherwood RA, Bryant CA, Swift CG, Jackson SH. Acute hypotensive effects of oral cisapride and erythromycin in healthy subjects. *Br J Clin Pharmacol* 2004; **58**: 223-224 [PMID: 15255808 DOI: 10.1111/j.1365-2125.2004.02118.x]
64 **Ganzini L**, Casey DE, Hoffman WF, McCall AL. The prevalence of metoclopramide-induced tardive dyskinesia and acute extrapyramidal movement disorders. *Arch Intern*

Med 1993; **153**: 1469-1475 [PMID: 8512437 DOI: 10.1001/archinte.153.12.1469]
65 **Garcea N**, Campo S, Siccardi P, Panetta V, Venneri M, Dargenio R. Effect of drug-induced hyper- and hypoprolactinemia on human corpus luteum. *Acta Eur Fertil* 1983; **14**: 35-40 [PMID: 6326451]
66 **Absher JR**, Bale JF. Aggravation of myasthenia gravis by erythromycin. *J Pediatr* 1991; **119**: 155-156 [PMID: 1648610 DOI: 10.1016/S0022-3476(05)81058-3]
67 **Ringel AF**, Jameson GL, Foster ES. Diarrhea in the intensive care patient. *Crit Care Clin* 1995; **11**: 465-477 [PMID: 7788541]
68 **Kelly TW**, Patrick MR, Hillman KM. Study of diarrhea in critically ill patients. *Crit Care Med* 1983; **11**: 7-9 [PMID: 6848311 DOI: 10.1097/00003246-198301000-00003]
69 **Landry C**, Vidon N, Sogni P, Nepveux P, Chaumeil JC, Chauvin JP, Couturier D, Chaussade S. Effects of erythromycin on gastric emptying, duodeno-caecal transit time, gastric and biliopancreatic secretion during continuous gastric infusion of a liquid diet in healthy volunteers. *Eur J Gastroenterol Hepatol* 1995; **7**: 797-802 [PMID: 7496872]
70 **Hernandez G**, Velasco N, Wainstein C, Castillo L, Bugedo G, Maiz A, Lopez F, Guzman S, Vargas C. Gut mucosal atrophy after a short enteral fasting period in critically ill patients. *J Crit Care* 1999; **14**: 73-77 [PMID: 10382787 DOI: 10.1016/S0883-9441(99)90017-5]
71 **Smith CE**, Marien L, Brogdon C, Faust-Wilson P, Lohr G, Gerald KB, Pingleton S. Diarrhea associated with tube feeding in mechanically ventilated critically ill patients. *Nurs Res* 1990; **39**: 148-152 [PMID: 2111543]
72 **Burgess DS**. Pharmacodynamic principles of antimicrobial therapy in the prevention of resistance. *Chest* 1999; **115**: 19S-23S [PMID: 10084455 DOI: 10.1378/chest.115.suppl_1.19S]
73 **DiBaise JK**, Quigley EM. Efficacy of prolonged administration of intravenous erythromycin in an ambulatory setting as treatment of severe gastroparesis: one center's experience. *J Clin Gastroenterol* 1999; **28**: 131-134 [PMID: 10078820 DOI: 10.1097/00004836-199903000-00009]
74 **Netzer P**, Schmitt B, Inauen W. Effects of ABT-229, a motilin agonist, on acid reflux, oesophageal motility and gastric emptying in patients with gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2002; **16**: 1481-1490 [PMID: 12182748 DOI: 10.1046/j.1365-2036.2002.01324.x]
75 **Talley NJ**, Verlinden M, Geenen DJ, Hogan RB, Riff D, McCallum RW, Mack RJ. Effects of a motilin receptor agonist (ABT-229) on upper gastrointestinal symptoms in type 1 diabetes mellitus: a randomised, double blind, placebo controlled trial. *Gut* 2001; **49**: 395-401 [PMID: 11511562 DOI: 10.1136/gut.49.3.395]
76 **Talley NJ**, Verlinden M, Snape W, Beker JA, Ducrotte P, Dettmer A, Brinkhoff H, Eaker E, Ohning G, Miner PB, Mathias JR, Fumagalli I, Staessen D, Mack RJ. Failure of a motilin receptor agonist (ABT-229) to relieve the symptoms of functional dyspepsia in patients with and without delayed gastric emptying: a randomized double-blind placebo-controlled trial. *Aliment Pharmacol Ther* 2000; **14**: 1653-1661 [PMID: 11121915 DOI: 10.1046/j.1365-2036.2000.00868.x]
77 **Torres A**, Serra-Batlles J, Ros E, Piera C, Puig de la Bellacasa J, Cobos A, Lomeña F, Rodríguez-Roisin R. Pulmonary aspiration of gastric contents in patients receiving mechanical ventilation: the effect of body position. *Ann Intern Med* 1992; **116**: 540-543 [PMID: 1543307 DOI: 10.7326/0003-4819-116-7-540]
78 **Drakulovic MB**, Torres A, Bauer TT, Nicolas JM, Nogué S, Ferrer M. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. *Lancet* 1999; **354**: 1851-1858 [PMID: 10584721 DOI: 10.1016/S0140-6736(98)12251-1]
79 **Dive A**, Foret F, Jamart J, Bulpa P, Installé E. Effect of dopamine on gastrointestinal motility during critical illness. *Intensive Care Med* 2000; **26**: 901-907 [PMID: 10990104 DOI: 10.1007/s001340051279]
80 **Corvilain B**, Abramowicz M, Féry F, Schoutens A, Verlinden M, Balasse E, Horowitz M. Effect of short-term starvation on gastric emptying in humans: relationship to oral glucose tolerance. *Am J Physiol* 1995; **269**: G512-G517 [PMID: 7485502]
81 **Nguyen NQ**, Fraser RJ, Bryant LK, Burgstad C, Chapman MJ, Bellon M, Wishart J, Holloway RH, Horowitz M. The impact of delaying enteral feeding on gastric emptying, plasma cholecystokinin, and peptide YY concentrations in critically ill patients. *Crit Care Med* 2008; **36**: 1469-1474 [PMID: 18434906 DOI: 10.1097/CCM.0b013e31816fc457]
82 **Nguyen NQ**, Besanko LK, Burgstad C, Bellon M, Holloway RH, Chapman M, Horowitz M, Fraser RJ. Delayed enteral feeding impairs intestinal carbohydrate absorption in critically ill patients. *Crit Care Med* 2012; **40**: 50-54 [PMID: 21926614 DOI: 10.1097/CCM.0b013e31822d71a6]

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REVIEW

Renal dysfunction in patients with cirrhosis: Where do we stand?

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Abstract

Patients with cirrhosis and renal failure are high-risk patients who can hardly be grouped to form precise instructions for diagnosis and treatment. When it comes to evaluate renal function in patients with cirrhosis, determination of acute kidney injury (AKI), chronic kidney disease (CKD) or AKI on CKD should be made. First it should be excluded the prerenal causes of AKI. All cirrhotic patients should undergo renal ultrasound for measurement of renal resistive index in every stage of liver dysfunction and urine microscopy for differentiation of all causes of AKI. If there is history of dehydration on the ground of normal renal ultrasound and urine microscopy the diuretics should be withdrawn and plasma volume expansion should be tried with albumin. If the patient does not respond, the correct diagnosis is HRS. In case there is recent use of nephrotoxic agents or contrast media and examination shows shock, granular cast in urinary sediment and proteinuria above 0.5 g daily, acute tubular necrosis is the prominent diagnosis. Renal biopsy should be performed when glomerular filtration rate is between 30-60 mL/min and there are signs of parenchymal renal disease. The acute renal function is preferable to be assessed with modified AKIN. Patients with AKIN stage 1 and serum creatinine $\geqslant$ 1.5 mg/dL should be at close surveillance. Management options include hemodynamic monitoring and management of fluid balance and infections, potentially driving to HRS. Terlipressin is the treatment of choice in case of established HRS, administered until there are signs of improvement, but not more than two weeks. Midodrine is the alternative for therapy continuation or when terlipressin is unavailable. Norepinephrine has shown similar effect with terlipressin in patients being in Intensive Care Unit, but with much lower cost than that of terlipressin. If the patient meets the requirements for transplantation, dialysis and transjugular intrahepatic portosystemic shunt are the bridging therapies to keep the transplant candidate in the best clinical status. The present review clarifies the latest therapeutic modalities and the proposed recommendations and algorithms in order to be applied in clinical practice.

Key words: Renal dysfunction; Cirrhosis; Assessment; Management; Hepatorenal syndrome

Core tip: Close surveillance, well -classified definitions and scoring systems will be helpful in recognizing the renal dysfunction. Noninvasive biomarkers (NGAL, sCysC) reflect the prospective method in identifying kidney damage and kidney function. The acute renal function is proposed to be assessed with modified acute kidney injury network (AKIN) and the baseline renal function in stable patients with MDRD-6 formula or chronic kidney disease epidemiology collaboration Cys C-Cr equation. MBRS score or RIFLE criteria for AKI evaluation should be tried in critically ill cirrhotic patients, while in candidates for transplantation, glomerular filtration rate should be preferably measured with exogenous markers for accurate assessment of renal function. Amelioration of the underlined liver disease is very impressive in patients with alcoholic liver disease after recovery from

alcoholic hepatitis, and in patients with decompensated cirrhosis due to hepatitis B virus infection after receiving antiviral therapy.

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INTRODUCTION

Physicians involved in the care of patients with cirrhosis recognize that the development of renal dysfunction is associated with significant morbidity and mortality[1-3]. Methods for early and accurate diagnosis of acute renal failure may assist initiate specific treatment at earlier stage and improve the outcome. Patients with cirrhosis can develop three main forms of acute renal failure and may suffer also from underline chronic kidney disease. Prerenal azotemia is the basis of acute renal injury, which can trigger hepatorenal syndrome type 1 (HRS-type 1) and evolve to acute tubular necrosis - according to the degree of splanchnic vasodilation/renal hypoperfusion and the reduced cardiac output[4]. HRS type-1 is a prevalently functional disease observed in patients with decompensated cirrhosis, which might remain in a chronic form with less severe renal impairment (HRS-type 2), or progress to acute tubular necrosis[5-7] and exaggerate systemic inflammatory response resulting in multiorgan failure[8]. Recently, patients with cirrhosis who have decreased renal plasma flow with normal or low/normal glomerular filtration rate (GFR) before to develop HRS were defined to be in "Pre-HRS" renal disease[6]. Moreover, the term 'Hepatorenal Disorders' has been proposed to group all forms of kidney disease in patients with cirrhosis so as to describe their prognosis and to assist treatment decisions[9]. However, in the majority of patients, HRS type-1 still remains a terminal condition of advanced liver disease requiring coordinated affords in the field of diagnosis, pathophysiology and treatment. In this paper, we are going to address the current knowledge on the evaluation and management of acute and chronic kidney failure presented on patients with cirrhosis. All the suggested directions highlight, to the best extent possible, the bibliographic studies, the expert opinions and recommendations.

BASELINE DIRECTIONS FOR ASSESSMENT OF KIDNEY INJURY IN PATIENTS WITH CIRRHOSIS

The appropriate clinical, biochemical and radiological markers with proven sensitivity for the diagnosis of renal disease in patients with cirrhosis have not been established yet. There are only recommendations for the unique form of kidney injury in patients with cirrhosis, the HRS (Table 1). Renal pathology in patients with cirrhosis includes not only functional abnormalities (developed as a result of changes in hemodynamics, in renal auto-regulation and cardiac dysfunction) but structural abnormalities as well[5].

Physicians caring for patients with cirrhosis should recognize the acute or chronic character of renal disease; the causes of renal injury; the clinical conditions leading concomitantly to acute kidney injury (AKI) and liver dysfunction, and the prognostic factors associated with the progression of AKI. Hypovolemia (due to diuretics, hemorrhage, diarrhoea), acute tubular necrosis, sepsis, nephrotoxic agents (such as nonsteroidal antiinflammatory drugs, aminoglycosides radiological contrasts) and hepatorenal syndrome-type 1 are the most common causes of AKI in cirrhotic patients[4]. It is underlined that type-1 HRS is considered a specific form of AKI[9]. The chronic causes include hepatorenal syndrome-type 2, glomerulonephritis due to hepatitis C virus and hepatitis B virus infection, IgA nephropathy mainly presenting in patients with alcoholic cirrhosis and diabetic nephropathy mainly combined with non alcoholic steatohepatitis[4]. The situations which may worsen the renal and liver function at the same time might be autoimmune diseases, granulomatous diseases, autosomal dominant polycystic kidney disease, shock, pregnancy induced liver disease and drugs (aspirin, NSAIDs and angiotensin converting enzyme inhibitors[4,10,11]. Ultimately, factors associated with the progression of AKI were the hepatic encephalopathy, severe liver and circulatory failure, chronic kidney disease (CKD), low serum sodium concentration and high leukocyte count[12]. This knowledge should be in hand when time for assessment of patients with cirrhosis comes.

In general, differentiation of the main causes of AKI, prerenal "Pre-HRS", HRS and acute tubular necrosis presents great influence on therapeutic decisions and patients' prognosis. An easily applicable algorithm proposed by Angeli *et al*[5], offer great assistance in clarification of the cause of the AKI in patients with cirrhosis. When there is history of dehydration, excessive use of diuretics and bacterial infection on the ground of normal urinary sediment, proteinuria below 0.5 g daily and normal renal ultrasound, the diuretics should be withdrawn and plasma volume expansion should be tried with albumin. If the patient responds to treatment the diagnosis is prerenal. If the patient does not respond, the correct diagnosis is HRS. In case there is recent use of nephrotoxic agents or contrast media and examination shows shock, granular cast in urinary sediment and proteinuria above 0.5 g daily, acute tubular necrosis is the prominent diagnosis. Furthermore, physicians should take into account that one form may convert into another thus HRS may develop on patient with chronic renal disease or evolve in time[4,5].

Moreover, the stage of liver disease will provide considerable hints for the evaluation of kidney injury. At the beginning of cirrhosis splanchnic vasodilatation is masked by increased cardiac output thus glomerulal filtration rate (GFR) is increased[13]. Patients with ascites present severe impairment of renal blood flow[14] and considerable

Table 1 International Ascites Club definition and diagnostic criteria for hepatorenal syndrome[7,116]

1996 criteria
Major criteria
Chronic or acute liver disease with advanced hepatic failure and portal hypertension
Serum creatinine > 1.5 mg/dL or 24-h creatinine clearance of < 40 mL/min
Absence of shock, ongoing bacterial infection, and current or recent treatment with nephrotoxic drugs. Absence of gastrointestinal fluid losses (repeated vomiting or intense diarrhea) or renal fluid losses
No sustained improvement in renal function defined as a decrease in serum creatinine to < 1.5 mg/dL or increase in creatinine clearance to 40 mL/min or more following diuretic withdrawal and expansion of plasma volume with 1.5 L of isotonic saline
Proteinuria < 500 mg/dL and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease
Minor criteria
Urine volume < 500 mL/d Urine osmolality > plasma osmolality
Urine sodium < 10 mEq/L Urine red blood cells < 50 per high power field

fluctuation of serum creatinine (sCr)[15]. Wide variations may be observed, in regards to volume paracentesis and volume expansion[15]. Patients with advanced liver disease and high bilirubin show overestimation of GFR if evaluation of renal function is based on sCr, since significant interaction may be observed between serum bilirubin and sCr[16,17]. Cirrhotic patients admitted to intensive care unit (ICU) have high mortality rates and may present separate predictors and scoring systems for hospital mortality[18-20]. Emphasis should be given to accurate assessment of renal function in candidates for liver transplantation[21].

The best method for renal function assessment in patients with cirrhosis is the clearance of exogenous markers such as iothalamate, 51Cr-EDTA and inulin[15]. However, its application is limited by the cost and complexity while other equivalent methods for estimating the GFR in patients with cirrhosis have not been established[15]. sCr still remains the key biomarker for the diagnosis of AKI in patients with cirrhosis. Despite all sCr limitations, there have not been detected other widely available and superior serum markers for assessing renal function and predicting outcome in patients with cirrhosis[15]. sCr is still the most practical serum marker for estimation of renal function in cirrhotic patients, it consists the basis of existing definitions of AKI and it is included in the Model for End -Stage Liver Disease (MELD) score {MELD = 3.8 [Ln serum bilirubin (mg/dL)] + 11.2 (Ln INR) + 9.6 [Ln serum creatinine (mg/dL)] + 6.4}, which is used to allocate patients for liver transplantation[22]. Nevertheless, sCr should be interpreted with caution, since there is no universal standardized creatinine assay; there are interlaboratory variations, interactions with bilirubin and great influence by numerous non-renal factors such as body weight, race, age, gender[23-25]. Moreover, sCr within the normal ranges does not exclude significant renal impairment in patients with cirrhosis[26] as it overestimates renal function due to decreased creatine production by liver malnutrition and muscle wasting[27].

RECENT KNOWLEDGE ON EVALUATION OF RENAL DYSFUNCTION IN PATIENTS WITH CIRRHOSIS

So far, the most widely used criterion for the diagnosis of acute renal failure in patients with cirrhosis is the sCr level ⩾ 1.5 mg/dL (133 μmol/L) (conventional criteria). A propose for the improvement on the current classification of acute renal dysfunction in cirrhosis is the diagnostic criteria developed by the Acute Kidney Injury Network (AKIN)[28] (Table 2). This is a consensus definition for acute kidney injury (AKI), a new term for acute renal failure, in order to be identified earlier patients with worse prognosis. According to AKIN criteria, AKI is defined as an increase in sCr level ⩾ 0.3 mg/dL (⩾ 26.4 μmol/L) or ⩾ 150% (1.5 fold from baseline) within 48 h from the first measurement or a urine output of less than 0.5 mL/kg per hour for more than 6 h[28-30] and is divided in three stages. AKIN criteria in cirrhotic patients have been validated with six prospective clinical trials[8,12,20,31-33]. The patient population in the five studies included hospitalized cirrhotic patients with or without ascites[8,12,31-33], while in one study patients with cirrhosis were admitted in ICU[20]. All studies concluded that AKIN criteria accurately predicted in- hospital mortality, length of hospital stay and organ failure. However, when AKIN criteria compared to conventional criteria, they were not found to be superior[33]. The authors of this study noted that the addition of either the progression of AKIN stage or the cut off sCr ⩾ 1.5 mg/dL to the AKIN improved their prognostic accuracy[33]. A step forward in this evaluation was made by Fagundes *et al*[12] who proposed modified cirrhosis-AKI classification and validated it in 375 consecutive patients hospitalized for complications of cirrhosis. Patients with cirrhosis were categorized into three groups: (1) patients with AKI stage 1 and peak of sCr ⩽ 1.5 mg/dL; (2) Patients with AKI stage 1 and peak of sCr > 1.5 mg/dL; and (3) patients with AKI stage 2 or 3. By applying this modified classification a better risk stratification for patients with cirrhosis was achieved considering also the cause of AKI.

Serum Cystatin C (CysC) is another marker for evaluation of acute renal dysfunction preferably in female patients with progressive cirrhosis[34]. It has been shown that in this cirrhotic population (women with cirrhosis Child - Pugh score C)[34]. CysC presented high diagnostic sensitivity, greater than sCr in detection of acute renal impairment[34,35]. Indeed it was proved that CysC correlated with the severity of liver fibrosis and with the GFR better than sCr[35-37], but this has not been confirmed in other studies[38].

Table 2 Acute kidney injury network and risk, injury, failure, loss, and end stage criteria for the diagnosis of acute kidney injury[117]

AKIN criteria	Urine output	RIFLE criteria	
Serum creatinine	(common to both AKIN and RIFLE)	Class	Serum creatinine or GFR
Stage 1 Increase of more than or equal to 0.3 mg/dL (≥ 26.5 μmol/L) or increase to more than or equal to 150% to 199% (1.5- to 1.9-fold) from baseline	Less than 0.5 mL/kg per hour for more than 6 h	Risk	Increase in serum creatinine × 1.5 or GFR decrease > 25%
Stage 2 Increased to more than 200% to 300% (≥ 2- to 2.9-fold) from baseline	Less than 0.5 mL/kg per hour for more than 12 h	Injury	Serum creatinine × 2 or GFR decreased > 50%
Stage 3 Increased to more than 300% (≥ 3-fold) from baseline, or more than or equal to 4.0 mg/dL (≥ 354 μmol/L) with an acute increase of at least 0.5 mg/dL (44 μmol/L) or on RRT	Less than 0.3 mL/kg per hour for 24 h or anuria for 12 h	Failure	Serum creatinine × 3, or serum creatinine > 4 mg/dL (> 354 μmol/L) with an acute rise > 0.5 mg/dL (> 44 μmol/L) or GFR decreased > 75%
		Loss	Persistent acute renal failure = complete loss of kidney function > 4 wk
		End-stage kidney disease	ESRD > 3 mo

For conversion of creatinine expressed in SI units to mg/dl, divide by 88.4. For both AKIN stage and RIFLE criteria, only one criterion (creatinine rise or urine output decline) needs to be fulfilled. Class is based on the worst of either GFR or urine output criteria. GFR decrease is calculated from the increase in serum creatinine above baseline. For AKIN, the increase in creatinine must occur in < 48 h. For RIFLE, AKI should be both abrupt (within 1–7 d) and sustained (more than 24 h). AKI: Acute kidney injury; AKIN: Acute Kidney Injury Network; ESRD: End-stage renal disease; GFR: Glomerular filtration rate; RIFLE: Risk, injury, failure, loss, and end stage; RRT: Renal replacement therapy.

Promising information for acute kidney dysfunction in cirrhotic could be also derived from urine. A novel kidney biomarker associated with early detection of acute tubular injury is neutrophil gelatinase -associated lipocalin (NGAL) measured in blood and in urine. Many studies in several clinical situations[39-41] have underlined that the NGAL increased two hours after the induction of AKI, before of the sCr elevation. In cirrhotic patients, preliminary studies have reported that NGAL levels were higher in those with HRS[42] compared to those without renal disease; NGAL was associated with the prediction of short-term mortality[43,44] and it could be used for differentiation of prerenal azotemia, acute tubular necrosis and HRS[45]. Urinary NGAL has been found to be 20 ng/mL in healthy population and in prerenal azotemia, 105 ng/mL in HRS, 325 ng/mL in AKI and 50 ng/mL in CKD[44]. Furthermore, another powerful tool in renal disease detection could be the ratio of urinary sodium to potassium. If that ratio in a random urine sample of patients with decompensated cirrhosis and ascites is less than 1 the diagnosis of renal dysfunction (GFR < 60 mL/min) is possible[46]. Nevertheless all these findings require confirmation in additional studies.

Ultimately, encouraging method for early acute detection of renal hemodynamic disturbances of patients with cirrhosis showed the measurement of renal resistive index (RI) by renal duplex doppler ultrasound. In general, a RI more the 0.7 is indicative of renal failure, confirming high blood velocity waveform of renal artery and high peripheral arterial resistance[47]. In patients with cirrhosis RI over 0.7 has been predictor of renal dysfunction and HRS[48,49] and it has correlated significantly with MELD score, MELD-Na score, sCr and hyponatriemia as well[50]. In addition, it might demonstrate the progress of renal disease since it reached its highest levels in patients with refractory ascites compared with patients with compensated cirrhosis and those with diuretic responsive ascites[48]. Future research is needed to elucidate RI role in this patient population.

In regards to the evaluation of CKD, the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines have been suggested[9]. According to KDOQI[51], CKD is defined as a GFR of less than 60 mL/min for more than three months, calculated using the modified diet in renal disease (MDRD)-6 formula (Appendix 4) supporting its potential usefulness in the decision making for simultaneous liver and kidney transplantation. This hypothesis has been tested in patients with stable cirrhosis in the study of Francoz *et al*[52]. They showed that MDRD-6 formula was superior to MDRD-4 and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas identifying stable cirrhotic patients with markedly impaired renal function, including those with ascites (Table 3). However, MDRD-6 formula underestimated renal function in patients with GFR more than 30 mL/min subjecting them to possible unnecessary combined kidney and liver transplantation. Recently, CKD-EPI Cys C-Cr equation was shown to be the most accurate GFR-estimating formula compared to sCr or CysC-based formulas in cirrhosis. This formula was proposed to evaluate non AKI in cirrhosis until a brand, radical and specific for this population equation is discovered[53].

Accurate evaluation of renal function in cirrhotic patients, who are candidates for liver transplantation (LT) is crucial. Kidney disease is the key factor for determination of transplant status and highly affects the choice

Table 3 Formulas for estimating the glomerular filtration rate: modified diet in renal disease-4, modified diet in renal disease-6, chronic kidney disease epidemiology collaboration (mL/min per 1.73 m^2)[118-120]

MDRD-4 formula (1)	186 × [creatinine (mg/dL)] -1.154 × [age (yr)] 0.203 × (0.742 if patient is female) × (1.21 if patient is black)
MDRD-6 formula (2)	170 × sCr (mg/dL)-0.999 × age-0.176 × 1.180 (if black) × 0.762 (if female) × serum urea nitrogen-0.170 × albumin 0.138
CKD-EPI equation (3)	141 × min (sCr/κ, 1)α × max (sCr/κ, 1)-1.209 × 0.993 Age × 1.018 (if female) × 1.159 (if black)

MDRD: Modified diet in renal disease; CKD-EPI: Chronic kidney disease epidemiology collaboration.

of simultaneous kidney and renal transplantation, the initial immunosuppression and the survival of these patients[54-56]. GFR, sCr and serum sodium have been recognized as independent predictors of mortality in patients with decompensated cirrhosis[57,58]. In this case estimation of GFR should be made accurately by exogenous filtration markers. Particularly for patients with established HRS, a modification of MELD calculation has been proposed, to obtain patients with HRS the right priority in the waiting list, concerning that therapy can reduce their baseline MELD score[59]. According to this modification, the baseline MELD score before starting therapy should be used in patients with HRS who have been stabilized with therapy; the MELD score considering the pharmacological treatment as dialysis should be applied in patients with continuous recurrence of HRS and the highest MELD-Na over time should be received in patients with repeated recurrence of HRS type-2. Renal biopsy is advisable if GFR is between 30-60 mL/min and there are signs of parenchymal renal disease -hematuria (more the 50 red cells per high power field), proteinuria > 0.5 g/daily-and chronic renal abnormalities on the ground of comorbidities such as diabetes mellitus, hypertension and viral infection[15]. The detection of potential reversible renal disease and vascular lesions- hazardous for calcineurin-inhibitors nephrotoxicity- may be of value for the management before and after transplantation.

Kidney failure at admission or during ICU stay is a crude predictor of mortality in critically ill patients with cirrhosis. Despite supportive treatment measures, mortality was high and the risk for death was multiplied with the increasing severity of the kidney disease[1,60]. In this patient population, RIFLE classification presents the best predictive ability for ICU and hospital mortality[18,19]. The RIFLE denomination is an acronym which refers to risk (risk of renal dysfunction); injury (injury or damage to the kidney); failure (renal failure); loss (loss of kidney function); end (end stage renal disease) (Table 2). It was entered by Acute Dialysis Quality Initiative (ADQI) as an attempt to standardize the definition of acute renal failure and to describe the severity of AKI[61]. It allows the evaluation of the progression of renal injury as AKI is a dynamic process[62]. However, RIFLE score lack of a uniform approach in a patient population presenting with multiorgan failure, since it is focused only on kidney pathology. In keeping with this, a new score (MBRS) has been introduced combining four parameters: mean arterial pressure, bilirubin, respiratory failure and sepsis displayed an excellent area under the receiver operating characteristic curve (0.898 ± 0.031) for prognosis of mortality. This tool has been applied in a total of 301 critically ill cirrhotic patients[63,64] and proved that is an accurate, handy, user-friendly and low -cost scoring system. If it is above 2, cirrhotic patients should be prioritized for LT[64].

Overall, when it comes to evaluate renal function in patients with cirrhosis determination of AKI, CKD or AKI on CKD should be made. HRS diagnosis is the first which should be excluded by the algorithm of Angeli *et al*[5]. The acute renal function is proposed to be assessed with modified AKIN and the baseline renal function in stable patients with MDRD-6 formula or CKD-EPI Cys C-Cr equation. MBRS score or RIFLE criteria for AKI evaluation should be tried in critically ill cirrhotic patients, while in candidates for transplantation, GFR should be preferably measured with exogenous markers for accurate assessment of renal function. Serial plasma measurements with delayed sampling to allow equilibrium between plasma and intracellular space, especially ascitic fluid would give a more precise GFR[65]. All cirrhotic patients should undergo renal ultrasound for measurement of RI, in every stage of liver dysfunction and urine microscopy for differentiation of all causes of AKI. Renal biopsy should be performed when GFR is between 30-60 mL/min and there are signs of parenchymal renal disease (Table 4).

INACCURACIES OF RENAL ASSESSMENT STRATEGIES IN PATIENTS WITH CIRRHOSIS

Regarding the AKIN criteria, the urine volume cannot be applied in patients with cirrhosis since it may be markedly biased. Errors in the timing and the complete of urine collection are very common. Moreover, AKIN overestimate mortality, because they detect earlier patients with worse prognosis[32]. Since sCr cannot be removed from clinical practice, physicians should use it with caution in patients with advanced cirrhosis. The inadequacies of sCr are more pronounced in this patient group, due to high bilirubin and refractory ascites. The establishment of creatinine levels with enzymatic assays partially overcame this problem, but there are more expensive[66]. Similarly, none of the creatinine -based mathematical equations are precise acute markers for renal function evaluation in cirrhosis[67]. The body weight cannot be accurately estimated on the ground of ascites and edema, and there is disproportional high creatinine secretion from the tubules in regards to the level of creatinine filtered by the glomerulus[23]. Similarly, evidence has not clarified whether sCysC offers clear advantage comparing to sCr in all cirrhotic patients,

Table 4 Recomendations for renal function evaluation in subgroups of patients with cirrhosis

Differentiate prerenal kidney disease, hepatorenal syndrome and acute tubular necrosis	Angeli *et al*[5] algorithm
Acute kidney injury	Modified cirrhosis–acute kidney injury classification sCr increase ⩾ 0.3 mg/dL (⩾ 26.4 μmol/L) or more than 150% (1.5 fold from baseline) within 48 h from the first measurement[12]
Chronic kidney disease	KDOQI[49] guidelines Glomerular filtration rate below 60 mL/min for more than three months, calculated using the modified diet in renal disease-6 formula chronic kidney disease epidemiology collaboration Cys C-Cr equation[51]
Critically ill cirrhotic patients	RIFLE score[18,19] MBRS score[61,62] combining mean arterial pressure, bilirubin, respiratory failure and sepsis
Candidates for liver transplantation	Exogenous filtration markers If there is suspicion for parenchymal disease and Glomerular filtration rate is between 30-60 mL/min consider renal biopsy
Advanced cirrhosis	Cystatin C
Difficulties in differentiation of acute tubular necrosis	NGAL
All patients with cirrhosis in every stage of liver disease	Renal resistive index estimation by renal duplex doppler ultrasound

KDOQI: Kidney disease outcomes quality initiative.

neither improve the predictive power of MELD score[68]. sCysC may also be influenced by body composition, abnormal thyroid function, systemic inflammation and corticosteroid use, while its assay although easy applicable is of high cost[41]. In parallel substitution of sCr by sCysC did not improve the prognositic ability of MELD-score and creatinine -based equations[38,68]. Estimating GFR with the gold standard measures is the method of choice, but in every day routine is expensive, time-consuming, radioactivity transmitter and fatiguing[21]. Ultimately, renal biopsy is not easily applicable to patients with cirrhosis. Coagulation disorders are common in cirrhotic and the prolonged INR predispose to high risk of hemorrhages. In this situation, transjugular route is preferable than the percutaneous route, since it has been proved equivalent efficient[69]. Contraindications for biopsy are small size kidneys, large volume ascites and poor cortical differentiation[15].

MANAGEMENT OF RENAL FUNCTION IN PATIENTS WITH CIRRHOSIS

Research has made an enormous progress by finding treatment directions for HRS, which was previously fatal within a few days or weeks. However, no guidelines have been established for the treatment of patients with cirrhosis and kidney disease. Management options should be based on expert recommendations[9], proposed algorithms[33] and knowledge of the nature of renal disease[6,8]. It is essential to recognize early AKI - mainly diagnosis of HRS, which should be detected within 48 h, following the currently accepted guidelines[10,59] (Table 1) - to determine the chronic damage of the kidneys and to take the best measures for improving hepatic function. Patients with renal disease due to HRS, have much worse prognosis compared to patients with parenchymal renal disease[59]. Amelioration of the underlined liver disease is very impressive in patients with alcoholic liver disease after recovery from alcoholic hepatitis, therapy with baclofen[70] and in patients with decompensated cirrhosis due to hepatitis B virus infection after receiving antiviral therapy[71-73]. The choice of therapy depend upon the experience of the medical centre, the availability of certain drugs, the unit in which patient is admitted (ICU or not ICU) and whether the patient is a candidate for LV.

First line treatment

First line treatment should aim at the elimination of the potential pathophysiological factors resulting on HRS. Hemodynamic monitoring and management of fluid balance is essential for preventing the relative renal hypoperfusion, maintaining effective circulatory volume and renal perfusion pressure. Traditional measures of intravascular volume evaluation such as right atrial and pulmonary artery pressures are not considered inadequate for this patient group, so continuous central venous pressures and serial indirect or/and direct measurements of cardiac indices are preferable[9]. The current classification systems are helpful in early recognition of AKI indices and therefore withdrawing the potential causes of renal injury. Patients with AKIN stage 1 and sCr ⩾ 1.5 or initial AKIN stage > 1 should be at close monitoring and receive therapeutic measures for maximum two days[33]. These involve nephrotoxic medications-antibiotics and analgetics-, gastrointestinal bleeding and diuretics, which exacerbate hypovolemia and trigger sympathetic and renin-angiotensin-aldosterone system (RAAS). High level of suspicion is needed regarding the spontaneous bacterial peritonitis since infections very common trigger HRS. Moreover, albumin infusions will correct hypoalbuminemia and partial ascites evacuation will alleviate circulation[33,74]. In the setting of alcohol-related cirrhosis and ascites, the intestinal decontamination with rifaximin may also improve systemic hemodynamics and renal function[75]. If the clinical condition of congested patients (the groups previously mentioned) does not improve within two days, differential diagnosis with HRS should be done

Table 5 Recomendations for management of patients with cirrhosis

First line therapy	
Recognize and withdraw all causes of acute kidney disease	
Resolve primary liver disease	
Encounter hypoalbuminemia with albumin infusion and tension ascites with repeated paracentesis plus albumin	
Have a high level of suspicion and treat spontaneous bacterial peritonitis	
Be vigilant and have into close monitoring patients win acute kidney injury network stage 1 and sCr > 1.5 mg/dL (133 μmol/L) or initial acute kidney injury network stage > 1	
If there is no improvement within 2 d, proceed to specific treatment measures	
Second line therapy	
Patients hospitalized at the ward	If the diagnosis of hepatorenal syndrome has been placed: Give albumin and terlipressin in continuous infusion If there is improvement within 4 d continue with oral midrodrine When terlipressin is unavailable: Give midrodrine plus octreotide plus albumin
Patients admitted to intensive care unit	Norepinephrine plus albumin
Third line therapy	
Patients who qualify for transplant	Consider liver or simultaneous liver kidney transplantation Give therapeutic bridges – Dialysis, transjugular intrahepatic portosystemic shunt
Patients who do not qualify for transplant	Continue the combination of terlipressin plus albumin Dialysis, TIPS

and other specific regimens are required[5] (Table 5).

Second line treatment

Second line therapy encompasses measures undertaken after posing the diagnosis of HRS. The supportive measures are directed mainly into portal hypertension and arterial vasodilatation reversal. Albumin effusion combined with vasoconstrictors is the basic therapy for effective management of hypovolemia[5,9]. The main effect of albumin is the oncotic pressure increase resulting in volume expansion. However, albumin shows additional effects which make it extremely beneficial for patients with HRS. It shows metabolic, immune and vasoconstrictor effects, through binding of endotoxin, nitric oxide, bilirubin, bile acid and fatty acids[76,77] and improves cardiac output, through improvement of cardiac contractility, cardiac preload and volume expansion[78,79]. On the other side, terlipressin is an agonist of renal vasopressin V2 receptors, which reduce splachnic vasodilatation, increase the MAP and reduce the nitric oxide synthesis during sepsis[80]. The combination of them leads to renal function normalization in 34%-65% of cases[81,82], expends the number of patients undergoing LT[83], additionally improving their outcome[84] and it increases short -term survival by 34%-43%[82,85,86]; while it is hypothesized that ameliorates also tubular damage[5]. They have been applied in a special protocol which has shown efficacy in 59% of cases[87] and its discontinuation has been followed by HRS recurrence in 15%-22%[82,85,86,88-91]. The protocol has been proposed to be administered until there are signs of improvement, but not more than two weeks. The decrease of sCr <1.5 mg/dL (133 μmol/L) or the decrease of sCr > 50% but ⩾ 1.5 mg/dL (133 μmol/L), the decrease of bilirubin < 10mg/dL and the elevation of MAP ⩾ 5 mmHg at day 3 of treatment are the predictors of response[87,92,93]. If patient respond, some centers continue therapy with midodrine (an oral α1-adrenergic agonist with vasoconstrictive properties) indefinitely to keep higher MAP and to compensate refractory ascites[94]. If there is no improvement in renal function after two weeks, the protocol maybe repeated -there have been reports for protocol administration up to eight months[9,74,95,96] - or other interventional options are applied regarding the patient status and the available treatment options of the centre. Moreover, changes on terlipressin administration modality (given as continuous infusion instead of *iv* pulses) accounted for enhancement of its efficacy[5,97] (Table 6).

In some cases terlipressin is not applicable. These are when there are contraindications of its use, when there is not available and when the patient is admitted on ICU. In general, the contraindications of terlipressin use are ischemic cardiovascular disease, heart failure, arrhythmias, asthma, respiratory failure and heavy hyponatriemia[4]. Terlipressin use is limited in some countries because of its high cost and the lack of randomized trials proving superiority of terlipressin in comparison to other vasoconstrictors. When patients are admitted to ICU they usually treated with terlipressin[76,98-100] in patients being in ICU and because the cost of norepinephrine therapy is three times less than the cost of terlipressin[100]. Norepinephrine is difficult to be administered in the ward since it requires continuous intravenous infusion and hemodynamic monitoring, so instead of terlipressin, other vasoconstrictors maybe used in combination with albumin. These are octreotide, a synthetic analog of somatostatin and midodrine. However, the effect of octreotide, either used alone or with albumin, does not appear to be beneficial for renal function improvement[99,101] and midodrine alone or in combination with albumin has not been evaluated in patients with HRS type -1. Only when octreotide was used in conjunction with midodrine and albumin has normalized renal function in 49%[77,102,103], has increased MAP[77] and survival[102].

Table 6 Scheme for terlipressin and albumin administration[5,97]

Terlipressin is given as an intravenous bolus 1 to 2 mg every four to six hours	Albumin is given for two days as an intravenous bolus 1 g/kg per day (100 g maximum) followed by 25 to 50 g /d until terlipressin therapy is discontinued

Table 7 Published guidelines on selection criteria for simultaneous liver-kidney transplantation

Davis *et al*[121], 2007
Patients with CKD with CrCl (preferentially iothalamate) of ≤ 30 mL/min for > 3 mo
Patients with AKI and/or HRS on dialysis for ≥ 6 wk
Patients with prolonged AKI with kidney biopsy showing fixed renal damage
SLK was not recommended in patients with AKI not requiring dialysis
Eason *et al*[122], 2008
Patients with CKD with GFR ≤ 30 mL/min > 3 mo
Patients with AKI/HRS with sCr ≥ 2 mg/dL and on dialysis ≥ 8 wk
Patients with evidence of CKD and kidney biopsy with > 30% GS or 30% fibrosis
Other criteria that was recommended to be considered: Presence of co-morbidities: Diabetes, Hypertension, age > 65 yr, renal size and duration of sCr > 2 mg/dL
Nadim *et al*[123], 2012
Persistent AKI ≥ 4 wk with one of the following:
Increase Scr ≥ 3-fold from baseline or on dialysis
GFR ≤ 35 mL/min (MDRD-6) or ≤ 25 mL/min (iothalamate)
CKD ≥ 3 mo with one of the following:
eGFR ≤ 40 mL/min (MDRD-6) or ≤ 30 mL/min (iothalamate)
Proteinuria ≥ 2 g/d
Kidney biopsy showing > 30% GS or > 30% interstitial fibrosis
Note: Higher GFR threshold with MDRD-6 was to account for the approximate 30%- 40% overestimation that has been described when compared to iothalamate.

CKD: Chronic kidney disease; CrCl: Creatinine clearance; HRS: Hepatorenal syndrome; AKI: Acute kidney injury; SLK: Simultaneous Liver-Kidney; sCr: Serum creatinine; GFR: Glomerular filtration rate; GS: Glomerulosclerosis; MDRD-6: Modification of diet in renal disease formula calculated using six variables of serum creatinine, serum urea, serum albumin, age, gender.

Third line treatment

When pharmacological measures are insufficient, transplantation is the treatment of choice[8]. MELD score permits selection of patients needing liver transplant, while patients who are risk for not -recovery of renal function simultaneous kidney and liver transplant is required[9]. In the direction of combined liver and kidney transplantation leads the duration of HRS (more than four weeks), AKI on CKD, and baseline diseases (such as hypertension, diabetes and obesity) which predispose to kidney disease progression (Table 7). If the patient meets the requirements to be listed for transplant, dialysis and transjugular intrahepatic portosystemic shunt (TIPS) are the bridging therapies to keep the transplant candidate in the best clinical status. It is essential to resolve HRS since is associated with many perioperative complications and decreases patient survival.

In general, dialysis procedures have not improved the long -term survival in patients with HRS and they have been associated with high risk of blood pressure decline, hypothermia, bradycardia, tissue hypoxia and clotting[4]. That is why they are applied under special situations, when there are indications for reversibility of AKI, hyperkalemia, hypervolemia not responding to diuretics, severe metabolic acidosis, acute on chronic liver failure and fulminant liver failure[9,104,105]. The choice of modality [continuous renal replacement therapy, intermittent hemodialysis, Molecular Adsorbent Recirculating System (MARS)] depends on the abilities and the experience of the centre, while non standard anticoagulation measures are indicated. Schemes with saline flushing, minimal dose of heparin or minimal dose of citrates are preferable. Peritoneal dialysis may be another option to remove ascites and resolve cirrhosis complications, such as encephalopathy, without exposing patient to anticoagulation and to other dialysis complications[106,107].

TIPS is an intervention that enhances the return of blood in the right heart and resolve the reduced sympathetic and RAAS activity in HRS type Ⅱ, suggesting an improvement in systematic hemodynamics[108-110]. It is indicated in cirrhotic patients with refractory ascites requiring repeated paracentesis[109-112] because it has conferred positive impact on ascites and renal function amelioration. Nevertheless, it has not improved significantly mortality[113]. Furthermore, renal function improvement does not come fast, it comes after weeks or months[114], so very ill patients, without significant liver function reserve (INR > 2, bilirubin> 5 mg/dL or Child Plugh > 11), hepatic encephalopathy and cardiopulmonary disease[9] should not undergo it. Complications of TIPS procedure are high rates of encephalopathy, liver insufficiency, cardiac failure, infection of the stent and hemolysis[111,115]. In patients with HRS 1, preliminary studies[108,111] about TIPS showed improvement of renal function in parallel with survival, but it cannot be applied in clinical practice yet as a main treatment. At present, TIPS can be used in selected patients without severe liver dysfunction as a bridge for LT or in patients with stabilized liver function not enlisted, as a long term -therapy[74] (Table 5).

CONCLUSION

Patients with cirrhosis and renal failure are high-risk patients who can hardly be grouped to form precise instructions for diagnosis and treatment. AKI is a portentous manifestation of circulatory dysfunction on patients with cirrhosis, which has a detrimental impact on their recovery and survival. Close surveillance, well -classified definitions and scoring systems (AKIN, RIFLE) aim in early recognition of renal disease. Attempts are made to correlate non invasive biomarkers of kidney damage and kidney function (NGAL, sCysC) to pathological findings. Studies on better using pharmacological and interventional measures are underway promising better and quick recovery. Physicians should be updated on new therapeutic modalities, proposed recommendations and algorithms in order to translate them into clinical practice.

REFERENCES

1 **Cholongitas E**, Senzolo M, Patch D, Shaw S, O'Beirne J, Burroughs AK. Cirrhotics admitted to intensive care unit: the impact of acute renal failure on mortality. *Eur J Gastroenterol Hepatol* 2009; **21**: 744-750 [PMID: 20160527 DOI: 10.1097/MEG.0b013e328308bb9c]

2 **Garcia-Tsao G**, Parikh CR, Viola A. Acute kidney injury in cirrhosis. *Hepatology* 2008; **48**: 2064-2077 [PMID: 19003880 DOI: 10.1002/hep.22605]

3 **Ginès P**, Schrier RW. Renal failure in cirrhosis. *N Engl J Med* 2009; **361**: 1279-1290 [PMID: 19776409 DOI: 10.1056/NEJMra0809139]

4 **Hartleb M**, Gutkowski K. Kidneys in chronic liver diseases. *World J Gastroenterol* 2012; **18**: 3035-3049 [PMID: 22791939 DOI: 10.3748/wjg.v18.i24.3035]

5 **Angeli P**, Sanyal A, Moller S, Alessandria C, Gadano A, Kim R, Sarin SK, Bernardi M. Current limits and future challenges in the management of renal dysfunction in patients with cirrhosis: report from the International Club of Ascites. *Liver Int* 2013; **33**: 16-23 [PMID: 22507181 DOI: 10.1111/j.1478-3231.2012.02807]

6 **Mindikoglu AL**, Weir MR. Current concepts in the diagnosis and classification of renal dysfunction in cirrhosis. *Am J Nephrol* 2013; **38**: 345-354 [PMID: 24107793 DOI: 10.1159/000355540]

7 **Salerno F**, Gerbes A, Ginès P, Wong F, Arroyo V. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut* 2007; **56**: 1310-1318 [PMID: 17389705]

8 **Wong F**, O'Leary JG, Reddy KR, Patton H, Kamath PS, Fallon MB, Garcia-Tsao G, Subramanian RM, Malik R, Maliakkal B, Thacker LR, Bajaj JS. New consensus definition of acute kidney injury accurately predicts 30-day mortality in patients with cirrhosis and infection. *Gastroenterology* 2013; **145**: 1280-1288.e1 [PMID: 23999172 DOI: 10.1053/j.gastro.2013.08.051]

9 **Nadim MK**, Kellum JA, Davenport A, Wong F, Davis C, Pannu N, Tolwani A, Bellomo R, Genyk YS. Hepatorenal syndrome: the 8th International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2012; **16**: R23 [PMID: 22322077 DOI: 10.1186/cc11188]

10 **European Association for the Study of the Liver.** EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. *J Hepatol* 2010; **53**: 397-417 [PMID: 20633946 DOI: 10.1016/j.jhep.2010.05.004]

11 **Sersté T**, Francoz C, Durand F, Rautou PE, Melot C, Valla D, Moreau R, Lebrec D. Beta-blockers cause paracentesis-induced circulatory dysfunction in patients with cirrhosis and refractory ascites: a cross-over study. *J Hepatol* 2011; **55**: 794-799 [PMID: 21354230 DOI: 10.1016/j.jhep.2011.01.034]

12 **Fagundes C**, Barreto R, Guevara M, Garcia E, Solà E, Rodríguez E, Graupera I, Ariza X, Pereira G, Alfaro I, Cárdenas A, Fernández J, Poch E, Ginès P. A modified acute kidney injury classification for diagnosis and risk stratification of impairment of kidney function in cirrhosis. *J Hepatol* 2013; **59**: 474-481 [PMID: 23669284 DOI: 10.1016/j.jhep.2013.04.036]

13 **Wong F**, Massie D, Colman J, Dudley F. Glomerular hyperfiltration in patients with well-compensated alcoholic cirrhosis. *Gastroenterology* 1993; **104**: 884-889 [PMID: 8440439]

14 **De Waele JJ**, De Laet I, Kirkpatrick AW, Hoste E. Intra-abdominal Hypertension and Abdominal Compartment Syndrome. *Am J Kidney Dis* 2011; **57**: 159-169 [PMID: 21184922 DOI: 10.1053/j.ajkd.2010.08.034]

15 **Francoz C**, Glotz D, Moreau R, Durand F. The evaluation of renal function and disease in patients with cirrhosis. *J Hepatol* 2010; **52**: 605-613 [PMID: 20185192 DOI: 10.1016/j.jhep.2009.11.025]

16 **Badiou S**, Dupuy AM, Descomps B, Cristolead JP. Comparison between the enzymatic vitros assay for creatinine determination and three other methods adapted on the Olympus analyzer. *J Clin Lab Anal* 2003; **17**: 235-240 [PMID: 14614747 DOI: 10.1002/jcla.10103]

17 **Durand F**, Valla D. Assessment of prognosis of cirrhosis. *Semin Liver Dis* 2008; **28**: 110-122 [PMID: 18293281 DOI: 10.1055/s-2008-1040325]

18 **Cholongitas E**, Calvaruso V, Senzolo M, Patch D, Shaw S, O'Beirne J, Burroughs AK. RIFLE classification as predictive factor of mortality in patients with cirrhosis admitted to intensive care unit. *J Gastroenterol Hepatol* 2009; **24**: 1639-1647 [PMID: 19788604 DOI: 10.1111/j.1440-1746.2009.05908.x]

19 **Jenq CC**, Tsai MH, Tian YC, Lin CY, Yang C, Liu NJ, Lien JM, Chen YC, Fang JT, Chen PC, Yang CW. RIFLE classification can predict short-term prognosis in critically ill cirrhotic patients. *Intensive Care Med* 2007; **33**: 1921-1930 [PMID: 17605129 DOI: 10.1007/s00134-007-0760-6]

20 **Tu KH**, Jenq CC, Tsai MH, Hsu HH, Chang MY, Tian YC, Hung CC, Fang JT, Yang CW, Chen YC. Outcome scoring systems for short-term prognosis in critically ill cirrhotic patients. *Shock* 2011; **36**: 445-450 [PMID: 21841535 DOI: 10.1097/SHK.0b013e31822fb7e2]

21 **Cholongitas E**, Shusang V, Marelli L, Nair D, Thomas M, Patch D, Burns A, Sweny P, Burroughs AK. Review article: renal function assessment in cirrhosis - difficulties and alternative measurements. *Aliment Pharmacol Ther* 2007; **26**: 969-978 [PMID: 17877504 DOI: 10.1111/j.1365-2036.2007.03443.x]

22 **Wiesner R**, Edwards E, Freeman R, Harper A, Kim R, Kamath P, Kremers W, Lake J, Howard T, Merion RM, Wolfe RA, Krom R. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology* 2003; **124**: 91-96 [PMID: 12512033 DOI: 10.1053/gast.2003.50016]

23 **Cholongitas E**, Xirouchakis E, Garcovich M, Burroughs AK. Evaluation of renal function in patients with cirrhosis. *J Hepatol* 2010; **53**: 589 [PMID: 20452084 DOI: 10.1016/j.jhep.2010.02.018]

24 **Cholongitas E**, Marelli L, Kerry A, Goodier DW, Nair D, Thomas M, Patch D, Burroughs AK. Female liver transplant recipients with the same GFR as male recipients have lower MELD scores--a systematic bias. *Am J Transplant* 2007; **7**: 685-692 [PMID: 17217437 DOI: 10.1111/j.1600-6143.2007.01666.x]

25 **Cholongitas E**, Marelli L, Kerry A, Senzolo M, Goodier DW, Nair D, Thomas M, Patch D, Burroughs AK. Different methods of creatinine measurement significantly affect MELD scores. *Liver Transpl* 2007; **13**: 523-529 [PMID: 17323365 DOI: 10.1002/lt.20994]

26 **Sherman DS**, Fish DN, Teitelbaum I. Assessing renal function in cirrhotic patients: problems and pitfalls. *Am J*

Kidney Dis 2003; **41**: 269-278 [PMID: 12552488 DOI: 0.1053/ajkd.2003.50035]
27 **Cholongitas E**, Germani G, Burroughs AK. Prioritization for liver transplantation. *Nat Rev Gastroenterol Hepatol* 2010; **7**: 659-668 [PMID: 21045793 DOI: 10.1038/nrgastro.2010.169]
28 **Mehta RL**, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007; **11**: R31 [PMID: 17331245 DOI: 10.1186/cc5713]
29 **Cruz DN**, Bagshaw SM, Ronco C, Ricci Z. Acute kidney injury: classification and staging. *Contrib Nephrol* 2010; **164**: 24-32 [PMID: 20427990 DOI: 10.1159/000313717]
30 **Ricci Z**, Cruz D, Ronco C. The RIFLE criteria and mortality in acute kidney injury: A systematic review. *Kidney Int* 2008; **73**: 538-546 [PMID: 18160961]
31 **Belcher JM**, Garcia-Tsao G, Sanyal AJ, Bhogal H, Lim JK, Ansari N, Coca SG, Parikh CR. Association of AKI with mortality and complications in hospitalized patients with cirrhosis. *Hepatology* 2013; **57**: 753-762 [PMID: 22454364 DOI: 10.1002/hep.25735]
32 **de Carvalho JR**, Villela-Nogueira CA, Luiz RR, Guzzo PL, da Silva Rosa JM, Rocha E, Moraes Coelho HS, de Mello Perez R. Acute kidney injury network criteria as a predictor of hospital mortality in cirrhotic patients with ascites. *J Clin Gastroenterol* 2012; **46**: e21-e26 [PMID: 21934526 DOI: 10.1097/MCG.0b013e31822e8e12]
33 **Piano S**, Rosi S, Maresio G, Fasolato S, Cavallin M, Romano A, Morando F, Gola E, Frigo AC, Gatta A, Angeli P. Evaluation of the Acute Kidney Injury Network criteria in hospitalized patients with cirrhosis and ascites. *J Hepatol* 2013; **59**: 482-489 [PMID: 23665185 DOI: 10.1016/j.jhep.2013.03.039]
34 **Gerbes AL**, Gülberg V, Bilzer M, Vogeser M. Evaluation of serum cystatin C concentration as a marker of renal function in patients with cirrhosis of the liver. *Gut* 2002; **50**: 106-110 [PMID: 11772976]
35 **Seo YS**, Jung ES, An H, Kim JH, Jung YK, Kim JH, Yim HJ, Yeon JE, Byun KS, Kim CD, Ryu HS, Um SH. Serum cystatin C level is a good prognostic marker in patients with cirrhotic ascites and normal serum creatinine levels. *Liver Int* 2009; **29**: 1521-1527 [PMID: 19725889 DOI: 10.1111/j.1478-3231.2009.02105.x]
36 **Takeuchi M**, Fukuda Y, Nakano I, Katano Y, Hayakawa T. Elevation of serum cystatin C concentrations in patients with chronic liver disease. *Eur J Gastroenterol Hepatol* 2001; **13**: 951-955 [PMID: 11507361]
37 **Ustundag Y**, Samsar U, Acikgoz S, Cabuk M, Kiran S, Kulah E, Aydemir S. Analysis of glomerular filtration rate, serum cystatin C levels, and renal resistive index values in cirrhosis patients. *Clin Chem Lab Med* 2007; **45**: 890-894 [PMID: 17617033]
38 **Xirouchakis E**, Marelli L, Cholongitas E, Manousou P, Calvaruso V, Pleguezuelo M, Guerrini GP, Maimone S, Kerry A, Hajjawi M, Nair D, Thomas M, Patch D, Burroughs AK. Comparison of cystatin C and creatinine-based glomerular filtration rate formulas with 51Cr-EDTA clearance in patients with cirrhosis. *Clin J Am Soc Nephrol* 2011; **6**: 84-92 [PMID: 20829419 DOI: 10.2215/CJN.03400410]
39 **Haase M**, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A. Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. *Am J Kidney Dis* 2009; **54**: 1012-1024 [PMID: 19850388 DOI: 10.1053/j.ajkd.2009.07.020]
40 **Singer E**, Elger A, Elitok S, Kettritz R, Nickolas TL, Barasch J, Luft FC, Schmidt-Ott KM. Urinary neutrophil gelatinase-associated lipocalin distinguishes pre-renal from intrinsic renal failure and predicts outcomes. *Kidney Int* 2011; **80**: 405-414 [PMID: 21412214 DOI: 10.1038/ki.2011.41]
41 **Kokkoris S**, Pipili C, Grapsa E, Kyprianou T, Nanas S. Novel biomarkers of acute kidney injury in the general adult ICU: a review. *Ren Fail* 2013; **35**: 579-591 [PMID: 23472851 DOI: 10.3109/0886022X.2013.773835]
42 **Cavallin M,** Fasolato S, Sticca A, Gola E, Bortoluzzi A, Gatta A, Angeli P. Increased urinary level of neutrophil gelatinase-associated lipocalin (NGAL) in patients with cirrhosis and type 1 HRS. *Hepatology* 2011; **54**: 1254A-1255A [DOI: 10.1002/hep.24666]
43 **Gungor G**, Ataseven H, Demir A, Solak Y, Gaipov A, Biyik M, Ozturk B, Polat I, Kiyici A, Cakir OO, Polat H. Neutrophil gelatinase-associated lipocalin in prediction of mortality in patients with hepatorenal syndrome: a prospective observational study. *Liver Int* 2014; **34**: 49-57 [PMID: 23799980 DOI: 10.1111/liv.12232]
44 **Verna EC**, Brown RS, Farrand E, Pichardo EM, Forster CS, Sola-Del Valle DA, Adkins SH, Sise ME, Oliver JA, Radhakrishnan J, Barasch JM, Nickolas TL. Urinary neutrophil gelatinase-associated lipocalin predicts mortality and identifies acute kidney injury in cirrhosis. *Dig Dis Sci* 2012; **57**: 2362-2370 [PMID: 22562534 DOI: 10.1007/s10620-012-2180-x]
45 **Fagundes C**, Pépin MN, Guevara M, Barreto R, Casals G, Solà E, Pereira G, Rodríguez E, Garcia E, Prado V, Poch E, Jiménez W, Fernández J, Arroyo V, Ginès P. Urinary neutrophil gelatinase-associated lipocalin as biomarker in the differential diagnosis of impairment of kidney function in cirrhosis. *J Hepatol* 2012; **57**: 267-273 [PMID: 22521351 DOI: 10.1016/j.jhep.2012.03.015]
46 **Cholongitas E**, Goulis J, Arsos G, Birtsou C, Nakouti T, Papadopoulou S, Chalevas P, Karakatsanis K, Akriviadis E. Association between ratio of sodium to potassium in random urine samples and renal dysfunction and mortality in patients with decompensated cirrhosis. *Clin Gastroenterol Hepatol* 2013; **11**: 862-867 [PMID: 23403009 DOI: 10.1016/j.cgh.2013.02.005]
47 **Platt JF**, Rubin JM, Ellis JH. Acute renal failure: possible role of duplex Doppler US in distinction between acute prerenal failure and acute tubular necrosis. *Radiology* 1991; **179**: 419-423 [PMID: 2014284]
48 **Fouad YM**, Mokarrab H, Elgebaly AF, El-Amin H, Abdel-Raheem EM, Sharawy MA, Shatat ME. Renal duplex Doppler ultrasound in patients with HCV related liver cirrhosis. *Trop Gastroenterol* 2009; **30**: 213-218 [PMID: 20426281]
49 **Kastelan S**, Ljubicic N, Kastelan Z, Ostojic R, Uravic M. The role of duplex-doppler ultrasonography in the diagnosis of renal dysfunction and hepatorenal syndrome in patients with liver cirrhosis. *Hepatogastroenterology* 2004; **51**: 1408-1412 [PMID: 15362765]
50 **Umbro I**, Tinti F, Fiacco F, Zavatto A, Piselli P, Di Natale V, Lai S, Vitarelli A, Corradini SG, Rossi M, Poli L, Berloco PB, Mitterhofer AP. Resistive index and MELD-Na: nephrologic monitoring in cirrhotic patients awaiting liver transplantation. *Transplant Proc* 2013; **45**: 2676-2679 [PMID: 24034022 DOI: 10.1016/j.transproceed.2013.07.040]
51 **National Kidney Foundation.** K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002; **39**: S1-266 [PMID: 11904577]
52 **Francoz C**, Nadim MK, Baron A, Prié D, Antoine C, Belghiti J, Valla D, Moreau R, Durand F. Glomerular filtration rate equations for liver-kidney transplantation in patients with cirrhosis: validation of current recommendations. *Hepatology* 2014; **59**: 1514-1521 [PMID: 24037821 DOI: 10.1002/hep.26704]
53 **Mindikoglu AL**, Dowling TC, Weir MR, Seliger SL, Christenson RH, Magder LS. Performance of chronic kidney disease epidemiology collaboration creatinine-cystatin C equation for estimating kidney function in cirrhosis. *Hepatology* 2014; **59**: 1532-1542 [PMID: 23744636 DOI: 10.1002/hep.26556]

54 **Davis CL**, Gonwa TA, Wilkinson AH. Identification of patients best suited for combined liver-kidney transplantation: part II. *Liver Transpl* 2002; **8**: 193-211 [PMID: 11910564]

55 **Emre S**, Gondolesi G, Polat K, Ben-Haim M, Artis T, Fishbein TM, Sheiner PA, Kim-Schluger L, Schwartz ME, Miller CM. Use of daclizumab as initial immunosuppression in liver transplant recipients with impaired renal function. *Liver Transpl* 2001; **7**: 220-225 [PMID: 11244163 DOI: 10.1053/jlts.2001.22455]

56 **Nair S**, Verma S, Thuluvath PJ. Pretransplant renal function predicts survival in patients undergoing orthotopic liver transplantation. *Hepatology* 2002; **35**: 1179-1185 [PMID: 11981768 DOI: 10.1053/jhep.2002.33160]

57 **Cholongitas E,** Arsos G, Goulis J, Birtsou C, Haidich AB, Nakouti T, Chalevas P, Ioannidou M, Karakatsanis K, Akriviadis E. Glomerular filtration rate is an independent factor of mortality in patients with decompensated cirrhosis. *Hepatol Res* 2013 Oct 11; Epub ahead of print [PMID: 24119148 DOI: 10.1111/hepr.12259]

58 **Lim YS**, Larson TS, Benson JT, Kamath PS, Kremers WK, Therneau TM, Kim WR. Serum sodium, renal function, and survival of patients with end-stage liver disease. *J Hepatol* 2010; **52**: 523-528 [PMID: 20185195 DOI: 10.1016/j.jhep.2010.01.009]

59 **Angeli P**, Gines P. Hepatorenal syndrome, MELD score and liver transplantation: an evolving issue with relevant implications for clinical practice. *J Hepatol* 2012; **57**: 1135-1140 [PMID: 22749942 DOI: 10.1016/j.jhep.2012.06.024]

60 **du Cheyron D**, Bouchet B, Parienti JJ, Ramakers M, Charbonneau P. The attributable mortality of acute renal failure in critically ill patients with liver cirrhosis. *Intensive Care Med* 2005; **31**: 1693-1699 [PMID: 16244877 DOI: 10.1007/s00134-005-2842-7]

61 **Bellomo R**, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004; **8**: R204-R212 [PMID: 15312219 DOI: 10.1186/cc2872]

62 **Bagshaw SM**, George C, Dinu I, Bellomo R. A multi-centre evaluation of the RIFLE criteria for early acute kidney injury in critically ill patients. *Nephrol Dial Transplant* 2008; **23**: 1203-1210 [PMID: 17962378 DOI: 10.1093/ndt/gfm744]

63 **Fang JT**, Tsai MH, Tian YC, Jenq CC, Lin CY, Chen YC, Lien JM, Chen PC, Yang CW. Outcome predictors and new score of critically ill cirrhotic patients with acute renal failure. *Nephrol Dial Transplant* 2008; **23**: 1961-1969 [PMID: 18187499 DOI: 10.1093/ndt/gfm914]

64 **Pan HC**, Jenq CC, Tsai MH, Fan PC, Chang CH, Chang MY, Tian YC, Hung CC, Fang JT, Yang CW, Chen YC. Risk models and scoring systems for predicting the prognosis in critically ill cirrhotic patients with acute kidney injury: a prospective validation study. *PLoS One* 2012; **7**: e51094 [PMID: 23236437 DOI: 10.1371/journal.pone.0051094]

65 **Davenport A**, Cholongitas E, Xirouchakis E, Burroughs AK. Pitfalls in assessing renal function in patients with cirrhosis--potential inequity for access to treatment of hepatorenal failure and liver transplantation. *Nephrol Dial Transplant* 2011; **26**: 2735-2742 [PMID: 21690201 DOI: 10.1093/ndt/gfr354]

66 **Delanghe JR**, Cobbaert C, Harmoinen A, Jansen R, Laitinen P, Panteghini M. Focusing on the clinical impact of standardization of creatinine measurements: a report by the EFCC Working Group on Creatinine Standardization. *Clin Chem Lab Med* 2011; **49**: 977-982 [PMID: 21428858 DOI: 10.1515/CCLM.2011.167]

67 **Francoz C**, Prié D, Abdelrazek W, Moreau R, Mandot A, Belghiti J, Valla D, Durand F. Inaccuracies of creatinine and creatinine-based equations in candidates for liver transplantation with low creatinine: impact on the model for end-stage liver disease score. *Liver Transpl* 2010; **16**: 1169-1177 [PMID: 20879015 DOI: 10.1002/lt.22128]

68 **Finkenstedt A**, Dorn L, Edlinger M, Prokop W, Risch L, Griesmacher A, Graziadei I, Vogel W, Zoller H. Cystatin C is a strong predictor of survival in patients with cirrhosis: is a cystatin C-based MELD better? *Liver Int* 2012; **32**: 1211-1216 [PMID: 22380485 DOI: 10.1111/j.1478-3231.2012.02766.x]

69 **Cluzel P**, Martinez F, Bellin MF, Michalik Y, Beaufils H, Jouanneau C, Lucidarme O, Deray G, Grenier PA. Transjugular versus percutaneous renal biopsy for the diagnosis of parenchymal disease: comparison of sampling effectiveness and complications. *Radiology* 2000; **215**: 689-693 [PMID: 10831685 DOI: 10.1148/radiology.215.3.r00ma07689]

70 **Runyon BA**. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. *Hepatology* 2013; **57**: 1651-1653 [PMID: 23463403 DOI: 10.1002/hep.26359]

71 **Veldt BJ**, Lainé F, Guillygomarc'h A, Lauvin L, Boudjema K, Messner M, Brissot P, Deugnier Y, Moirand R. Indication of liver transplantation in severe alcoholic liver cirrhosis: quantitative evaluation and optimal timing. *J Hepatol* 2002; **36**: 93-98 [PMID: 11804670 DOI: 10.1016/S0168-8278(01)00228-8]

72 **Villeneuve JP**, Condreay LD, Willems B, Pomier-Layrargues G, Fenyves D, Bilodeau M, Leduc R, Peltekian K, Wong F, Margulies M, Heathcote EJ. Lamivudine treatment for decompensated cirrhosis resulting from chronic hepatitis B. *Hepatology* 2000; **31**: 207-210 [PMID: 10613747 DOI: 10.1002/hep.510310130]

73 **Papatheodoridis GV**, Cholongitas E, Archimandritis AJ, Burroughs AK. Current management of hepatitis B virus infection before and after liver transplantation. *Liver Int* 2009; **29**: 1294-1305 [PMID: 19619264 DOI: 10.1111/j.1478-3231.2009.02085.x]

74 **Lata J**. Hepatorenal syndrome. *World J Gastroenterol* 2012; **18**: 4978-4984 [PMID: 23049205 DOI: 10.3748/wjg.v18.i36.4978]

75 **Kalambokis GN**, Mouzaki A, Rodi M, Pappas K, Fotopoulos A, Xourgia X, Tsianos EV. Rifaximin improves systemic hemodynamics and renal function in patients with alcohol-related cirrhosis and ascites. *Clin Gastroenterol Hepatol* 2012; **10**: 815-818 [PMID: 22391344 DOI: 10.1016/j.cgh.2012.02.025]

76 **Alessandria C**, Ottobrelli A, Debernardi-Venon W, Todros L, Cerenzia MT, Martini S, Balzola F, Morgando A, Rizzetto M, Marzano A. Noradrenalin vs terlipressin in patients with hepatorenal syndrome: a prospective, randomized, unblinded, pilot study. *J Hepatol* 2007; **47**: 499-505 [PMID: 17560680 DOI: 10.1016/j.jhep.2007.04.010]

77 **Angeli P**, Volpin R, Gerunda G, Craighero R, Roner P, Merenda R, Amodio P, Sticca A, Caregaro L, Maffei-Faccioli A, Gatta A. Reversal of type 1 hepatorenal syndrome with the administration of midodrine and octreotide. *Hepatology* 1999; **29**: 1690-1697 [PMID: 10347109 DOI: 10.1002/hep.510290629]

78 **Sort P**, Navasa M, Arroyo V, Aldeguer X, Planas R, Ruizdel-Arbol L, Castells L, Vargas V, Soriano G, Guevara M, Ginès P, Rodés J. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med* 1999; **341**: 403-409 [PMID: 10432325 DOI: 10.1056/NEJM199908053410603]

79 **Papparella I,** I Cavalli M, Sticca A, Franco L, Bova S, Semplicini A, Gatta A, Angeli P. First evidence that albumin can directly improve cardiac contractility in cirrhotic rats. *Hepatology* 2007; **46** (Suppl 1): 865A-866a [DOI: 10.1002/hep.22022]

80 **Fernández J**, Navasa M, Garcia-Pagan JC, G-Abraldes J, Jiménez W, Bosch J, Arroyo V. Effect of intravenous albumin on systemic and hepatic hemodynamics and vasoactive neurohormonal systems in patients with cirrhosis and spontaneous bacterial peritonitis. *J Hepatol* 2004; **41**: 384-390 [PMID: 15336440 DOI: 10.1016/j.jhep.2004.05.009]

81 **Martín-Llahí M**, Pépin MN, Guevara M, Díaz F, Torre A, Monescillo A, Soriano G, Terra C, Fábrega E, Arroyo V, Rodés J, Ginès P. Terlipressin and albumin vs albumin in patients with cirrhosis and hepatorenal syndrome: a randomized study. *Gastroenterology* 2008; **134**: 1352-1359 [PMID: 18471512 DOI: 10.1053/j.gastro.2008.02.024]

82 **Sanyal AJ**, Boyer T, Garcia-Tsao G, Regenstein F, Rossaro L, Appenrodt B, Blei A, Gülberg V, Sigal S, Teuber P. A randomized, prospective, double-blind, placebo-controlled trial of terlipressin for type 1 hepatorenal syndrome. *Gastroenterology* 2008; **134**: 1360-1368 [PMID: 18471513 DOI: 10.1053/j.gastro.2008.02.014]

83 **Angeli P**. Review article: prognosis of hepatorenal syndrome--has it changed with current practice? *Aliment Pharmacol Ther* 2004; **20** Suppl 3: 44-46; discussion 47-48 [PMID: 15335400 DOI: 10.1111/j.1365-2036.2004.02113.x]

84 **Restuccia T**, Gomez-Anson B, Guevara M, Alessandria C, Torre A, Alayrach ME, Terra C, Martin M, Castellvi M, Rami L et al: Effects of dilutional hyponatremia on brain organic osmolytes and water content in patients with cirrhosis. *Hepatology* 2004; **39**: 1613-1622 [DOI: 10.1002/hep.20237]

85 **Fabrizi F**, Dixit V, Messa P, Martin P. Terlipressin for hepatorenal syndrome: A meta-analysis of randomized trials. *Int J Artif Organs* 2009; **32**: 133-140 [PMID: 19440988]

86 **Triantos CK**, Samonakis D, Thalheimer U, Cholongitas E, Senzolo M, Marelli L, Leandro G, Patch D, Burroughs AK. Terlipressin therapy for renal failure in cirrhosis. *Eur J Gastroenterol Hepatol* 2010; **22**: 481-486 [PMID: 19952764 DOI: 10.1097/MEG.0b013e3283345524]

87 **Rajekar H**, Chawla Y. Terlipressin in hepatorenal syndrome: Evidence for present indications. *J Gastroenterol Hepatol* 2011; **26** Suppl 1: 109-114 [PMID: 21199521 DOI: 10.1111/j.1440-1746.2010.06583.x]

88 **Dobre M**, Demirjian S, Sehgal AR, Navaneethan SD. Terlipressin in hepatorenal syndrome: a systematic review and meta-analysis. *Int Urol Nephrol* 2011; **43**: 175-184 [PMID: 20306131 DOI: 10.1007/s11255-010-9725-8]

89 **Gluud LL**, Christensen K, Christensen E, Krag A. Systematic review of randomized trials on vasoconstrictor drugs for hepatorenal syndrome. *Hepatology* 2010; **51**: 576-584 [PMID: 19885875 DOI: 10.1002/hep.23286]

90 **Sagi SV**, Mittal S, Kasturi KS, Sood GK. Terlipressin therapy for reversal of type 1 hepatorenal syndrome: a meta-analysis of randomized controlled trials. *J Gastroenterol Hepatol* 2010; **25**: 880-885 [PMID: 20074149 DOI: 10.1111/j.1440-1746.2009.06132.x]

91 **Solà E**, Lens S, Guevara M, Martín-Llahí M, Fagundes C, Pereira G, Pavesi M, Fernández J, González-Abraldes J, Escorsell A, Mas A, Bosch J, Arroyo V, Ginès P. Hyponatremia in patients treated with terlipressin for severe gastrointestinal bleeding due to portal hypertension. *Hepatology* 2010; **52**: 1783-1790 [PMID: 20931555 DOI: 10.1002/hep.23893]

92 **Boyer TD**, Sanyal AJ, Garcia-Tsao G, Blei A, Carl D, Bexon AS, Teuber P. Predictors of response to terlipressin plus albumin in hepatorenal syndrome (HRS) type 1: relationship of serum creatinine to hemodynamics. *J Hepatol* 2011; **55**: 315-321 [PMID: 21167235 DOI: 10.1016/j.jhep.2010.11.020]

93 **Nazar A**, Pereira GH, Guevara M, Martín-Llahi M, Pepin MN, Marinelli M, Solá E, Baccaro ME, Terra C, Arroyo V, Ginès P. Predictors of response to therapy with terlipressin and albumin in patients with cirrhosis and type 1 hepatorenal syndrome. *Hepatology* 2010; **51**: 219-226 [PMID: 19877168 DOI: 10.1002/hep.23283]

94 **Singh V**, Dhungana SP, Singh B, Vijayverghia R, Nain CK, Sharma N, Bhalla A, Gupta PK. Midodrine in patients with cirrhosis and refractory or recurrent ascites: a randomized pilot study. *J Hepatol* 2012; **56**: 348-354 [PMID: 21749847 DOI: 10.1016/j.jhep.2011.04.027]

95 **Caraceni P**, Santi L, Mirici F, Montanari G, Bevilacqua V, Pinna AD, Bernardi M. Long-term treatment of hepatorenal syndrome as a bridge to liver transplantation. *Dig Liver Dis* 2011; **43**: 242-245 [PMID: 20833118 DOI: 10.1016/j.dld.2010.08.001]

96 **Piano S**, Morando F, Fasolato S, Cavallin M, Boscato N, Boccagni P, Zanus G, Cillo U, Gatta A, Angeli P. Continuous recurrence of type 1 hepatorenal syndrome and long-term treatment with terlipressin and albumin: a new exception to MELD score in the allocation system to liver transplantation? *J Hepatol* 2011; **55**: 491-496 [PMID: 21334405 DOI: 10.1016/j.jhep.2011.02.002]

97 **Morelli A**, Ertmer C, Lange M, Westphal M. Continuous terlipressin infusion in patients with septic shock: less may be best, and the earlier the better? *Intensive Care Med* 2007; **33**: 1669-1670 [PMID: 17530219 DOI: 10.1007/s00134-007-0676-1]

98 **Duvoux C**, Zanditenas D, Hézode C, Chauvat A, Monin JL, Roudot-Thoraval F, Mallat A, Dhumeaux D. Effects of noradrenalin and albumin in patients with type I hepatorenal syndrome: a pilot study. *Hepatology* 2002; **36**: 374-380 [PMID: 12143045 DOI: 10.1053/jhep.2002.34343]

99 **Kiser TH**, Fish DN, Obritsch MD, Jung R, MacLaren R, Parikh CR. Vasopressin, not octreotide, may be beneficial in the treatment of hepatorenal syndrome: a retrospective study. *Nephrol Dial Transplant* 2005; **20**: 1813-1820 [PMID: 15956066 DOI: 10.1093/ndt/gfh930]

100 **Singh V**, Ghosh S, Singh B, Kumar P, Sharma N, Bhalla A, Sharma AK, Choudhary NS, Chawla Y, Nain CK. Noradrenaline vs. terlipressin in the treatment of hepatorenal syndrome: a randomized study. *J Hepatol* 2012; **56**: 1293-1298 [PMID: 22322237 DOI: 10.1016/j.jhep.2012.01.012]

101 **Pomier-Layrargues G**, Paquin SC, Hassoun Z, Lafortune M, Tran A. Octreotide in hepatorenal syndrome: a randomized, double-blind, placebo-controlled, crossover study. *Hepatology* 2003; **38**: 238-243 [PMID: 12830007 DOI: 10.1053/jhep.2003.50276]

102 **Esrailian E**, Pantangco ER, Kyulo NL, Hu KQ, Runyon BA. Octreotide/Midodrine therapy significantly improves renal function and 30-day survival in patients with type 1 hepatorenal syndrome. *Dig Dis Sci* 2007; **52**: 742-748 [PMID: 17235705 DOI: 10.1007/s10620-006-9312-0]

103 **Wong F**, Pantea L, Sniderman K. Midodrine, octreotide, albumin, and TIPS in selected patients with cirrhosis and type 1 hepatorenal syndrome. *Hepatology* 2004; **40**: 55-64 [PMID: 15239086 DOI: 10.1002/hep.20262]

104 **Davenport A**. Management of acute kidney injury in liver disease. *Contrib Nephrol* 2010; **165**: 197-205 [PMID: 20427970 DOI: 10.1159/000313759]

105 **Wong F**, Nadim MK, Kellum JA, Salerno F, Bellomo R, Gerbes A, Angeli P, Moreau R, Davenport A, Jalan R, Ronco C, Genyk Y, Arroyo V. Working Party proposal for a revised classification system of renal dysfunction in patients with cirrhosis. *Gut* 2011; **60**: 702-709 [PMID: 21325171 DOI: 10.1136/gut.2010.236133]

106 **Mackelaite L**, Alsauskas ZC, Ranganna K. Renal failure in patients with cirrhosis. *Med Clin North Am* 2009; **93**: 855-869, viii [PMID: 19577118 DOI: 10.1016/j.mcna.2009.03.003]

107 **Pipili C**, Polydorou A, Pantelias K, Korfiatis P, Nikolakopoulos F, Grapsa E. Improvement of hepatic encephalopathy by application of peritoneal dialysis in a patient with non-end-stage renal disease. *Perit Dial Int* 2013; **33**: 213-216 [PMID: 23478376 DOI: 10.3747/pdi.2011.00271]

108 **Guevara M**, Ginès P, Bandi JC, Gilabert R, Sort P, Jiménez W, Garcia-Pagan JC, Bosch J, Arroyo V, Rodés J. Transjugular intrahepatic portosystemic shunt in hepatorenal syndrome: effects on renal function and vasoactive systems. *Hepatology* 1998; **28**: 416-422 [PMID: 9696006 DOI: 10.1002/hep.510280219]

109 **Quiroga J**, Sangro B, Núñez M, Bilbao I, Longo J, García-Villarreal L, Zozaya JM, Betés M, Herrero JI, Prieto J. Transjugular intrahepatic portal-systemic shunt in the treatment

of refractory ascites: effect on clinical, renal, humoral, and hemodynamic parameters. *Hepatology* 1995; **21**: 986-994 [PMID: 7705810 DOI: 10.1016/0270-9139(95)90245-7]

110 **Wong F**, Sniderman K, Liu P, Allidina Y, Sherman M, Blendis L. Transjugular intrahepatic portosystemic stent shunt: effects on hemodynamics and sodium homeostasis in cirrhosis and refractory ascites. *Ann Intern Med* 1995; **122**: 816-822 [PMID: 7741365 DOI: 10.7326/0003-4819-122-11-199506010-00002]

111 **Brensing KA**, Textor J, Perz J, Schiedermaier P, Raab P, Strunk H, Klehr HU, Kramer HJ, Spengler U, Schild H, Sauerbruch T. Long term outcome after transjugular intrahepatic portosystemic stent-shunt in non-transplant cirrhotics with hepatorenal syndrome: a phase II study. *Gut* 2000; **47**: 288-295 [PMID: 10896924 DOI: 10.1136/gut.47.2.288]

112 **Somberg KA**, Lake JR, Tomlanovich SJ, LaBerge JM, Feldstein V, Bass NM. Transjugular intrahepatic portosystemic shunts for refractory ascites: assessment of clinical and hormonal response and renal function. *Hepatology* 1995; **21**: 709-716 [PMID: 7875668 DOI: 10.1016/0270-9139(95)90522-7]

113 **Testino G**, Ferro C, Sumberaz A, Messa P, Morelli N, Guadagni B, Ardizzone G, Valente U. Type-2 hepatorenal syndrome and refractory ascites: role of transjugular intrahepatic portosystemic stent-shunt in eighteen patients with advanced cirrhosis awaiting orthotopic liver transplantation. *Hepatogastroenterology* 2003; **50**: 1753-1755 [PMID: 14696397]

114 **Wong F**, Sniderman K, Liu P, Blendis L. The mechanism of the initial natriuresis after transjugular intrahepatic portosystemic shunt. *Gastroenterology* 1997; **112**: 899-907 [PMID: 9041252 DOI: 10.1053/gast.1997.v112.pm9041252]

115 **Martinet JP**, Fenyves D, Legault L, Roy L, Dufresne MP, Spahr L, Lafortune M, Pomier-Layrargues G. Treatment of refractory ascites using transjugular intrahepatic portosystemic shunt (TIPS): a caution. *Dig Dis Sci* 1997; **42**: 161-166 [PMID: 9009133]

116 **Arroyo V**, Ginès P, Gerbes AL, Dudley FJ, Gentilini P, Laffi G, Reynolds TB, Ring-Larsen H, Schölmerich J. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club. *Hepatology* 1996; **23**: 164-176 [PMID: 8550036]

117 **KDIGO.** Clinical Practice Guideline for Acute Kidney Injury. *Kidney Inter Suppl* 2012; **2**: 19-36 [DOI: 10.1038/kisup.2011.32]

118 **Levey AS**, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006; **145**: 247-254 [PMID: 16908915 DOI: 10.7326/0003-4819-145-4-200608150-00004]

119 **Lewis EJ**, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med* 1993; **329**: 1456-1462 [PMID: 8413456]

120 **Levey AS**, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150**: 604-612 [PMID: 19414839]

121 **Davis CL**, Feng S, Sung R, Wong F, Goodrich NP, Melton LB, Reddy KR, Guidinger MK, Wilkinson A, Lake J. Simultaneous liver-kidney transplantation: evaluation to decision making. *Am J Transplant* 2007; **7**: 1702-1709 [PMID: 17532752]

122 **Eason JD**, Gonwa TA, Davis CL, Sung RS, Gerber D, Bloom RD. Proceedings of Consensus Conference on Simultaneous Liver Kidney Transplantation (SLK). *Am J Transplant* 2008; **8**: 2243-2251 [PMID: 18808402 DOI: 10.1111/j.1600-6143.2008.02416.x]

123 **Nadim MK**, Sung RS, Davis CL, Andreoni KA, Biggins SW, Danovitch GM, Feng S, Friedewald JJ, Hong JC, Kellum JA, Kim WR, Lake JR, Melton LB, Pomfret EA, Saab S, Genyk YS. Simultaneous liver-kidney transplantation summit: current state and future directions. *Am J Transplant* 2012; **12**: 2901-2908 [PMID: 22822723 DOI: 10.1111/j.1600-6143.2012.04190.x]

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MINIREVIEWS

Inflammatory bowel diseases: Current problems and future tasks

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Abstract

Current knowledge on inflammatory bowel disease (IBD) is mainly endorsed by controlled trials and epidemiologic studies. Yet, we seldom look at the messages from real-world practice. Among a patient population followed since 2008, we looked at an unselected sample of 64 IBD patients [26 Crohn's disease (CD) and 38 ulcerative colitis (UC)] who had been seen as out-patients in the last year. Inducing remission, mesalamines (86% for UC/69% for CD/33%-16% as MMX formulation) prevailed as prescriptions; steroids (55%/19% for UC/CD) ranked second. Prescription of third-party drugs (antibiotics, NSAIDs, biologics) and adherence, were issues in the maintenance. 34% of CD, and 23% of UC patients showed accompanying immunologic diseases: CD-associated familiar psoriasis (4:9) ranked first. Main Message. The association between IBD (CD mainly) and psoriasis, now found in our practice, matches current basic science gathering IBD together with psoriasis (and perhaps chronic respiratory disease) under the comprehensive term "barrier organ disease" wherein an epithelial surface with sensor systems rules contacts between outer antigens and a reactive underneath tissue, with the balance between inflammation and quiescence kept at any time by mucosal permeability. IBD is thus viewed as a polyfactorial/polygenic/syndromic disorder, embedded into a galaxy of immune conditions offering multiple points of attack. This mindset of splitting the IBDs into pathogenic categories may allow overcoming the uniformly targeting of a single cytokine by biological drugs, in favor of demarcating the boundaries between different disease-subtype-specific indications, and paving the way to future personalized strategies.

Key words: Inflammatory bowel disease; Immunopharmacology; Barrier organs; Future trends in inflammatory bowel disease; Microbiome

Core tip: Long after their description, ulcerative colitis and Crohn's disease (IBD) are still treated but not cured. This somber spell has now begun to be broken by genetic discoveries and by the study of the human microbiome. The former have uncovered hundreds of genetic variants lending support to the clinical hint that IBD is a syndrome encompassing discrete polymorphisms of the immune response pathways, each requiring a personalized approach. The latter has shown the microbiome to be a cell universe which, if disrupted, can provoke IBD together with a myriad of disturbances apparently unrelated with the gut. A frame of mind seeing the IBDS as embedded into a plethora of genetically linked immune disturbances must fuel IBD research from now on.

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STUDY SETTING AND SCOPE OF THE ANALYSIS

Supported by the Italian Health System, in 2008 Grad-

Table 1 Contains patients' demographics and disease characteristics

	UC (38, 24 m)		CD(26, 16 m)
Age, yr	Extension	Age, yr	Extension
18-80	Proctitis, 12	16-73	Ileo-colonic 15
	Sub-total, 11		Colitis, 5
	Left, 8		Universal, 4
	Pancolitis, 6		Ileitis, 2
	IPAA, 1		

UC: Ulcerative colitis; CD: Crohn's Disease; IPAA: Ileo-pouch anal anastomosis.

Table 2 Gives the frequencies of use of the main drugs *n* (%)

Ulcerative colitis	Crohn's disease
Mesalamines 33 (86)	18 (69)
Steroids 21 (55)	5 (19)
Thiopurines 14 (36)	8 (30)
Biologics 1(2.6)	1 (3.8)

Table 3 Illustrates the distribution of the main extra-intestinal affections

	n	Familial	Personal
Ulcerative colitis			
Psoriasis	2	0	2
Inflammatory bowel disease	3	3	0
Asthma	2	1	1
Rheumatoid Arthritis	2	0	2
Crohn's disease			
Psoriasis	4	3	1
Inflammatory bowel disease	3	3	0
Asthma	1	1	0
Rheumatoid Arthritis	1	1	0

enigo Hospital has launched an out-patient service mainly devoted to patients with inflammatory bowel disease (IBD). An interim analysis of the activities of this service has already appeared in 2010[1]. Eversince its establishment, the service has mostly been conducted by one of us (GCA), enrolling some 200 IBD patients. The scope of the present analysis was to reappraise the data under the light of modern achievements (for example the concept of "barrier organ disease"); to gain more insight into the drawbacks and the limits of traditional therapy with special regard to factors countering maintenance of remission; then, to cast a glimpse into the future of treatment approaches for IBD. We deliberately meant to not loose adherence to our daily clinical experience in this out-patient setting, when either dissecting actual difficulties or visualizing future therapeutic scenarios (personalized treatment for example). At a time when the literature is being "flooded" by a number of large epidemiologic and population studies, we chose to present the limits and the peculiarities of a study that pivots on the narrow environment of an outpatient office conducted by one physician.

STUDY POPULATION

Sixty-four IBD patients, gathered in the most recent interim analysis between 6.6.2012 and 04-24-2013 included 26 Crohn's affections (CD) and 38 ulcerative colitis (UC) cases, corresponding to some 6 IBD patients per month; overall analysis in the previous 31 months had yielded 119 IBD patients. Changes in the core storage system beginning 2010 have imposed a discontinuity in the data collection modalities, a fault that is now mended (Tables 1-3).

Managing chronic remission: open questions

Both medical and budget issues make the maintenance of remission of IBD a crucial challenge. The relevant literature has particularly expanded on UC[2]. A variegated list of factors may provoke loss of IBD remission, and we ourselves had the chance to face some of the conditions in our real-world practice. (1) lack of adherence to prescriptions, mostly mesalamine and thiopurine medications. Among the 64 patients in this report, the adherence rate for mesalamines and thiopurines was found to attain 90% and 94%, ranking high with regard to literature data[2]; (2) unavailability of a non-replaceable drug; we had to face this event for a few patients, who, owing to their intolerance of azathioprine, were prescribed 6-mercaptopurine, at a moment when the latter had become unavailable in our country (see below); (3) toxicity of a pivotal drug (mesalamine, azathioprine). Noteworthy, based on the results of an English survey which was able to reveal only 11 alleged cases of renal damage per million prescriptions, mesalamine is listed among the most tolerated drugs[3]. Our own present series included a rare case of mesalamine-induced cholestasis[4,5] which responded to patient's transitioning to balsalazide. As described in various publications[6,7], we faced a rather common azathioprine toxicity. In a population of 42 UC patients and 37 subjects with CD (females mostly) we recently found an 11% of gastric intolerance to azathioprine. Transition to 6-MP was tolerated in 6 cases which acquired disease control[8]; (4) undermining of remission because of the introduction of third party drugs: antibiotics and NSAIDs are mostly recognized as capable to reactivate IBD or induce it de-novo. Indeed, analysis of our office experience has gathered convincing evidence of a role for antibiotics and/or non-steroid anti-inflammatory drugs (NSAIDs) in active episodes of IBD, requiring the consideration of prescribing physicians[9]. A specific attention must be devoted to the Crohn's-like colitis[10] that is not rarely found as an accompaniment to immune-mediated diseases from rheumatoid arthritis to multiple sclerosis: its inciting factors have been recognized in anti-tumor necrosis factor (TNF) formulations and/or rituximab[11], the impact matching the rising prescription rate of these drugs. In our opinion, these observation are an indicator of the pathophysiologic and genetic commonalities linking the IBDs with their surrounding galaxy of immune disorders of which psoriasis is just the most obvious instance; and (5) the issue of

the ancillary symptoms in IBD. Likewise any other individual, IBD patients may present with bowel abnormalities being due to a plethora of factors from irritable bowel syndrome to celiac disease. Such situations must be borne in mind, in order to avoid prescribing IBD drugs for the wrong indication (so-called over-treatment)[12].

EXOGENOUS AND ENDOGENOUS FACTORING

Among variables factoring in the management of IBD, smoking is obviously the most studied, with a detrimental action being demonstrated for CD[13], and a protective one for UC[14].Sometimes overlooked in clinical practice, passive smoking must by contrast be given adequate consideration. The causative role of NSAIDs and antibiotics has already been touched on.

Genomic instability is gaining crucial importance among endogenous factors in IBD management, with excessive frequency of hematologic or immune-allergic disorders in the patient or among his/her relatives.

PROGNOSIS

The anticipation that the IBDs that are followed in an out-patient environment might be benign is sometimes contradicted by data. Beginning 2008, for example, in our series we recorded at least three fatalities, including one hematologic malignancy, and two cases of septicemia. One drop-out patient was reported with colonic malignancy from another hospital.

WRAPPING UP SUMMARY

This data were gathered from a random sample of 64 IBD patients (38 UC, 26 CD), who were followed in the last year at an out-patient unit with a 5-year service history. Proctitis was common among the UC patients; mesalamines were the most prescribed drugs, with the MMX formulation attaining 16% in CD and 33% in UC; beclomethasone prescriptions were prominent among steroids, ranking to 12 prescriptions including 9 of local formulations; remission maintenance was a significant challenge, pivoting over two main aspects: the control of third-party drugs, and maintenance of adherence.

At least two patients on biologics presented with superimposed immune disorders: a young female receiving adalimumab for diffuse CD developed psoriasis of the sculp; a young male with juvenile rheumatoid arthritis received three different anti-TNF formulations and developed UC on each of the three[15]; switched finally to certolizumab presented with psoriasis of the elbows.

The tables hint to an association between psoriasis and rheumatoid arthritis. Such clinical evidence in our opinion launches a few messages of a theoretical and clinical impact, and in the lines to follow we shall try to gain more insight into this matter.

Modern understanding of the anatomy of the gut and of the pathophysiology of its associated immune system all convey a concept of the IBDs as disorders pivoting on a disrupted balance between the gut mucosal immune tissue and luminal antigens, with gut microbiota as one crucially causative variable in favoring or countering the rise of an inflammatory response; the underlying dogmatic view supporting this reasoning is that while the mucosal immune system has evolved following a tolerization tune, the submucosal lymphoid tissue is highly reactive and can mount a significant inflammatory response should any antigen breach the mucosal barrier.

IBD is now thought to best be described using a concept of a "contextualized syndrome"[16]. The basis of this concept is double: (1) a uniform curative strategy for the IBDs is yet far from reach; and (2) though often presenting with obvious clinical commonalities, in fact the IBDs do hide distinct serological or genetic subtypes that are best accounted for by a process of splitting rather than one of lumping up[17].

The frequent observation of a co-morbidity between IBD and psoriasis, such as that observed in our office, served as one of the triggers for this frame of mind. A part of the scientific community has thus begun to conceive IBD as an archetype of "barrier organ diseases" whereby the essential ingredients are a mucosal surface endowed with sensor molecules of the outer environment (see the NOD system for example), and an underneath lymphoid tissue, this mixing being ruled in the background by an abundant metagenomic microbiota load (see below).

At least three systems with similar characteristics have nowadays been defined in human beings: the gut (chiefly the colon); the skin; and respiratory epithelia. It is not by chance that clinical experience has long highlighted that disorders of these three districts might be co-morbid. Our case series recorded hereby emphasize a coincidence between CD and psoriasis, but others have written about chronic obstructive pulmonary disease and IBD[18]. It is worth noting that the concept of barrier organ has been pioneered in 2005 by the brilliant work of Stefan Schreiber[19]; the Italian research has recently contributed to this field by a comprehensive dermatologic review[20] and by a gastroenterologic paper from our own[21]. As to the state of the art, it seems uneasy to identify a morphological or molecular marker to distinguish those IBDs that associate with psoriasis from those which do not. A few years ago, a North-European group focused their attention on polymorphisms of the Il23 receptor (IL23R) in both IBD and psoriasis, thus perhaps envisaging a genetic link between the two disorders[22].

Interest in the issue of the systemic positioning of IBD has been fostered by the increasingly frequent observation of ancillary immune diseases arising in patients on biologic treatments: development of IBD in rheumatic subjects receiving etanercept[23], presentation with IBD of hematologic patients treated with rituximab[24], and observation of psoriasis in cases of IBD prescribed adalimumab[25]. The bulk of these observations implies the existence of a galaxy of immune-inflammatory con-

ditions (of which IBD is just one component) spanning from the gut to skin, lungs, and joints. The link between these conditions might be represented by anatomic/physiologic commonalities (barrier organ diseases) or a generic genetic instability perhaps sustained by polymorphisms of STAT transducers[26].

This scenario recommends that the IBDs no longer be conceived as one nosographic entity. The bulk of the following observations: (1) NOD receptor polymorphism might drive CD phenotypes; (2) there is a link between serologic subtypes and clinical presentations; and (3) some CD presentations do depend on ethnic factors, All of these data contribute to build up a vision of IBD like a non-dichotomic collection of different (though linked) entities that are best described using the definition of "syndrome"[16].

The implications of this changed frame of mind cannot be ignored. If it is understood that the entity "IBD" contains in fact multiple distinct syndromes along a clinical-serologic-genetic axis, then this must somehow be reflected in differentiated clinical interventions. Such a cutting-edge frame of mind can now hardly fit the widespread recommendation and use of biologic approaches[27], which target one cytokine in an homogenized-pragmatic attempt to interfere with the common downstream pathways in the mechanisms of IBD.

A GLIMPSE INTO FUTURE TARGETS TO STUDY AND TREAT THE IBDs

Attempts to ensure "sealing" of the gut mucosa with the scope to limit contacts between the immunogenic luminal content and the lymphoid tissue underneath. Partial results of an approach using phosphatidylcholine have already been published[28].

Triggered by the classic evidence that germ-free animals do not develop IBD, investigators could not neglect the colonic microbiota, which constitutes a heavier meta genoma than somatic cells themselves. Various attempts to modify the amount and composition of colic metagenoma have thus proliferated: (1) oral administration of pro-biotic lysates[29]; (2) fecal transplants[30]; and (3) diet modifications[31].

The data from the bulk of these studies is conveying the message that a quantitative or qualitative change of gut microbiota colonization (dysbiosis) might associate with a plethora of (auto)immune and (auto)inflammatory disorders[32], with a particular emphasis on rheumatoid arthritis (RA)[33]. Relevant cutting-edge results[34] are now showing that Prevotella Copri (an in-habitant species of the microbiome) might train T-lymphocytes to secrete IL-17, a key mediator in the pathogenesis of RA. To this end, attention is concentrating on the recent claim that NOD receptors on colonic epithelial cells (whether tolerant or reactive against colonic flora at birth) might drive the metagenomic phenotype of the newborn: rather a breakthrough, in view of the ability of colonic species to condition a whole array of affections, from IBD itself to hepatic steatosis[35].

Research directed to identify and change factors in the genesis of IBD, such as life style and diet composition[36].

Along a totally different line, the results have been published of attempts at unraveling genetic IBD surrogates, that though mimicking IBD, might atypically respond according to the signal conveyed by the hidden gene: Behcet mimicking IBD[37] and familial mediterranean fever are instructive example[38].

CONCLUSION

Though generated in a limited environment, the analysis of the data from our office has led to general considerations. The IBDs can no longer be considered as autonomous entities, but rather as poly-organic and poly-genic syndromes wherein a critical mass of polymorphic genetic information and environmental factors must interact for full-blown disease to develop[39]. Visualizing the IBDs like archetypes disorders of the immunological interaction between the "in" and the "out" (together with skin and pulmonary epithelia disorders) to make the umbrella label of "barrier organ disease" seems particularly seminal. This novel positioning of IBD might at first sight increase the degree of complexity, but on the other hand can favor novel therapeutic approaches and pave the way towards the conception of a personalized therapy.

Though apparently stable in the Western World, IBD has two formidable avenues to run. Firstly, Far East populations seem no longer to be immune from the IBDs, and in the next few years may witness an epidemic explosion of these disease[40]; secondly, populations that immigrate to countries with a higher hygiene standard seem to be particularly prone to develop IBD[41]. For certain countries, such challenges are not an issue of tomorrow, but are already here today.

REFERENCES

1 **Actis GC**, Rosina F. Outpatient care for inflammatory bowel disease at a primary referral hospital in Turin. *Minerva Gastroenterol Dietol* 2010; **56**: 27-34 [PMID: 20190722]

2 **Tindall WN**, Boltri JM, Wilhelm SM. Mild-to-moderate ulcerative colitis: your role in patient compliance and health care costs. *J Manag Care Pharm* 2007; **13**: S2-12; quiz S13-4 [PMID: 17874873]

3 **Ransford RA**, Langman MJ. Sulphasalazine and mesalazine: serious adverse reactions re-evaluated on the basis of suspected adverse reaction reports to the Committee on Safety of Medicines. *Gut* 2002; **51**: 536-539 [PMID: 12235076 DOI: 10.1136/gut.51.4.536]

4 **Khokhar OS**, Lewis JH. Hepatotoxicity of agents used in the management of inflammatory bowel disease. *Dig Dis* 2010; **28**: 508-518 [PMID: 20926880 DOI: 10.1159/000320410]

5 **Actis GC,** Pellicano R, Rosina F. Mesalamine-related cholestasis in a patient with Bruton's disease receiving mesalamines for co-morbid Crohn's disease. *J Pharmacol Pharmacother* 2014; **5**: 151-152 [DOI: 10.4103/0976-500X.130071]

6 **Actis GC**, Pellicano R, Rizzetto M, Ayoubi M, Leone N, Tappero G, Pazienza P, Rosina F. Individually administered or co-prescribed thiopurines and mesalamines for inflammatory bowel disease. *World J Gastroenterol* 2009; **15**: 1420-1426

[PMID: 19322913 DOI: 10.3748/wjg.15.1420]
7 **Actis GC**, Rosina F, Pellicano R, Rizzetto M. An aggressive medical approach for inflammatory bowel disease: clinical challenges and therapeutic profiles in a retrospective hospital-based series. *Curr Clin Pharmacol* 2012; **7**: 209-213 [PMID: 22564119 DOI: 10.2174/157488412800958730]
8 **Actis GC.** Thiopurines for inflammatory bowel disease: indications, therapeutic profiles, and unwanted effects. *J Sym and Signs* 2014; **3**: 1-6
9 **Actis GC,** Pellicano R, Fadda M, Rosina F. Antibiotics and Non-Steroidal Anti-Inflammatory Drugs in Outpatient Practice: Indications and Unwanted Effects in a Gastroenterological Setting. *Curr Drug Saf* 2014; **9**: 133-137 [PMID: 24446890]
10 **Freeman HJ**. Colitis associated with biological agents. *World J Gastroenterol* 2012; **18**: 1871-1874 [PMID: 22563166 DOI: 10.3748/wjg.v18.i16.1871]
11 **Ardelean DS**, Gonska T, Wires S, Cutz E, Griffiths A, Harvey E, Tse SM, Benseler SM. Severe ulcerative colitis after rituximab therapy. *Pediatrics* 2010; **126**: e243-e246 [PMID: 20566611 DOI: 10.1542/peds.2009-3395]
12 **Meng J**, Agrawal A, Whorwell PJ. Refractory inflammatory bowel disease-could it be an irritable bowel? *Nat Rev Gastroenterol Hepatol* 2013; **10**: 58-61 [PMID: 22965430 DOI: 10.1038/nrgastro.2012.173]
13 **Lakatos PL**, Vegh Z, Lovasz BD, David G, Pandur T, Erdelyi Z, Szita I, Mester G, Balogh M, Szipocs I, Molnar C, Komaromi E, Golovics PA, Mandel M, Horvath A, Szathmari M, Kiss LS, Lakatos L. Is current smoking still an important environmental factor in inflammatory bowel diseases? Results from a population-based incident cohort. *Inflamm Bowel Dis* 2013; **19**: 1010-1017 [PMID: 23399739 DOI: 10.1097/MIB.0b013e3182802b3e]
14 **Montbarbon M**, Pichavant M, Langlois A, Erdual E, Maggiotto F, Neut C, Mallevaey T, Dharancy S, Dubuquoy L, Trottein F, Cortot A, Desreumaux P, Gosset P, Bertin B. Colonic inflammation in mice is improved by cigarette smoke through iNKT cells recruitment. *PLoS One* 2013; **8**: e62208 [PMID: 23638007]
15 **Actis GC**, Lagget M, Pellicano R, Rosina F. Pancolitis during etanercept treatment of rheumatoid arthritis relapsing on the administration of further two TNF-alpha inhibitors. *Int J Colorectal Dis* 2012; **27**: 547-548 [PMID: 21656142 DOI: 10.1007/s00384-011-1250-4]
16 **Dotan I**. New serologic markers for inflammatory bowel disease diagnosis. *Dig Dis* 2010; **28**: 418-423 [PMID: 20926866 DOI: 10.1159/000320396]
17 **Sachar DB**, Walfish A. Inflammatory bowel disease: one or two diseases? *Curr Gastroenterol Rep* 2013; **15**: 298 [PMID: 23250698 DOI: 10.1007/s11894-012-0298-9]
18 **Keely S**, Talley NJ, Hansbro PM. Pulmonary-intestinal cross-talk in mucosal inflammatory disease. *Mucosal Immunol* 2012; **5**: 7-18 [PMID: 22089028 DOI: 10.1038/mi.2011.55]
19 **Schreiber S**, Rosenstiel P, Albrecht M, Hampe J, Krawczak M. Genetics of Crohn disease, an archetypal inflammatory barrier disease. *Nat Rev Genet* 2005; **6**: 376-388 [PMID: 15861209 DOI: 10.1038/nrg1607]
20 **Mattozzi C**, Richetta AG, Cantisani C, Macaluso L, Calvieri S. Psoriasis: new insight about pathogenesis, role of barrier organ integrity, NLR/CATERPILLER family genes and microbial flora. *J Dermatol* 2012; **39**: 752-760 [PMID: 22698089 DOI: 10.1111/j.1346-8138.2012.01606.x]
21 **Actis GC**, Rosina F. Inflammatory bowel disease: An archetype disorder of outer environment sensor systems. *World J Gastrointest Pharmacol Ther* 2013; **4**: 41-46 [PMID: 23919214 DOI: 10.4292/wjgpt.v4.i3.00]
22 **Einarsdottir E,** Koskinen LL, Dukes E, Kainu K, Suomela S, Lappalainen M, Ziberna F, Korponay-Szabo IR, Kurppa K, Kaukinen K, Adny R, Pocsai Z, Szles G, Frkkil M, Turunen U, Halme L, Paavola-Sakki P, Not T, Vatta S, Ventura A, Lfberg R, Torkvist L, Bresso F, Halfvarson J, Mki M, Kontula K, Saarialho-Kere U, Kere J, D'Amato M, Saavalainen P. IL23R in the Swedish, Finnish, Hungarian and Italian populations: association with IBD and psoriasis, and linkage to celiac disease. *BMC Med Genet* 2009; **10**: 8 [DOI: 10.1186/1471-2350-10-8]
23 **Toussirot É**, Houvenagel É, Goëb V, Fouache D, Martin A, Le Dantec P, Dernis E, Wendling D, Ansemant T, Berthelot JM, Bader-Meunier B, Kantelip B. Development of inflammatory bowel disease during anti-TNF-α therapy for inflammatory rheumatic disease: a nationwide series. *Joint Bone Spine* 2012; **79**: 457-463 [PMID: 22088934 DOI: 10.1016/j.jbspin.2011.10.001]
24 **Bhalme M**, Hayes S, Norton A, Lal S, Chinoy H, Paine P. Rituximab-associated colitis. *Inflamm Bowel Dis* 2013; **19**: E41-E43 [PMID: 22488947 DOI: 10.1002/ibd.22963]
25 **Kip KE**, Swoger JM, Grandinetti LM, Barrie AM, Greer JB, Regueiro MD. Tumor necrosis factor α antagonist-associated psoriasis in inflammatory diseases: an analysis of the FDA adverse event reporting system. *Inflamm Bowel Dis* 2013; **19**: 1164-1172 [PMID: 23518804 DOI: 10.1097/MIB.0b013e31828075bd]
26 **Moon CM**, Cheon JH, Kim SW, Shin DJ, Kim ES, Shin ES, Kang Y, Park JJ, Hong SP, Nam SY, Kim TI, Kim WH. Association of signal transducer and activator of transcription 4 genetic variants with extra-intestinal manifestations in inflammatory bowel disease. *Life Sci* 2010; **86**: 661-667 [PMID: 20176035 DOI: 10.1016/j.lfs.2010.02.016]
27 **D'Haens GR**, Panaccione R, Higgins PD, Vermeire S, Gassull M, Chowers Y, Hanauer SB, Herfarth H, Hommes DW, Kamm M, Löfberg R, Quary A, Sands B, Sood A, Watermeyer G, Lashner B, Lémann M, Plevy S, Reinisch W, Schreiber S, Siegel C, Targan S, Watanabe M, Feagan B, Sandborn WJ, Colombel JF, Travis S. The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organization: when to start, when to stop, which drug to choose, and how to predict response? *Am J Gastroenterol* 2011; **106**: 199-212; quiz 213 [PMID: 21045814 DOI: 10.1038/ajg.2010.392]
28 **Stremmel W**, Ehehalt R, Autschbach F, Karner M. Phosphatidylcholine for steroid-refractory chronic ulcerative colitis: a randomized trial. *Ann Intern Med* 2007; **147**: 603-610 [PMID: 17975182 DOI: 10.7326/0003-4819-147-9-200711060-00004]
29 **Zakostelska Z**, Kverka M, Klimesova K, Rossmann P, Mrazek J, Kopecny J, Hornova M, Srutkova D, Hudcovic T, Ridl J, Tlaskalova-Hogenova H. Lysate of probiotic Lactobacillus casei DN-114 001 ameliorates colitis by strengthening the gut barrier function and changing the gut microenvironment. *PLoS One* 2011; **6**: e27961 [PMID: 22132181 DOI: 10.1371/journal.pone.0027961]
30 **Borody TJ,** Brandt LJ, Paramsothy S. Therapeutic fecal microbiota transplantation; current status and future development. *Curr Opin Gastroenterol* 2014; **30**: 97-105 [DOI: 10.1097/MOG.0000000000000027]
31 **Flint HJ**. The impact of nutrition on the human microbiome. *Nutr Rev* 2012; **70** Suppl 1: S10-S13 [PMID: 22861801 DOI: 10.1111/j.1753-4887.2012.00499.x]
32 **Garn H**, Neves JF, Blumberg RS, Renz H. Effect of barrier microbes on organ-based inflammation. *J Allergy Clin Immunol* 2013; **131**: 1465-1478 [PMID: 23726530 DOI: 10.1016/j.jaci.2013.04.031]
33 **Owen JL**, Mohamadzadeh M. Microbial activation of gut dendritic cells and the control of mucosal immunity. *J Interferon Cytokine Res* 2013; **33**: 619-631 [PMID: 23962004 DOI: 10.1089/jlr.2013.0046]
34 **Scher JU**, Sczesnak A, Longman RS, Segata N, Ubeda C, Bielski C, Rostron T, Cerundolo V, Pamer EG, Abramson SB, Huttenhower C, Littman DR. Expansion of intestinal Prevotella copri correlates with enhanced susceptibility to arthritis. *Elife* (Cambridge) 2013; **2**: e01202 [PMID: 24192039 DOI: 10.7554/eLife.01202]

35 **Rosenstiel P**. Stories of love and hate: innate immunity and host-microbe crosstalk in the intestine. *Curr Opin Gastroenterol* 2013; **29**: 125-132 [PMID: 23337934 DOI: 10.1097/MOG.0b013e32835da2c7]
36 **Leone V**, Chang EB, Devkota S. Diet, microbes, and host genetics: the perfect storm in inflammatory bowel diseases. *J Gastroenterol* 2013; **48**: 315-321 [PMID: 23475322 DOI: 10.1007/s00535-013-0777-2]
37 **Grigg EL**, Kane S, Katz S. Mimicry and deception in inflammatory bowel disease and intestinal behçet disease. *Gastroenterol Hepatol* (N Y) 2012; **8**: 103-112 [PMID: 22485077]
38 **Sari S**, Egritas O, Dalgic B. The familial Mediterranean fever (MEFV) gene may be a modifier factor of inflammatory bowel disease in infancy. *Eur J Pediatr* 2008; **167**: 391-393 [PMID: 17520284 DOI: 10.1007/s00431-007-0508-x]
39 **Lees CW**, Barrett JC, Parkes M, Satsangi J. New IBD genetics: common pathways with other diseases. *Gut* 2011; **60**: 1739-1753 [PMID: 21300624 DOI: 10.1136/gut.2009.199679]
40 **Zhao J**, Ng SC, Lei Y, Yi F, Li J, Yu L, Zou K, Dan Z, Dai M, Ding Y, Song M, Mei Q, Fang X, Liu H, Shi Z, Zhou R, Xia M, Wu Q, Xiong Z, Zhu W, Deng L, Kamm MA, Xia B. First prospective, population-based inflammatory bowel disease incidence study in mainland of China: the emergence of "western" disease. *Inflamm Bowel Dis* 2013; **19**: 1839-1845 [PMID: 23669403]
41 **Barreiro-de Acosta M**, Alvarez Castro A, Souto R, Iglesias M, Lorenzo A, Dominguez-Muñoz JE. Emigration to western industrialized countries: A risk factor for developing inflammatory bowel disease. *J Crohns Colitis* 2011; **5**: 566-569 [PMID: 22115376 DOI: 10.1016/j.crohns.2011.05.009]

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MINIREVIEWS

Prevention of hepatocellular carcinoma in patients with chronic hepatitis B

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Abstract

Patients with chronic hepatitis B are at significant risk for hepatocellular carcinoma (HCC). Globally, over half a million people each year are diagnosed with HCC, with marked geographical variations. Despite overwhelming evidence for a causal role of hepatitis B virus (HBV) infection in the development of HCC and a well-established relationship between high baseline hepatitis B viral load and cumulative risk of HCC, the molecular basis for this association has not been fully elucidated. In addition, a beneficial role for antiviral therapy in preventing the development of HCC has been difficult to establish. This review examines the biological and molecular mechanisms of HBV-related hepatocarcinogenesis, recent results on the effect of modern nucleos(t)ides on the rate of HCC development in high risk HBV cohorts and the potential mechanisms by which long-term antiviral therapy with potent inhibitors of HBV replication might reduce the risk of HCC in patients with chronic hepatitis B. Although evidence from randomized controlled trials shows the favourable effects of antiviral agents in achieving profound and durable suppression of HBV DNA levels while improving liver function and histology, robust evidence of other long-term clinical outcomes, such as prevention of HCC, are limited.

Key words: Chronic hepatitis B; Entecavir; Hepatitis B virus; Hepatocellular carcinoma; Hepatocarcinogenesis; Nucleoside analogues; Risk reduction

Core tip: There is overwhelming evidence for the causal role of hepatitis B virus (HBV) infection in the development of hepatocellular carcinoma (HCC). However, evidence for the role of antiviral therapy in HCC prevention is inconclusive, in part due to the slow course of HCC development, which makes conducting outcome studies very challenging, while the effectiveness of modern antiviral agents in suppressing HBV means that untreated control group comparisons are ethically unacceptable. We review the impact of HBV treatment on the risk of HCC development, with special focus on emerging data for modern anti-HBV drugs such as entecavir and tenofovir.

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INTRODUCTION

Worldwide, hepatocellular carcinoma (HCC) is diagnosed in over 500000 people each year[1]. Increasing age, male sex and chronic alcohol consumption are significant risk factors for the development of HCC. Although there is substantial geographical variation, the greatest burden

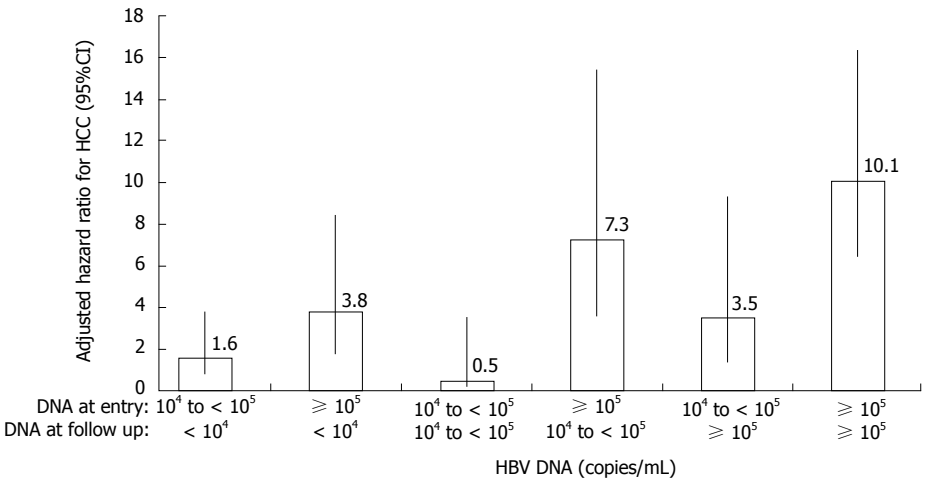

Figure 1 Adjusted hazard ratio for hepatocellular carcinoma by serum hepatitis B virus DNA levels at study entry and last follow-up. Data were adjusted for gender, age, cigarette smoking and alcohol consumption using Cox proportional hazards model. HCC: hepatocellular carcinoma; HBV: Hepatitis B virus. Data sourced from Chen *et al*[11].

of the disease is in East Asia, Eastern Europe and sub-Saharan Africa, where hepatitis B virus (HBV) infection is highly prevalent[1-4].

Globally, HBV infection is associated with approximately half of all cases of HCC, and almost all cases of HCC in children[1]. Chronic HBV infection may progress to cirrhosis and liver decompensation and, the majority (up to 80%) of patients with HBV-related HCC have underlying cirrhosis. The known risk factors for HBV-related HCC can be categorized into host factors, virus factors, and host-virus interactions. Host factors include male gender, Asian race, age older than 40 years, exposure to the mycotoxin aflatoxin, habitual smoking or alcohol consumption, and a family history of HCC[1-3,5,6]. Virus factors can include coinfection with hepatitis C virus (HCV) or hepatitis delta virus, pre-core (Pre-C) or basal core promoter mutations, high levels of HBV hepatocellular replication, and HBV genotype C. Host-virus interactions include the presence of cirrhosis, prolonged circulating hepatitis B surface antigen (HBsAg) and hepatitis Be antigen (HBeAg), and high levels of DNA-HBV and HBsAg.

Familial aggregation of risk for HCC has been well described in case-control studies in Asia[7-9]. In one study, the risk associated with having parents and/or siblings with HCC was evaluated in a large cohort of male HBV carriers, in a case-control study of HBV carriers with newly diagnosed HCC and HBV-positive subjects without HCC[9]. There was an increased risk for both HCC and cirrhosis for mothers and siblings but, of interest, not for fathers of case subjects[9]. For HCC, the adjusted odds ratios (ORs) according to kinship were 2.64 for mothers (95%CI: 1.60-4.34), 3.73 (2.64-5.27) for brothers, and 4.55 (2.22-9.31) for sisters, while the OR for fathers was only 1.36 (0.86-2.11). Overall, HBV carriers with a family history of HCC had an adjusted OR of 2.41 (95%CI: 1.47-3.95) for HCC if one relation was affected, rising to 5.55 (2.02-15.26) when two or more relations had HCC.

The precise mechanism of this familial aggregation is unclear, but may in part be a result of a higher HBsAg carrier rate among mothers and siblings of HBV carriers compared with fathers, as a result of vertical transmission. Furthermore, although less well investigated, a family history of HCC also appears to increase HCC risk in Western populations[10].

There is a well-established relationship between cumulative risk of HBV-related HCC and baseline viral load (baseline serum HBV DNA). Elevated HBV DNA level is strongly predictive of HCC, independent of HBeAg status, serum alanine aminotransferase (ALT) level and cirrhosis, with a cumulative incidence rate of HCC at the end of the 13th year of follow up in a large prospective cohort study of 3653 subjects ranging from 1.30% for subjects with serum HBV DNA level of less than 300 copies/mL at study entry to 14.89% for an HBV DNA level of 10^6 copies/mL or greater at study entry[11]. A significant biological gradient of HCC risk in patients with higher baseline levels was also observed, independent of viral load achieved after treatment[11]. Subjects with similar HBV DNA levels at last follow-up but with higher viral loads at study entry had significantly higher risk of HCC than those with lower HBV DNA levels at study entry (Figure 1).

These findings suggest the importance of close clinical monitoring for those with elevated serum HBV DNA, and that effective antiviral treatment may be valuable to lower the risk of HCC in patients with chronic HBV.

This article will review the current knowledge of the mechanisms of HBV-related hepatocarcinogenesis, examine the role of antiviral agents in reducing the risk of HCC, and discuss potential mechanisms for HCC risk reduction during long-term antiviral therapy.

LONG-TERM VIRAL SUPPRESSION AND LIVER-RELATED OUTCOMES IN CHRONIC HEPATITIS B

Long-term suppression of HBV is associated with sub-

stantial histological improvement and reversal of fibrosis or cirrhosis[12-15]. Strong correlations between viral load and histological grading, and between serum viral suppression and histological improvement have been observed[15], with indications that a greater than 1 $\log_{10}$ copies/mL change in median serum HBV DNA level will convert into a 2-point change in median histological grade. However, the direct contribution of antiviral treatment to the prevention of HBV-related HCC is less clear-cut. Interestingly, in HBeAg-negative patients, genotype B or C, low HBV-DNA and ALT levels and circulating HBsAg levels > 1000 IU/mL can predict hepatitis flares and progression[16].

The clinical benefit of first generation nucleoside analogues used in the treatment of HBV, such as lamivudine, is limited by the development of resistance and virological relapse after treatment cessation[12,17-19]. Entecavir and tenofovir dipivoxil are second generation nucleos(t)ide analogue reverse transcriptase inhibitors with potent activity against HBV and high genetic barrier to resistance[20-24]. Indeed, the cumulative annual incidence of resistance by year 6 of treatment may reach 76% (lamivudine) 29% (adefovir) and 25% (telbivudine), compared with 0%-1.2% for tenofovir dipivoxil and entecavir, respectively[25].

A systematic review and meta-analysis found that entecavir, which is an acyclic guanosine nucleoside analogue, and tenofovir dipivoxil, an acyclic adenine nucleotide, are the most effective antiviral agents for the treatment of chronic hepatitis B[26]. In evaluations of lamivudine, pegylated interferon, adefovir, entecavir, telbivudine, and tenofovir, as monotherapies and combination therapies in treatment-naive individuals, entecavir and tenofovir dipivoxil consistently ranked in the top five treatments for surrogate outcomes, whereas entecavir was ranked first with regard to improving liver histology, and tenofovir dipivoxil was ranked first for inducing undetectable HBV DNA and normalizing ALT levels[26].

The long-term efficacy of entecavir was demonstrated in an open-label extension study following two phase 3 clinical studies, in which entecavir for a total duration of at least 3 years significantly improved liver histology, biochemical markers and fibrosis, accompanied by potent viral suppression in nucleoside-naïve, HBeAg-positive and HBeAg-negative patients with advanced fibrosis or cirrhosis[27]. Similarly, in an open-label extension study after two 48-wk phase 3 studies in patients with advanced fibrosis or cirrhosis, long-term suppression of HBV DNA during treatment with tenofovir dipivoxil for at least 5 years led to regression of fibrosis and cirrhosis[13]. In these studies, long-term maintenance of viral suppression with entecavir and tenofovir dipivoxil was feasible because of favourable safety profiles and the absence of virological rebound or genotypic resistance[14,27].

BIOLOGICAL AND MOLECULAR MECHANISMS OF HEPATOCARCINOGENESIS

While there is overwhelming epidemiological evidence for a causal role of chronic HBV infection in the development of hepatocellular carcinoma, the molecular mechanisms of HBV tumourigenesis remain incompletely understood, although it can be seen as a multi-factorial process involving both direct and indirect components, some of which may act synergistically. A summary of potential mechanisms for the development of HCC in patients with chronic HBV infection is shown in Figure 2. It has been proposed that insertional activation of cellular cancer-related genes by HBV DNA integration, induction of genetic instability by viral integration or by the regulatory protein HBx, and host DNA mutations due to high hepatocyte turnover, cytokine and growth factor release in the setting of chronic liver inflammation, hepatocyte injury, proliferating fibroblasts, and fibrosis/cirrhosis, may be mechanisms associated with HBV-induced carcinogenesis[28-32].

Among factors implicated in chronic HBV infection and hepatocarcinogenesis, HBx has an important role in activating HBV transcription and replication, and in the development of HCC, because it is involved in the activation of numerous signalling pathways and cellular promotors, activating the expression of genes involved in cell cycle control, oncogenesis, proliferation, inflammation and apoptosis[28-32]. HBx also modulates the transcriptional activity of CREB (cAMP responsive element-binding protein), which plays an essential role in liver metabolism and proliferation, and is associated with hepatocarcinogenesis[31].

A key mechanism for hepatocarcinogenesis is the integration of HBV DNA into the host genome and the formation of covalently closed circular DNA (cccDNA). This episomal form of viral DNA, which acts as a template for the transcription of viral genes and is responsible for the persistence of viral replication, is derived *via* a succession of biological steps following the transportation of relaxed HBV DNA into the nuclei of hepatocytes. Both cccDNA and HBV DNA sequences integrated into the host genome have transcriptional activity, resulting in synthesis of HBsAg[33].

Clearance of intrahepatic cccDNA and/or HBsAg is difficult to achieve but clinically meaningful endpoints for antiviral therapy in chronic hepatitis B, and may be associated with a decreased risk of developing HCC[33,34]. However, the exact role of antiviral treatment in preventing HBV-related HCC has been difficult to establish. Because of the slow biological evolution of HBV, longitudinal studies may necessitate continuation of antiviral treatment over decades, longer than most researchers or pharmaceutical companies can wait[2,35]. Furthermore, as modern antiviral agents are effective in suppressing viral replication[25,26,36-38], untreated control group comparisons are considered unethical and cannot be performed.

Recently, a large Taiwanese study showed that in HBsAg-positive patients, predictors of HCC included age, HBeAg status, HBV genotype, and ALT and HBV DNA levels, but not HBsAg levels; however, in a subgroup of HBeAg-negative patients with viral HBV-DNA < 2000 IU/mL, the risk of HCC significantly correlated with

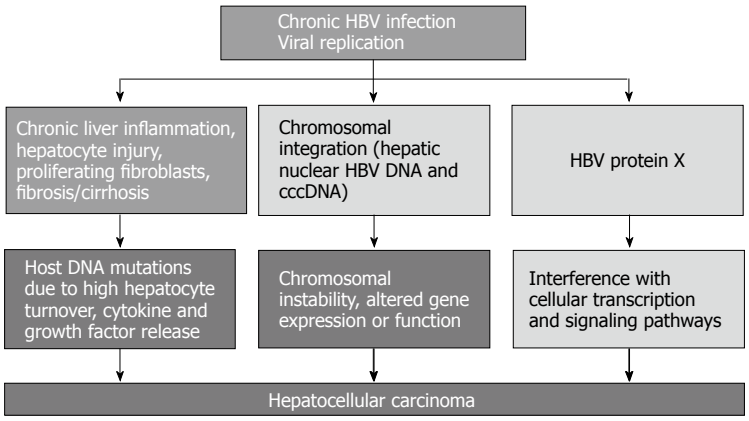

Figure 2 Mechanisms of chronic hepatitis B virus infection-related hepato-carcinogenesis[27-32]. cccDNA: Covalently closed circular DNA. HBV: Hepatitis B virus.

high HBsAg (≥ 1000 IU/mL), ALT and age, but not HBV-DNA[39].

ANTIVIRAL TREATMENT AND RISK OF HCC IN PATIENTS WITH CHRONIC HBV INFECTION

A number of systematic reviews and meta-analyses of the role of anti-HBV treatment in the prevention of HCC have been conducted[26,40-43], without conclusively demonstrating a beneficial impact on the preventing the development of HCC[2]. This is in part because of the inclusion of studies of older antiviral agents with limited antiviral potency and low genetic barriers, which are, therefore, associated with an increased risk of the development of HBV antiviral resistance mutations. In a recent electronic health records review of 2671 adults with chronic HBV infection enrolled in the Chronic Hepatitis Cohort Study, the adjusted hazard ratio (HR) for HCC risk in those receiving antiviral treatment was (HR = 0.39; 95%CI: 0.27-0.56; $P < 0.001$). In a subgroup analysis of patients with baseline laboratory data for serum fibrosis markers, antiviral treatment was associated with a lower risk of HCC after adjusting for cirrhosis markers of (adjusted HR, 0.24; 95%CI: 0.15-0.39; $P < 0.001$). In another subgroup analysis of patients with HBV DNA viral load data, in patients with HBV DNA > 20000 IU/mL, treated patients had a significantly lower risk of HCC compared with untreated patients[44].

In a recent meta-analysis of available randomized controlled trials, prospective cohort studies and case-control studies included 3433 treated patients and 4625 controls[42]. Antiviral treatment was shown to modestly reduce the incidence of HCC in patients with established cirrhosis, but there was no reduction in non-cirrhotic patients. A recent critical review[40] found that potent and persistent suppression of HBV viral load was more effectively maintained with nucleoside analogues than with other antivirals, leading to reversal of fibrosis and cirrhosis, and indications of a reduction in the incidence of HCC. However, this cannot be taken as high level evidence, as no direct data relating to entecavir and tenofovir dipivoxil were available in this analysis. Of five studies of oral antiviral agents included in the review (2036 patients treated with nucleoside analogues), all except one were retrospective, and most of were with lamivudine or adefovir, older agents[40]. However, all studies showed some reduction in HCC. The only randomized trial included in the systematic review was published in 2004, and showed that lamivudine reduced the incidence of cirrhosis and HCC in patients with chronic hepatitis B and advanced cirrhosis[18]. Ten studies of interferon-α showed inconsistent results, in part because interferon-α was associated with only moderate suppression of HBV DNA. However, recent evidence from two phase 3 clinical trials presented at the 2013 Annual Meeting of the European Association for the Study of the Liver (EASL) suggests that the observed incidence of HCC is lower than expected in patients with chronic hepatitis B treated with tenofovir dipivoxil[45]. The incidence of HCC was lower than predicted (as assessed by the REACH-B risk model), with a measurable effect in non-cirrhotic patients after 2 years, reaching a 55% reduction at 6 years of treatment ($P = 0.05$)[45]. Tenofovir dipivoxil had less effect in patients with cirrhosis.

The evidence base for the effect of entecavir on HCC risk is somewhat stronger than that for tenofovir dipivoxil, and will therefore be addressed separately in a subsequent section.

EVIDENCE FOR HCC RISK REDUCTION WITH ENTECAVIR

Although the major goals for therapy in chronic hepatitis B are to delay or prevent progressive liver disease and the development of cirrhosis and HCC[2], as yet no definitive evidence from randomized controlled trials has shown that antiviral therapy delays or prevents the development of HCC. However, there are a number of recent studies analyzing a potential beneficial impact of entecavir on the development of HCC.

A case-control study that followed a large cohort of Japanese patients with HBV for more than 5 years, compared 472 patients treated with entecavir with a historical cohort without treatment as a control group ($n = 1143$)[6]. The use of a propensity matching score, applied to match patients from both groups with the same baseline covari-

ates of risk for HCC, minimized study biases. A total of 316 patients in each group (control and entecavir) were matched for comparison. The median follow-up was 3.3 years in the entecavir group and 7.6 years in the historical control group ($P < 0.001$). The cumulative rates of HCC at 5 years were 3.7% in the entecavir group and 13.7% in controls ($P < 0.001$), showing that entecavir significantly reduced the 5-year risk of developing HCC in treatment-naïve patients, compared with control (adjusted HR = 0.37, 95%CI: 0.15-0.91; $P = 0.030$). After multivariate analysis, age, alcohol consumption, pre-existing cirrhosis, HBeAg positive status and platelet count lower than 150000/mL were associated with risk of HCC development. Only entecavir was significantly associated with a reduction of HCC incidence (HR = 0.23, $P = 0.001$). The mutation resistance to drug was 0.8% (4/472) in the entecavir group. The reduction was greater in patients with cirrhosis, and was higher than that observed with a propensity score matched lamivudine cohort[6]. To assess the impact of entecavir treatment further, the authors applied several established risk models to three studies that utilized HCC risk scales, based on established risk factors for HCC[6].

Entecavir treatment significantly reduced the risk of HCC development in patients with high risk according to risk scores in the Yang *et al*[46] ($P = 0.006$) and Yuen studies *et al*[47] ($P = 0.002$), but not in low score patients. Likewise, in the Wong study[48], patients with a high risk score had a significant reduction in risk of developing HCC ($P < 0.01$), whereas there was a borderline significance in those with intermediate risk ($P = 0.062$) and no reduction in low risk patients.

Furthermore, entecavir may reduce the risk of HCC recurrence in patients with chronic hepatitis B. In a longitudinal study in patients with newly-diagnosed HCC treated with curative percutaneous radiofrequency ablation (RFA), entecavir administration significantly reduced the incidence of new HCC lesions, compared with patients who did not received treatment after RFA[49]. The risk of HCC recurrence was significantly lower in entecavir recipients than in nucleoside-naïve patients (OR = 0.077, $P = 0.016$), as well as in those treated with another nucleoside analogue (OR = 0.145, $P = 0.012$). Even when cases of marginal recurrence and recurrence within 6 months of initial treatment were excluded, eliminating the possibility of residual tumour or missed tumour at initial diagnosis, the risk of HCC recurrence was still significantly lower in the entecavir group than in nucleoside-naïve patients (OR = 0.198, $P = 0.004$).

However, in a recent "real life" multicentre Italian study, patients with cirrhosis were still at risk of developing HCC over time, despite profound and durable viral suppression with entecavir. A total of 418 nucleoside-naïve patients with HBV received entecavir for up to 66 mo in the study[50]. All patients achieved undetectable HBV DNA by year 5, regardless of baseline histology or HBeAg status; 62% achieved HBeAg seroconversion and the HBsAg loss rate was 33%[50]. Clinical decompensation did not occur during follow-up among the 164 patients with cirrhosis, indicating that entecavir was effective in preventing the progression of cirrhosis. Nevertheless, despite long-term viral suppression and successful prevention of decompensation of cirrhosis, the cumulative incidence of HCC in cirrhotic patients was still 14% at year 5 (2.8% per year). This suggests that some cellular clones of pre-malignant cells may have already developed before treatment was initiated, and emphasizes the importance of ongoing surveillance for HCC, particularly in patients with cirrhosis. Reviewing the evidence for a multistep model for the process of hepatocarcinogenesis, YN Park[35] concluded that dysplastic lesions consisting of microscopic dysplastic foci and macroscopic dysplastic nodules may be precursor lesions of HCC. Early detection of precursor lesions may be important in identifying patients at higher risk of developing HCC and, together with diagnosing early HCC, may improve long-term survival for patients with chronic hepatitis B by allowing early initiation of effective antiviral therapy.

As there is stronger evidence that entecavir reduces the risk of developing HCC in patients with associated risk factors such as older age, gender, high HBV viral load, cirrhosis, fibrosis, liver laboratory markers, and core promoter mutations, targeting HCC prophylaxis with entecavir to high-risk patients with chronic hepatitis B may be a rational therapeutic approach. However, this suggestion should be supported by appropriately designed trials.

POTENTIAL MECHANISMS OF HCC RISK REDUCTION IN PATIENTS ON LONG-TERM ANTIVIRAL TREATMENT

In addition to the robust relationship between higher baseline viral load and cumulative risk of HBV-related HCC, several other mechanisms may contribute to reducing HCC risk.

As cirrhosis is in itself a risk factor for HCC development[1,5], the reversal of cirrhosis associated with long-term HBV viral suppression by effective antiviral therapy may, at least in part, decrease the risk for HCC development. Patients treated with entecavir in two phase 3 studies in nucleoside-naïve patients with HBeAg-positive and HBeAg-negative disease, respectively, and who subsequently were treated in a long-term extension study, underwent liver biopsy after at least 3 years of treatment. Improvement in liver histology was observed in 96% of patients, including all patients with advanced fibrosis or cirrhosis at the phase 3 baseline[27].

Tenofovir dipivoxil also improved liver histology at week 240 of treatment in an open-label extension study following two 48-week phase 3 trials in which patients received tenofovir dipivoxil plus adefovir[14]. At the time of a repeat liver biopsy, 73% of HBeAg-positive patients and 85% of HBeAg-negative patients had normal serum levels of ALT, accompanied by profound viral suppression. A total of 87% of patients had histological improvement, including reversal of cirrhosis in 74% of those with cirrhosis at baseline[14].

These findings of biochemical and histological improvement with entecavir and tenofovir dipivoxil may partly explain a reduction of HCC development in high risk patients.

Inhibition of the intracellular recycling pathway leading to a decrease in levels of intrahepatic cccDNA has been observed during long-term viral suppression, and depletion of cccDNA occurs by hepatocyte turnover as a result of loss by natural liver cell division and/or cell death during injury/regeneration cycles[33,51]. Currently, determination of cccDNA is not feasible by non-invasive means as a liver biopsy is required, and it has been proposed that serum HBsAg quantification may be used as a surrogate marker for cccDNA levels[2,33]. However, a recent study showed that, despite profound HBV DNA reduction, HBsAg and cccDNA decline was small on a short-term basis (1 year), and the magnitude of HBsAg reduction did not correlate with cccDNA[34].

Overall, these results suggest that even when HBV DNA intermediates are suppressed by nucleoside analogues, HBV may still replenish cccDNA by preferentially transporting the viral genome back to the hepatocyte nucleus instead of being enveloped and exocytosed to peripheral blood[34].

If clearance of cccDNA might contribute to decreased risk of HCC[23,33], it is likely that long-term therapy is needed to eliminate intrahepatic cccDNA, and it is therefore interesting that 48 wk of treatment with entecavir has very recently been shown to result in significantly greater reductions from baseline hepatic HBV cccDNA levels, as well as total hepatic HBV DNA, than lamivudine[52]. In this, the ETV-022 trial, cccDNA reduction was related to lower baseline serum HBV DNA and lower baseline necroinflammation. In addition, greater reduction of cccDNA at week 48 was associated with a higher on-treatment reduction in HBV DNA, Knodell necroinflammatory score and serum ALT, as well as higher HBeAg clearance[52].

CONCLUSION

Although there is overwhelming evidence of the causal role of HBV infection in the development of hepatocarcinogenesis, the evidence for the role of long-term antiviral therapy in the prevention of HCC in patients with chronic hepatitis B is modest. The limited evidence may, in part, be related to the difficulties of conducting longitudinal outcome studies, as HCC develops slowly, necessitating very long-term follow-up studies, and the effectiveness of modern antiviral agents in suppressing viral replication means that untreated control group comparisons are not considered ethically acceptable. However, there is persuasive evidence that entecavir reduces the risk of developing HBV-related HCC, particularly in high-risk patients. Entecavir also lowers the risk of recurrence after radiofrequency ablation of HCC. As HCC development is rare in low-risk patients, longer follow-up durations are needed to fully assess the potential effect of entecavir on preventing the development of HCC in patients with HBV infection.

In summary, there is emerging evidence suggesting that treatment with entecavir or tenofovir dipivoxil (though less extensive than with entecavir) significantly reduces, but does not completely eliminate, HCC risk in patients with HBV-associated cirrhosis.

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REFERENCES

1 **El-Serag HB**. Hepatocellular carcinoma. *N Engl J Med* 2011; **365**: 1118-1127 [PMID: 21992124 DOI: 10.1056/NEJMra1001683]

2 **Sorrell MF**, Belongia EA, Costa J, Gareen IF, Grem JL, Inadomi JM, Kern ER, McHugh JA, Petersen GM, Rein MF, Strader DB, Trotter HT. National Institutes of Health consensus development conference statement: management of hepatitis B. *Hepatology* 2009; **49**: S4-S12 [PMID: 19399804 DOI: 10.1002/hep.22946]

3 **Beasley RP**, Hwang LY, Lin CC, Chien CS. Hepatocellular carcinoma and hepatitis B virus. A prospective study of 22 707 men in Taiwan. *Lancet* 1981; **2**: 1129-1133 [PMID: 6118576]

4 **Rossi C**, Shrier I, Marshall L, Cnossen S, Schwartzman K, Klein MB, Schwarzer G, Greenaway C. Seroprevalence of chronic hepatitis B virus infection and prior immunity in immigrants and refugees: a systematic review and meta-analysis. *PLoS One* 2012; **7**: e44611 [PMID: 22957088 DOI: 10.1371/journal.pone.0044611]

5 **Fattovich G**, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology* 2004; **127**: S35-S50 [PMID: 15508101 DOI: 10.1053/j.gastro.2004.09.014]

6 **Hosaka T**, Suzuki F, Kobayashi M, Seko Y, Kawamura Y, Sezaki H, Akuta N, Suzuki Y, Saitoh S, Arase Y, Ikeda K, Kobayashi M, Kumada H. Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. *Hepatology* 2013; **58**: 98-107 [PMID: 23213040 DOI: 10.1002/hep.26180]

7 **Gao Y**, Jiang Q, Zhou X, Ding B, Wang R, Zhao G, Chen Y. HBV infection and familial aggregation of liver cancer: an analysis of case-control family study. *Cancer Causes Control* 2004; **15**: 845-850 [PMID: 15456998 DOI: 10.1023/B: CACO.0000043435.59195.3c]

8 **Park CH**, Jeong SH, Yim HW, Kim JD, Bae SH, Choi JY, Yoon SK. Family history influences the early onset of hepatocellular carcinoma. *World J Gastroenterol* 2012; **18**: 2661-2667 [PMID: 22690075 DOI: 10.3748/wjg.v18.i21.2661]

9 **Yu MW**, Chang HC, Liaw YF, Lin SM, Lee SD, Liu CJ, Chen PJ, Hsiao TJ, Lee PH, Chen CJ. Familial risk of hepatocellular carcinoma among chronic hepatitis B carriers and their relatives. *J Natl Cancer Inst* 2000; **92**: 1159-1164 [PMID: 10904089]

10 **Turati F**, Edefonti V, Talamini R, Ferraroni M, Malvezzi M, Bravi F, Franceschi S, Montella M, Polesel J, Zucchetto A, La Vecchia C, Negri E, Decarli A. Family history of liver cancer and hepatocellular carcinoma. *Hepatology* 2012; **55**: 1416-1425 [PMID: 22095619 DOI: 10.1002/hep.24794]

11 **Chen CJ**, Yang HI, Su J, Jen CL, You SL, Lu SN, Huang GT, Iloeje UH. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006; **295**: 65-73 [PMID: 16391218 DOI: 10.1001/

jama.295.1.65]
12 **Liaw YF**. Impact of therapy on the outcome of chronic hepatitis B. *Liver Int* 2013; **33** Suppl 1: 111-115 [PMID: 23286854 DOI: 10.1111/liv.12057]
13 **Schiff ER**, Lee SS, Chao YC, Kew Yoon S, Bessone F, Wu SS, Kryczka W, Lurie Y, Gadano A, Kitis G, Beebe S, Xu D, Tang H, Iloeje U. Long-term treatment with entecavir induces reversal of advanced fibrosis or cirrhosis in patients with chronic hepatitis B. *Clin Gastroenterol Hepatol* 2011; **9**: 274-276 [PMID: 21145419 DOI: 10.1016/j.cgh.2010.11.040]
14 **Marcellin P**, Gane E, Buti M, Afdhal N, Sievert W, Jacobson IM, Washington MK, Germanidis G, Flaherty JF, Schall RA, Bornstein JD, Kitrinos KM, Subramanian GM, McHutchison JG, Heathcote EJ. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. *Lancet* 2013; **381**: 468-475 [PMID: 23234725 DOI: 10.1016/S0140-6736(12)61425-1]
15 **Mommeja-Marin H**, Mondou E, Blum MR, Rousseau F. Serum HBV DNA as a marker of efficacy during therapy for chronic HBV infection: analysis and review of the literature. *Hepatology* 2003; **37**: 1309-1319 [PMID: 12774009 DOI: 10.1053/jhep.2003.50208]
16 **Tseng TC**, Liu CJ, Yang HC, Su TH, Wang CC, Chen CL, Hsu CA, Kuo SF, Liu CH, Chen PJ, Chen DS, Kao JH. Serum hepatitis B surface antigen levels help predict disease progression in patients with low hepatitis B virus loads. *Hepatology* 2013; **57**: 441-450 [PMID: 22941922 DOI: 10.1002/hep.26041]
17 **Liang Y**, Jiang J, Su M, Liu Z, Guo W, Huang X, Xie R, Ge S, Hu J, Jiang Z, Zhu M, Wong VW, Chan HL. Predictors of relapse in chronic hepatitis B after discontinuation of anti-viral therapy. *Aliment Pharmacol Ther* 2011; **34**: 344-352 [PMID: 21671967 DOI: 10.1111/j.1365-2036.2011.04738.x]
18 **Liaw YF**, Sung JJ, Chow WC, Farrell G, Lee CZ, Yuen H, Tanwandee T, Tao QM, Shue K, Keene ON, Dixon JS, Gray DF, Sabbat J. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med* 2004; **351**: 1521-1531 [PMID: 15470215 DOI: 10.1056/NEJMoa033364]
19 **Wong GL**, Chan HL, Mak CW, Lee SK, Ip ZM, Lam AT, Iu HW, Leung JM, Lai JW, Lo AO, Chan HY, Wong VW. Entecavir treatment reduces hepatic events and deaths in chronic hepatitis B patients with liver cirrhosis. *Hepatology* 2013; **58**: 1537-1547 [PMID: 23389810 DOI: 10.1002/hep.26301]
20 **Jenh AM**, Pham PA. Tenofovir disoproxil fumarate in the treatment of chronic hepatitis B. *Expert Rev Anti Infect Ther* 2010; **8**: 1079-1092 [PMID: 20954872 DOI: 10.1586/eri.10.91]
21 **Buti M**, Homs M. Tenofovir disoproxil fumarate in the treatment of chronic hepatitis B. *Expert Rev Gastroenterol Hepatol* 2012; **6**: 413-421 [PMID: 22928893 DOI: 10.1586/egh.12.19]
22 **Scott LJ**, Keating GM. Entecavir: a review of its use in chronic hepatitis B. *Drugs* 2009; **69**: 1003-1033 [PMID: 19496629 DOI: 10.2165/00003495-200969080-00005]
23 **Perry CM**, Simpson D. Tenofovir disoproxil fumarate: in chronic hepatitis B. *Drugs* 2009; **69**: 2245-2256 [PMID: 19852527 DOI: 10.2165/10482940-000000000-00000]
24 **Keating GM**. Entecavir: a review of its use in the treatment of chronic hepatitis B in patients with decompensated liver disease. *Drugs* 2011; **71**: 2511-2529 [PMID: 22141390 DOI: 10.2165/11208510-000000000-00000]
25 **Petersen J**, Buti M. Considerations for the long-term treatment of chronic hepatitis B with nucleos(t)ide analogs. *Expert Rev Gastroenterol Hepatol* 2012; **6**: 683-693; quiz 694 [PMID: 23237254 DOI: 10.1586/egh.12.52]
26 **Woo G**, Tomlinson G, Nishikawa Y, Kowgier M, Sherman M, Wong DK, Pham B, Ungar WJ, Einarson TR, Heathcote EJ, Krahn M. Tenofovir and entecavir are the most effective antiviral agents for chronic hepatitis B: a systematic review and Bayesian meta-analyses. *Gastroenterology* 2010; **139**: 1218-1229 [PMID: 20600036 DOI: 10.1053/j.gastro.2010.06.042]
27 **Chang TT**, Liaw YF, Wu SS, Schiff E, Han KH, Lai CL, Safadi R, Lee SS, Halota W, Goodman Z, Chi YC, Zhang H, Hindes R, Iloeje U, Beebe S, Kreter B. Long-term entecavir therapy results in the reversal of fibrosis/cirrhosis and continued histological improvement in patients with chronic hepatitis B. *Hepatology* 2010; **52**: 886-893 [PMID: 20683932 DOI: 10.1002/hep.23785]
28 **Lupberger J**, Hildt E. Hepatitis B virus-induced oncogenesis. *World J Gastroenterol* 2007; **13**: 74-81 [PMID: 17206756]
29 **But DY**, Lai CL, Yuen MF. Natural history of hepatitis-related hepatocellular carcinoma. *World J Gastroenterol* 2008; **14**: 1652-1656 [PMID: 18350595]
30 **Friedman SL**. Mechanisms of hepatic fibrogenesis. *Gastroenterology* 2008; **134**: 1655-1669 [PMID: 18471545 DOI: 10.1053/j.gastro.2008.03.003]
31 **Neuveut C**, Wei Y, Buendia MA. Mechanisms of HBV-related hepatocarcinogenesis. *J Hepatol* 2010; **52**: 594-604 [PMID: 20185200 DOI: 10.1016/j.jhep.2009.10.033]
32 **Tan YJ**. Hepatitis B virus infection and the risk of hepatocellular carcinoma. *World J Gastroenterol* 2011; **17**: 4853-4857 [PMID: 22171125 DOI: 10.3748/wjg.v17.i44.4853]
33 **Zoulim F**, Testoni B, Lebossé F. Kinetics of intrahepatic covalently closed circular DNA and serum hepatitis B surface antigen during antiviral therapy for chronic hepatitis B: lessons from experimental and clinical studies. *Clin Gastroenterol Hepatol* 2013; **11**: 1011-1013 [PMID: 23602824 DOI: 10.1016/j.cgh.2013.04.010]
34 **Wong DK**, Seto WK, Fung J, Ip P, Huang FY, Lai CL, Yuen MF. Reduction of hepatitis B surface antigen and covalently closed circular DNA by nucleos(t)ide analogues of different potency. *Clin Gastroenterol Hepatol* 2013; **11**: 1004-1010.e1 [PMID: 23376799 DOI: 10.1016/j.cgh.2013.01.026]
35 **Park YN**. Update on precursor and early lesions of hepatocellular carcinomas. *Arch Pathol Lab Med* 2011; **135**: 704-715 [PMID: 21631263 DOI: 10.1043/2010-0524-RA.1]
36 **Lam YF**, Yuen MF, Seto WK, Lai CL. Current Antiviral Therapy of Chronic Hepatitis B: Efficacy and Safety. *Curr Hepat Rep* 2011; **10**: 235-243 [PMID: 22131901 DOI: 10.1007/s11901-011-0109-z]
37 **Hoofnagle JH**, Doo E, Liang TJ, Fleischer R, Lok AS. Management of hepatitis B: summary of a clinical research workshop. *Hepatology* 2007; **45**: 1056-1075 [PMID: 17393513 DOI: 10.1002/hep.21627]
38 **Ayoub WS**, Keeffe EB. Review article: current antiviral therapy of chronic hepatitis B. *Aliment Pharmacol Ther* 2011; **34**: 1145-1158 [PMID: 21978243 DOI: 10.1111/j.1365-2036.2011.04869.x]
39 **Tseng TC**, Liu CJ, Yang HC, Su TH, Wang CC, Chen CL, Kuo SF, Liu CH, Chen PJ, Chen DS, Kao JH. High levels of hepatitis B surface antigen increase risk of hepatocellular carcinoma in patients with low HBV load. *Gastroenterology* 2012; **142**: 1140-1149.e3; quiz e13-e14 [PMID: 22333950 DOI: 10.1053/j.gastro.2012.02.007]
40 **Lai CL**, Yuen MF. Prevention of hepatitis B virus-related hepatocellular carcinoma with antiviral therapy. *Hepatology* 2013; **57**: 399-408 [PMID: 22806323 DOI: 10.1002/hep.25937]
41 **Papatheodoridis GV**, Lampertico P, Manolakopoulos S, Lok A. Incidence of hepatocellular carcinoma in chronic hepatitis B patients receiving nucleos(t)ide therapy: a systematic review. *J Hepatol* 2010; **53**: 348-356 [PMID: 20483498 DOI: 10.1016/j.jhep.2010.02.035]
42 **Thiele M**, Gluud LL, Dahl EK, Krag A. Antiviral therapy for prevention of hepatocellular carcinoma and mortality in chronic hepatitis B: systematic review and meta-analysis. *BMJ Open* 2013; **3**: [PMID: 23945731 DOI: 10.1136/bmjopen-2013-003265]
43 **Sung JJ**, Tsoi KK, Wong VW, Li KC, Chan HL. Meta-analysis: Treatment of hepatitis B infection reduces risk of hepatocellular carcinoma. *Aliment Pharmacol Ther* 2008; **28**: 1067-1077

[PMID: 18657133 DOI: 10.1111/j.1365-2036.2008.03816.x]
44 **Gordon SC**, Lamerato LE, Rupp LB, Li J, Holmberg SD, Moorman AC, Spradling PR, Teshale EH, Vijayadeva V, Boscarino JA, Henkle EM, Oja-Tebbe N, Lu M. Antiviral therapy for chronic hepatitis B virus infection and development of hepatocellular carcinoma in a US population. *Clin Gastroenterol Hepatol* 2014; **12**: 885-893 [PMID: 24107395 DOI: 10.1016/j.cgh.2013.09.062]
45 **Kim W**, Berg T, Loomba R, Schall RA, Dinh P, Yee L, Martins E, Flaherty J, Gurel S, Buti M. Long term tenofovir disoproxil fumarate (TDF) therapy and the risk of hepatocellular carcinoma [Abstract]. 48th Annual Meeting of the European Association for the Study of the Liver (EASL 2013); 2013 April 24-28; Amsterdam, The Netherlands: S19
46 **Yang HI**, Yuen MF, Chan HL, Han KH, Chen PJ, Kim DY, Ahn SH, Chen CJ, Wong VW, Seto WK. Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. *Lancet Oncol* 2011; **12**: 568-574 [PMID: 21497551 DOI: 10.1016/S1470-2045(11)70077-8]
47 **Yuen MF**, Tanaka Y, Fong DY, Fung J, Wong DK, Yuen JC, But DY, Chan AO, Wong BC, Mizokami M, Lai CL. Independent risk factors and predictive score for the development of hepatocellular carcinoma in chronic hepatitis B. *J Hepatol* 2009; **50**: 80-88 [PMID: 18977053 DOI: 10.1016/j.jhep.2008.07.023]
48 **Wong VW**, Chan SL, Mo F, Chan TC, Loong HH, Wong GL, Lui YY, Chan AT, Sung JJ, Yeo W, Chan HL, Mok TS. Clinical scoring system to predict hepatocellular carcinoma in chronic hepatitis B carriers. *J Clin Oncol* 2010; **28**: 1660-1665 [PMID: 20194845 DOI: 10.1200/JCO.2009.26.2675]
49 **Lee D**, Lee J-H, Cho Y, Lee YB, Kwon JH, Yu SJ, Kim YJ, Yoon J-H, Lee H-S, Kim CY. Entecavir treatment significantly reduces the risk of hepatocellular carcinoma recurrence in patients with chronic hepatitis B [Abstract]. 63rd Annual Meeting of the American Association for the Study of Liver Diseases (AASLD) 2012; 2012 November 9-13, 2012; Boston, MA, USA: Wiley-Blackwell 111 River St, Hoboken 07030-5774, NJ USA: 371A-371A
50 **Lampertico P**, Soffredini R, Vigano M, Minola E, Cologni G, Rizzi M, Zaltron S, Vavassori A, Carosi G, Angeli E. Entecavir treatment for NUC naïve, field practice patients with chronic hepatitis B: excellent viral suppression and safety profile over 5 years of treatment. 63rd Annual Meeting of the American Association for the Study of Liver Diseases (AASLD) 2012; 2012 November 9-13, 2012; Boston, MA, USA: Wiley-Blackwell 111 River St, Hoboken 07030-5774, NJ USA: 370A-371A
51 **Wong DK**, Yuen MF, Ngai VW, Fung J, Lai CL. One-year entecavir or lamivudine therapy results in reduction of hepatitis B virus intrahepatic covalently closed circular DNA levels. *Antivir Ther* 2006; **11**: 909-916 [PMID: 17302253]
52 **Bowden S**, Locarnini SA, Chang TT, Chao Y-C, Han KH, Gish RG, de Man R, Llamoso C, Tang H. Impact of Entecavir versus lamivudine on hepatic covalently closed-circular DNA and total hepatic HBV DNA in nucleoside-naïve HBeAg positive chronic hepatitis B patients [Poster]. 48th EASL The International Liver Congress 2013; 2013 April 24-28, 2013; Amsterdam, The Netherlands

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CASE CONTROL STUDY

Ischemic heart disease, factor predisposing to Barrett's adenocarcinoma: A case control study

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Abstract

AIM: To define the significance of ischemic heart disease (IHD) (stable angina to infarction) co-existance in Barrett esophagus (BE) patients and patients with esophageal adenocarcinoma (AdE).

METHODS: All BE/AdE patients in Blackpool-Wyre-Fylde area and Trikala prefecture identified from medical records. Patient clinical details were obtained from hospital and General Practitioner records. Additional information was gathered from validated questionnaire.

RESULTS: Forty (33%) AdE and 83 (19%) BE patients had IHD (P = 0.002). Eighteen (15%) AdE and 34 (8%) BE patients had suffered a myocardial infarction (P = 0.03). Three (3%) AdE and 7 (2%) BE patients had severe heart failure (P = 0.82). Thirty-nine (47%) BE with IHD and 8 (20%) AdE patients with IHD consumed aspirin daily (P = 0.004). Seventh-seven (93%) BE patients with IHD and 36 (90%) AdE patients with IHD were on statins (P = 0.86). Logistic regression analysis: AdE was more frequent in the elderly, with long term reflux, long BE and concurrent IHD (odds ratio: 2.086, P = 0.001) not consuming statins. Eighteen (22%) BE patients with IHD [16 (84%) with myocardial infarction] *vs* 33 (10%) without IHD died from non-neoplastic causes within 24 mo from BE diagnosis (P = 0.005).

CONCLUSION: IHD is more prevalent in AdE than BE patients. Increased prevalence of AdE is related with the presence of myocardial infarction but not severe heart failure, possibly because patients with BE and severe IHD have low life expectancy.

Key words: Barrett esophagus; Esophageal adenocarcinoma; Ischemic heart disease; Myocardial infarction; Non-steroidal anti-inflammatory drugs

Core tip: Esophageal adenocarcinoma is a major health problem. We performed a population based retrospective comparison, shown that ischemic heart disease is twice as common among patients with esophageal adenocarcinoma than among those with uncomplicated Barrett esophagus. Although myocardial infarction was more frequently acquired in patients with esophageal adenocarcinoma, grade Ⅲ or Ⅳ class heart failure was not, because patients with Barrett esophagus and severe heart failure usually have a low life expectancy and rarely survive longer than 2 years. Patients with Barrett esophagus and ischemic heart disease receive aspirin or nitrates every day more frequently than patients with esophageal adenocarcinoma.

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INTRODUCTION

Gastro-esophageal reflux disease (GERD), a pathology characterized by reflux of gastric juice into the esophagus is rather common[1]. In case of prolonged and excessive GERD esophageal mucosa is replaced by metaplastic columnar epithelium. This condition is called Barrett's oesophagus (BE)[2], and represents the main risk factor for esophageal adenocarcinoma (AdE) development[3].

One of the main macroscopic features of BE is a net of new blood vessels formed within esophageal mucosa. Although Barrett's epithelium is mainly supplied from the submucosal lamina propria vasculature, presence of neovasculirization emphasizes why BE is a precancerous lesion and why it can predispose to dysplasia and AdE development[4]. Barrett epithelium oxygen saturation remains high (approximately 90%) throughout the metaplastic process[5], because microvasculature density rises stepwise as BE evolves towards AdE[6]. Esophageal inflammation enriches stromal angiogenesis[7], while acid reflux causes periodic hypoxia[8]. Several markers of hypoxia, including oxygen-regulated transcription factor subunit hypoxia inducible factor-1alpha and vascular endothelial growth factor, have been related toadvanced BE[9,10], Neovascularization markers, such as endoglin (CD-105), have been reported to be up-regulated in patients with high-grade dysplasia and AdE[11].

It is not uncommon, to mix up esophageal with cardiac pain. Therefore GERD may be misclassified as ischemic heart disease (IHD) and vice versa[12]. Moreover GERD is rather common among patients with IHD, especially those with unstable angina[13]. Circulating angiogenetic markers are increased in patients with IHD especially those with myocardial infarction (MI)[14] or severe congestive heart failure[15]. In addition, IHD could alter mucosal microcirculation causing topical ischemia[16] and through nitric oxide reduction, impairment of the mucosal defense[17] and mucosal adaptation to noxious stimuli[18]. Thus, it is expected that IHD might increase the risk of BE patients to develop AdE. Nevertheless, there are no data on the role of concurrent IHD in BE patients.

Our study aimed to calculate the prevalence of IHD (stable angina to infarction) in BE and AdE patients and study its significance in this patient group.

MATERIALS AND METHODS

BE-AdE case finding

The study included all BE or AdE cases, aged over 18 years living permanently either in Blackpool-Wyre-Fylde (BWF) NHS area (318886 inhabitants during 1991 census), between August 1, 1996 and July 31, 2001 or in the prefecture of Trikala (132689 inhabitants during 2001 census), between January 1, 2002 and December 31, 2005. Study design was similar in both study periods[19]. Endoscopy service was available only in Victoria Hospital in BWF, while it was available both in Trikala General Hospital and private services in Trikala prefecture. Nevertheless we requested private service gastroenterologists to refer both BE and AdE cases in Trikala General Hospital during the study period. To secure complete case identification PT searched patient clinical notes, hospital endoscopy records, histology registers, operating theatre registers and death certificates to ascertain full case identification and gather a full clinical and drug history for every patient. General practitioners (GPs) and adjacent district hospitals were also contacted to provide additional cases who had an endoscopy outside the study hospitals during the study period as well as additional clinical information.

All BE or AdE subjects provided and completed an adapted and validated version of Reflux Symptom Questionnaire[20], on their first visit after endoscopical and histological case verification.The study questionnaire provided clinical and drug details as described elsewhere[19]. For deceased patients the closest relative provided information to complete the study questionnaire. Thirty percent of patients failed to return the study questionnaire. We contacted them by phone and collected relevant data during the phone call.

For any discrepancy between questionnaire data and clinical records we favor the latter with the exception of over the counter non-steroidal anti-inflammatory drugs (NSAIDs) consumption, and deliberate ignorance to GP prescriptions.

Patient characteristics

Patient characteristics definition has been described in detail elsewhere[19]. Thus, we recorded as active smokers all cases reporting any cigarette consumption the 10 year period preceding case recording. Total cigarette consumption recorded separately in pack-years. We recorded as alcohol abusers all cases consuming daily more than 50 g of pure alcohol the 10 year period preceding case recording We recorded as NSAIDs consumers all cases consuming NSAIDs at least once a week the 10 year period preceding case recording. Daily NSAID consumption for at least 2 years NSAIDs users was recorded as daily one. Aspirin and non-aspirin NSAID consumption was recorded separately. Patients were considered users of nitrates, calcium channel blockers, beta blockers and statins if they consumed them at least 3 d/wk, the 10 year period preceding case recording. To avoid reverse causality, any medical therapy started less than 4 years before the study period was disregarded.

Based on body mass index (BMI) all cases were classified in 4 grades: grade 0: BMI $<$ 20, grade 1: 20 $\leqslant$ BMI $<$ 25, grade 2: 25 $\leqslant$ BMI $<$ 30, grade 3: BMI $\geqslant$ 30.

We calculated the mean of frequency and duration of reflux recordings checked in every patient visit.

Diagnosis of ischemic heart disease (IHD) was based on clinical (angina), electrocardiographic, echocardiographic, scintigraphic and coronary arteriographic data Hospitalizations for unstable angina or MI were recorded separately. PT and PI discussed objective findings and agreed IHD diagnosis. We used New York Heart Association Functional Classification to classify heart failure[21].

We calculated socioeconomic status, as described by Ford *et al*[22], utilizing patient residential postcode and data from 1991 census (for BWF or 2001 Greek census for Greek patients). According to their socioeconomic status all cases were classified in three classes: lower, middle and high socioeconomic status.

Endoscopy

We defined BE endoscopically as salmon pink mucosa extending at least 2 cm above the proximal end of the gastric folds. We measured BE length during endoscope withdrawal, and calculated tumor size measuring the distance between the two tumor edges and the incisors. Only adenocarcinomas co-existing with BE were included in case analysis and only when the centre of the tumour was over or above the gastroesophageal junction.

We recorded only hiatal hernias greater than 3 cm of length.

Histology

During endoscopy we obtained biopsies in BE patients every 2 cm from all 4 quadrants. Presence of goblet cells and villi defined specialised epithelium[23]. We grades dysplasia as negative, low grade, high grade[24]. Cases with high grade dysplasia were not recorded as AdEs.

Two pathologists reviewed the pathology of all resected AdE specimens. Mucinous tumors, adenosquamous cancers, and poorly differentiated tumors not expressing cytokeratins 7 and 13 were excluded from the analysis.

Ethics

Both BWF Ethics Committee and Trikala Hospital Scientific Council standing for Trikala Hospital Ethics Committee approved the study. All cases signed informed consent before entering the study.

Statistical analysis

We used chi-square test with Yates' correction for non-parametric comparisons and student's *t*-test for parametric values. We overcomed biases due to known risk factors using logistic regression analysis Dependent parameters entered in the analysis were: age (per decade), male gender, BE length (per 5 cm), hiatal hernia length (per 5 cm), duration of reflux, daily use of aspirin, use of statins, high socioeconomic status. All of them represented well known risk factors for AdE development. We also evaluated the role of IHD. For each parameter we calculated the odds ratio (OR) and the corresponding 95%CI of OR.

Taking into consideration the results of a pilot study performed in BWF[25] and found that 20% of BE and 41% of AdE patients had IHD, we calculated that the study should include at least 36 BE patients with IHD to reach a power of 80%.

RESULTS

Patients

We found 193 patients with a lower esophageal adenocarcinoma in BWF. After histologic evaluation we excluded 30 (18%) patients with a tumor of the gastric cardia, 30 (18%) with an AdE without any co-existing BE, and 19 (12%) AdEs withscarce traces of BE. In the latter it was impossible to calculate Barrett length. We also found 10 lower esophageal adenocarcinomas in Trikala prefecture. We excluded 2 (20%) patients with a tumor of the gastric cardia and another 2 (20%) with an AdE without co-existing BE. Thus from the two hospitals 120 AdE patients were entered the study.

We identified 869 patients with salmon pink mucosa in the lower esophagus in BWF, compartible with BE. We excluded 238 (27%) patients because histologic definition was unavailable and 249 (39%) because histology reported the presence of fundic, cardiac or junctional mucosa instead of specialized columnar epithelium. We found another 78 patients with endoscopic BE in Trikala prefecture. We excluded 34 (44%) of them because histology identified only fundic, cardiac or junctional mucosa. Thus 426 BE patients were entered the study.

Both BE and AdE patients who entered the study were not different than those excluded (Table 1).

Patients with AdE were older than BE ones; presented a longer BE; which was less frequently co-existed with a hiatal hernia and they were complained for heartburn for a longer period of time (Table 2). Main demographic and BE related characteristics were independent to reflux complaints (Table 3).

Patients with IHD

Forty (33%) AdE and 83 (19%) BE patients had IHD ($P = 0.002$). Of them 18 (15%) AdE and 34 (8%) BE patients had suffered a MI ($P = 0.03$), while 3 (3%) AdE and 7 (2%) BE patients had grade Ⅲ or Ⅳ class heart failure ($P = 0.82$).

Patients with IHD and AdE, when compared to BE patients with IHD were less frequently diabetics had consumed fewer cigarettes and had a longer reflux history. Forty-two (51%) BE patients with IHD and 12 (30%) AdE patients with IHD were on aspirin treatment ($P = 0.03$). Of them 39 (47%) BE and 8 (20%) AdE patients consumed aspirin daily ($P = 0.004$). Twelve (14%) BE patients with IHD and 20 (50%) AdE patients with IHD were on clopidogrel ($P < 0.0001$). All of them persistent dyspepsia, when they have tried aspirin short-term. Twenty-nine (35%) BE patients with IHD had stopped antiplatelet treatment, due to persistent ulcerative lesions (14 duodenal ulcers, 8 gastric ulcers and 10 esophageal ulcers). Eight (20%) AdE patients with IHD had abandoned antiplatelet treatment ($P = 0.14$); 3 due to persistent duodenal ulcer, 1 due to persistent gastric ulcer and 4 due to persistent esophageal ulcer. Seventh-seven (93%) BE patients with IHD were on statins for hypelipidemia. Thirty-six (90%) AdE patients with IHD were also on statins ($P = 0.86$). Six (7%) BE and 4 (10%) AdE patients had stopped statin treatment due to side effects ($P = 0.86$), mainly elevation of transaminases, resolved after medication cessation. Seventy-nine (95%)

Table 1 Clinical effects of aspirin in high risk population (clinical trials) *n* (%)

Characteristics	Patients in the analysis	Patients excluded from the analysis	*P*
Patients with esophageal adenocarcinoma			
n	83	120	
Age [mean (SD)], yr	73 (SD = 11.3)	73 (SD = 11.5)	1.00
Male gender	73 (61)	58 (70)	0.19
Current smokers	44 (37)	33 (40)	0.66
Cig. Cons. (in PY) [mean (SD)]	22.5 (SD = 30.2)	22.1 (SD = 27.3)	0.92
Alcohol abusers	32 (27)	21 (25)	0.96
BMI ⩾ 25	57 (48)	40 (47)	0.96
Presence of hiatus hernia	73 (61)	52 (63)	0.91
Ischemic heart disease	40 (33)	27 (33)	0.97
Use of aspirin	17 (14)	12 (14)	0.88
Low socioeconomic status	26 (22)	18 (22)	0.87
Dur of reflux [in Y-mean (SD)]	28.5 (SD = 10.1)	27.8 (SD = 12.2)	0.66
Freq of refl (d/wk) [mean (SD)]	5.4 (SD = 2.4)	5.4 (SD = 2.6)	1.00
Patients with Barrett's esophagus			
n	426	521	
Age [mean (SD)], yr	68 (SD = 14)	68 (SD = 13)	1.00
Male gender	264 (62)	316 (61)	0.73
Current smokers	136 (32)	174 (33)	0.68
Cig. Cons. (in PY) [mean (SD)]	19.8 (SD = 28.4)	20.3 (SD = 29.4)	0.79
Alcohol abusers	108 (25)	130 (25)	0.95
BMI ⩾ 25	232 (54)	283 (54)	0.98
Barrett's length (in cm)	6.6 (SD = 3.9)	6.6 (SD = 3.7)	1.00
Presence of hiatus hernia	304 (71)	371 (71)	0.98
Ischemic heart disease	83 (19)	99 (19)	0.92
Use of aspirin	87 (20)	109 (21)	0.91
Low socioeconomic status	69 (16)	83 (16)	0.98
Dur of reflux [in Y-mean (SD)]	16.1 (SD = 9.9)	16.4 (SD = 10.2)	0.65
Freq of refl (d/wk) [mean (SD)]	5.1 (SD = 2.3)	5.1 (SD = 2.5)	1.00

Cig. Cons.: Cigarette consumption in total throughout life; PY: Pack-years; BMI: Body mass index; Dur of reflux: Duration of reflux; Freq of refl (d/wk): Frequency of reflux episodes in days/week.

Table 2 Comparison of the main demographic endoscopic and clinical characteristics between patients with Barrett's esophagus and esophageal adenocarcinoma *n* (%)

Characteristics	Barrett's esophagus (*n* = 426)	Esophageal adenocarcinoma (*n* = 120)	*P*
Age [mean (SD)], yr	68 (SD = 14)	73 (SD = 11)	0.0003
Male gender	264 (61)	73 (61)	0.82
Smokers	136 (32)	44 (37)	0.39
Cig. Cons. (in PY) [mean (SD)]	19.8 (SD = 28.4)	22.5 (SD = 30.2)	0.36
Alcohol abusers	108 (25)	32 (27)	0.86
Barrett's length (in cm)	6.6 (SD = 3.9)	7.5 (SD = 4.2)	0.03
Presence of hiatus hernia	304 (71)[1]	73 (61)	0.04
BMI ⩾ 25	232 (54)	57 (48)	0.21
Low socioeconomic status	69 (16)	26 (22)	0.21
Dur of reflux (in Y) [mean (SD)]	16.1 (SD = 9.9)	28.5 (SD = 10.1)	< 0.0001
Freq of reflux (d/wk) [mean (SD)]	5.1 (SD = 2.3)	5.4 (SD = 2.4)	0.21

[1]Thirty/fifty (60%) of patients with short segment Barrett present a hiatus hernia, as well as 5/10 (50%) with AdE on short segment Barrett esophagus. Y: Years; Cig. Cons.: Cigarette consumption in total throughout life; PY: Pack-years; BMI: Body mass index; Dur of reflux: Duration of reflux; Freq of reflux (d/wk): Frequency of reflux episodes in days/week.

BE patients with IHD and 37 (93%) AdE patients with IHD were on beta-blockers ($P = 0.85$). Sixty-two (75%) BE patients with IHD and 19 (47%) AdE patients with IHD were on sphincter relaxing medication ($P = 0.005$). Of them 57 (69%) BE and 14 (35%) AdE patients were on nitrates ($P = 0.0004$), while 15 (18%) BE and 15 (38%) AdE patients were on calcium channel blockers ($P = 0.02$). Main risk factors and treatment receiving in BE and AdE patients with IHD are presenting in Table 4.

Logistic regression analysis

Logistic regression analysis in the whole study population revealed that AdE was more frequent in the elderly; in those with long term reflux complaints; with longer BE and and in those with concurrent IHD (odds ratio: 2.086, 95%CI: 1.339-2.257, $P = 0.001$), AdE was less frequent

Table 3 Comparison of the main demographic endoscopic and clinical characteristics between patients with Barrett esophagus without reflux symptoms and those with gastroesophageal reflux *n* (%)

Characteristics	Asymptomatic patients *n* = 40	Patients with GERD *n* = 386	*P*
Age [mean (SD)], yr	68 (SD = 8)	68 (SD = 15)	0.50
Male gender	28 (70)	236 (61)	0.35
Smokers	17 (43)	119 (31)	0.18
Cig. Cons. (in PY) [mean (SD)]	22.7 (SD = 29.6)	17.4 (SD = 25.6)	0.12
Alcohol abusers	13 (33)	95 (25)	0.37
Barrett's length (in cm)	7.4 (SD = 5.1)	6.6 (SD = 3.9)	0.12
Presence of hiatus hernia	26 (65)	278 (72)	0.45
BMI ⩾ 25	18 (45)	214 (55)	0.27
Low socioeconomic status	7 (18)	62 (16)	0.99

GERD: Gastroesophageal reflux disease; Cig. Cons.: Cigarette consumption in total throughout life; PY: Pack-years; BMI: Body mass index.

Table 4 Main demographic and disease related characteristics and treatment received in patients with ischemic heart disease and Barrett esophagus or esophageal adenocarcinoma *n* (%)

Characteristic	BE *n* = 83	AdE *n* = 40	*P*
Age [mean (SD)], yr	75 (SD = 10)	78 (SD = 10)	0.12
Male gender	54 (65)	23 (58)	0.54
Active smokers	23 (28)	10 (25)	0.92
Alcohol abusers	18 (22)	8 (20)	0.98
Cig. Cons. (in PY) [mean (SD)]	43 (SD = 25)	33 (SD = 17)	0.02
Low socioeconomic status	21 (25)	12 (30)	0.74
Diabetes	16 (19)	1 (3)	0.02
Barrett's length (in cm)	6.4 (SD = 3.6)	7.1 (SD = 4.4)	0.35
Presence of hiatal hernia	55 (66)	27 (68)	0.95
Hyperlipidemia under treatment	77 (93)	36 (90)	0.86
Hypertension	58 (70)	30 (75)	0.71
Dur ref (in years) [mean (SD)]	19 (SD = 10)	28 (SD = 10)	< 0.0001
Freq ref (d/wk): [mean (SD)]	5.3 (SD = 2.3)	6 (SD = 2)	0.1
BMI ⩾ 25	45 (54)	19 (48)	0.61
Use of beta-blockers	79 (95)	37 (93)	0.85
Sphincter relaxing medication	62 (75)	19 (47)	0.005
Low dose aspirin	42 (51)	12 (30)	0.03
Low dose aspirin daily	39 (47)	8 (20)	0.004

Cig. Cons.: Cigarette consumption in total throughout life; PY: Pack years; BMI: Body mass index; Dur ref: Duration of reflux; Freq ref (d/wk): Frequency of reflux episodes; BE: Barrett esophagus; AdE: Esophageal adenocarcinoma.

in statin consumers (Table 5).

Follow-up

Nineteenth (23%) BE patients with IHD *vs* 33 (10%) without IHD died from non-neoplastic causes within 24 mo from BE diagnosis ($P = 0.002$). Sixteen (84%) BE patients with IHD who deceased within 2 years from BE diagnosis, had suffered a MI or had grade Ⅲ or Ⅳ class heart failure ($P = 0.01$).

DISCUSSION

We performed a population based retrospective study and found that IHD was almost twice as frequent in AdE patients as those with uncomplicated BE. Although MI was more frequently acquired in AdE patients, grade Ⅲ or Ⅳ class heart failure was not, because the majority of BE patients with severe heart failure do not survive longer than 2 years. BE patients with IHD consumed aspirin daily and nitrates more frequently than AdE patients and calcium channel blocker less frequently.

Despite its population-based design and thorough case evaluation our study has several drawbacks. It is retrospective, and not large enough to draw strong conclusions.

Patients with AdE have no choice but to come to medical attention. On the other hand BE patients are usually referred for endoscopy only if they present severe persistent GERD. It is very difficult to exclude reference related biases, nevertheless a small minority of BE patients without GERD were referred for endoscopy[26] and we can speculate the features of BE population escaping medical attention by studying this population. We have shown that patients with BE and reflux symptoms were not different than BE patients without reflux in various demographic and disease related characteristics. Thus, we expect that our study population might be representative of the total BE population in BWF.

It is still uncertain whether the presence of specialized epithelium in the lower esophagus is exclusively related to AdE development[27]. Some authorities believe intestinal metaplasia absence is only a reflection of sampling error and that it will invariably be present if meticulously searched[28]. Nevertheless, the risk of non-columnar intestinal metaplasia to progress to AdE is still debatable[29]. By excluding patients without a histological verification of intestinal metaplasia, we limited our BE population and increasing bias due to BE underreporting. On the other hand, because there was no difference between patients included and those excluded from the analysis in any demographic or disease related characteristic, we avoided bias related to poor defined cases or overestimation of BE length due to esophageal inflammation.

Over-expression of various angiogenetic factors, such as hypoxia-inducible factor or vascular endothelial growth factor permits human myocardium to adapt to coronary ischemia[30]. Nevertheless, as those angiogenetic factors enter general circulation they can produce BE

Table 5 Logistic regression analysis, in the whole study population, for known risk factors for esophageal adenocarcinoma development, various conditions co-existing with non-steroidal anti-inflammatory drugs use and various subgroups of non-steroidal anti-inflammatory drugs use

Variable	Odds ratio	CI of odds ratio	*P*
Age (per decade)	1.315	1.220-1.514	<0.001
Male gender	0.946	0.622-1.437	0.75
BE length (per 5 cm)	1.289	1.043-1.547	0.045
Length of HH (per 5 cm)	0.924	0.847-1.007	0.06
Duration of reflux (in decades)	1.848	1.686-2.060	<0.001
IHD	2.086	1.339-3.257	0.001
Daily aspirin use	0.623	0.346-1.111	0.65
Use of statins	0.576	0.356-0.918	0.02
Low socioeconomic status	1.411	0.844-2.351	0.43

IHD: Ischaemic heart disease; BE: Barrett esophagus.

hyperproliferation and augment BE malignant potential[4]. After all, tissue hypoxia has been related to cancer development[31] and epidermal growth factor up-regulation due to cardiac ischemia[32], can favor carcinogenesis within BE[33]. Finally, oxidative phosphorylation up-regulation[34] and subsequent reactive oxygen species overproduction, due to peripheral hypoperfusion increases the mutagenic pressure and raises genetic instability[35]. Thus, we expected and we found that IHD is more frequently acquired in AdE than BE patients, especially those suffered an MI.

Old age is more prevalent in AdE patients and IHD is a disease of old age[36]. Thus it is possible that higher IHD incidence in AdE patients is solely a result of old age. Nevertheless, IHD was an independent risk factor for AdE in multiple regression analysis and pathogenetic mechanisms support a deleterious effect of IHD in BE patients.

Deleterious effect of IHD on BE progression to malignancy is balanced by reduced life expectancy of those patients, especially those with severe heart failure[37]. In concordance to Moayyedi *et al*[38] we have reported a high mortality in BE patients with concurrent IHD, especially those with a MI or with severe heart failure.

Observational study data from BE patients are disappointing concerning aspirin protective effect. Both our case control study in BE/AdE patients[19] and Kastelein *et al*[39] prospective study identified no protection from low-dose aspirin use in BE patients. Opposing our findings in general BE population, daily aspirin use in BE patients with IHD seems to be beneficial, possibly because of it improves cardiac and peripheral circulation and prevents over-expression of angiogenetic factors.

Epidemiological data agree that statin use could protect BE patients from AdE development[39-42]. Although use of statins was less frequent in AdE than BE patients, its use was almost universal in patients with IHD, preventing identification of their possible beneficial properties.

We have already reported, in concordance with Ladanchuk *et al*[43] that nitrates have no influence in BE patients[19]. Nevertheless, we found that nitrates had a beneficial role in BE patients with IHD. Beneficial role of nitrates/sphincter relaxing medication in BE patients with IHD could be incidental, mirroring not a truly protective relationship but the small number of patients studied. Nevertheless it could also be a result of cardiac and peripheral perfusion improvement after nitrate use.

In conclusion IHD is more prevalent in AdE than BE patients. Use of low-dose aspirin and nitrates in this study group is encouraging. More studies are needed to show if IHD is more frequent in BE patients because they are older or verify that IHD is deleterious for BE patients and unveil the pathogenetic mechanisms (increase of angiogenetic and growth factors) beneath it. Those studies should be prospective, multicentric and large enough to overcome possible biases faced in our study.

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COMMENTS

Background

Gastro-esophageal reflux disease is a common condition resulting from reflux of gastric or intestinal contents into the esophagus. Prolonged reflux may lead to replacement of esophageal lining by pathological lining resembling large bowel, a condition known as Barrett's oesophagus. The most serious complication of Barrett's oesophagus is the development of esophageal adenocarcinoma. Barrett's lining is characterised by the presence of pathological vessels and overproduction of various substances promoting the production of pathological vessels. Such substances are overproduced in ischemic heart disease. No studies today have addressed any correlation of Barrett's esophagus to ischemic heart disease. People only know that ischemic heart disease is the main cause of death in Barrett's patients.

Research frontiers

Various substances promoting the production of pathological vessels have a key role in the development of esophageal adenocarcinoma in patients with Barrett's esophagus. Population studies suggest that aspirin and statins, to cornerstones of ischemic heart disease treatment can prevent the development of esophageal adenocarcinoma in patients with Barrett's esophagus.

Innovations and breakthroughs

This study has shown that ischemic heart disease was almost twice as frequent in cancer patients as those with uncomplicated Barrett's esophagus. Myocardial infarction, as severe complication of ischemic heart disease was more frequent as well. Severe heart failure was not, because the majority of Barrett's esophagus patients do not survive longer than 2 years. Barrett patients more frequently used daily aspirin and nitrate use with ischemic heart disease than patients with esophageal adenocarcinoma.

Applications

Patients with Barrett's esophagus and ischemic heart disease disserve more frequent endoscopies in order to identify esophageal adenocarcinoma early. Aspirin and statin treatment is useful in this patient group and can reduce the risk to develop esophageal adenocarcinoma.

Peer review

This is an excellent study as it's the first report to explore the relationship be-

tween ischemic heart disease and Barrett esophageal adenocarcinoma. The case control study was well designed and carried out, and the manuscript is clearly written. The results are believable, and the conclusions are acceptable.

REFERENCES

1 **Pope CE**. Acid-reflux disorders. *N Engl J Med* 1994; **331**: 656-660 [PMID: 8052276 DOI: 10.1056/NEJM199409083311007]
2 **Spechler SJ**, Goyal RK. The columnar-lined esophagus, intestinal metaplasia, and Norman Barrett. *Gastroenterology* 1996; **110**: 614-621 [PMID: 8566611 DOI: 10.1053/gast.1996.v110.agast960614]
3 **Cook MB**, Wild CP, Everett SM, Hardie LJ, Bani-Hani KE, Martin IG, Forman D. Risk of mortality and cancer incidence in Barrett's esophagus. *Cancer Epidemiol Biomarkers Prev* 2007; **16**: 2090-2096 [PMID: 17890521 DOI: 10.1158/1055-9965.EPI-07-0432]
4 **Auvinen MI**, Sihvo EI, Ruohtula T, Salminen JT, Koivistoinen A, Siivola P, Rönnholm R, Rämö JO, Bergman M, Salo JA. Incipient angiogenesis in Barrett's epithelium and lymphangiogenesis in Barrett's adenocarcinoma. *J Clin Oncol* 2002; **20**: 2971-2979 [PMID: 12089227 DOI: 10.1200/JCO.2002.09.011]
5 **Amelink A**, Haringsma J, Sterenborg HJ. Noninvasive measurement of oxygen saturation of the microvascular blood in Barrett's dysplasia by use of optical spectroscopy. *Gastrointest Endosc* 2009; **70**: 1-6 [PMID: 19249768 DOI: 10.1016/j.gie.2008.08.039]
6 **Konda VJ**, Hart J, Lin S, Tretiakova M, Gordon IO, Campbell L, Kulkarni A, Bissonnette M, Seewald S, Waxman I. Evaluation of microvascular density in Barrett's associated neoplasia. *Mod Pathol* 2013; **26**: 125-130 [PMID: 22918163 DOI: 10.1038/modpathol.2012.146]
7 **Moriyama N**, Amano Y, Mishima Y, Okita K, Takahashi Y, Yuki T, Ishimura N, Ishihara S, Kinoshita Y. What is the clinical significance of stromal angiogenesis in Barrett's esophagus? *J Gastroenterol Hepatol* 2008; **23** Suppl 2: S210-S215 [PMID: 19120900 DOI: 10.1111/j.1440-1746.2008.05440.x]
8 **Baatar D**, Jones MK, Tsugawa K, Pai R, Moon WS, Koh GY, Kim I, Kitano S, Tarnawski AS. Esophageal ulceration triggers expression of hypoxia-inducible factor-1 alpha and activates vascular endothelial growth factor gene: implications for angiogenesis and ulcer healing. *Am J Pathol* 2002; **161**: 1449-1457 [PMID: 12368217 DOI: 10.1016/S0002-9440(10)64420-3]
9 **Griffiths EA**, Pritchard SA, McGrath SM, Valentine HR, Price PM, Welch IM, West CM. Increasing expression of hypoxia-inducible proteins in the Barrett's metaplasia-dysplasia-adenocarcinoma sequence. *Br J Cancer* 2007; **96**: 1377-1383 [PMID: 17437013]
10 **Lord RV**, Park JM, Wickramasinghe K, DeMeester SR, Oberg S, Salonga D, Singer J, Peters JH, Danenberg KD, Demeester TR, Danenberg PV. Vascular endothelial growth factor and basic fibroblast growth factor expression in esophageal adenocarcinoma and Barrett esophagus. *J Thorac Cardiovasc Surg* 2003; **125**: 246-253 [PMID: 12579092 DOI: 10.1067/mtc.2003.203]
11 **Bellone G**, Solerio D, Chiusa L, Brondino G, Carbone A, Prati A, Scirelli T, Camandona M, Palestro G, Dei Poli M. Transforming growth factor-beta binding receptor endoglin (CD105) expression in esophageal cancer and in adjacent nontumorous esophagus as prognostic predictor of recurrence. *Ann Surg Oncol* 2007; **14**: 3232-3242 [PMID: 17682823 DOI: 10.1245/s10434-007-9528-z]
12 **Kato H**, Ishii T, Akimoto T, Urita Y, Sugimoto M. Prevalence of linked angina and gastroesophageal reflux disease in general practice. *World J Gastroenterol* 2009; **15**: 1764-1768 [PMID: 19360921 DOI: 10.3748/wjg.15.1764]
13 **Schultz T**, Mannheimer C, Dellborg M, Pilhall M, Börjesson M. High prevalence of gastroesophageal reflux in patients with clinical unstable angina and known coronary artery disease. *Acute Card Care* 2008; **10**: 37-42 [PMID: 17851977 DOI: 10.1080/17482940701364877]
14 **Iribarren C**, Phelps BH, Darbinian JA, McCluskey ER, Quesenberry CP, Hytopoulos E, Vogelman JH, Orentreich N. Circulating angiopoietins-1 and -2, angiopoietin receptor Tie-2 and vascular endothelial growth factor-A as biomarkers of acute myocardial infarction: a prospective nested case-control study. *BMC Cardiovasc Disord* 2011; **11**: 31 [PMID: 21672190 DOI: 10.1186/1471-2261-11-31]
15 **Min SY**, Park DW, Yun SC, Kim YH, Lee JY, Kang SJ, Lee SW, Lee CW, Kim JJ, Park SW, Park SJ. Major predictors of long-term clinical outcomes after coronary revascularization in patients with unprotected left main coronary disease: analysis from the MAIN-COMPARE study. *Circ Cardiovasc Interv* 2010; **3**: 127-133 [PMID: 20407112 DOI: 10.1161/CIRCINTERVENTIONS.109.890053]
16 **Furkalo NK**, Tsygankov AT, Radzivil VV. Clearance of radioactive xenon in evaluating microcirculation in patients with ischaemic heart disease. *Cor Vasa* 1985; **27**: 60-67 [PMID: 3995994]
17 **Lanas A**, Soteras F, Jimenez P, Fiteni I, Piazuelo E, Royo Y, Ortego J, Iñarrea P, Esteva F. Superoxide anion and nitric oxide in high-grade esophagitis induced by acid and pepsin in rabbits. *Dig Dis Sci* 2001; **46**: 2733-2743 [PMID: 11768267 DOI: 10.1023/A:1012735714983]
18 **Lanas AI**, Blas JM, Ortego J, Soria J, Sáinz R. Adaptation of esophageal mucosa to acid- and pepsin-induced damage: role of nitric oxide and epidermal growth factor. *Dig Dis Sci* 1997; **42**: 1003-1012 [PMID: 9149055]
19 **Tsibouris P**, Hendrickse MT, Isaacs PE. Daily use of non-steroidal anti-inflammatory drugs is less frequent in patients with Barrett's oesophagus who develop an oesophageal adenocarcinoma. *Aliment Pharmacol Ther* 2004; **20**: 645-655 [PMID: 15352913 DOI: 10.1111/j.1365-2036.2004.02150.x]
20 **Locke GR**, Talley NJ, Weaver AL, Zinsmeister AR. A new questionnaire for gastroesophageal reflux disease. *Mayo Clin Proc* 1994; **69**: 539-547 [PMID: 8189759 DOI: 10.1016/S0025-6196(12)62245-9]
21 **The Criteria Committee of the New York Heart Association.** Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co, 1994: 253-256
22 **Ford AC**, Forman D, Reynolds PD, Cooper BT, Moayyedi P. Ethnicity, gender, and socioeconomic status as risk factors for esophagitis and Barrett's esophagus. *Am J Epidemiol* 2005; **162**: 454-460 [PMID: 16076833 DOI: 10.1093/aje/kwi218]
23 **Paull A**, Trier JS, Dalton MD, Camp RC, Loeb P, Goyal RK. The histologic spectrum of Barrett's esophagus. *N Engl J Med* 1976; **295**: 476-480 [PMID: 940579 DOI: 10.1056/NEJM197608262950904]
24 **Reid BJ**, Weinstein WM, Lewin KJ, Haggitt RC, VanDeventer G, DenBesten L, Rubin CE. Endoscopic biopsy can detect high-grade dysplasia or early adenocarcinoma in Barrett's esophagus without grossly recognizable neoplastic lesions. *Gastroenterology* 1988; **94**: 81-90 [PMID: 3335302]
25 **Tsibouris P.** Ischemic heart disease, factor predisposing to Barrett's adenocarcinoma. *Gut* 2000; **47**(Suppl III): A69 [Abstract]
26 **Rudolph RE**, Vaughan TL, Storer BE, Haggitt RC, Rabinovitch PS, Levine DS, Reid BJ. Effect of segment length on risk for neoplastic progression in patients with Barrett esophagus. *Ann Intern Med* 2000; **132**: 612-620 [PMID: 10766679 DOI: 10.7326/0003-4819-132-8-200004180-00003]
27 **Wang KK**, Sampliner RE. Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett's esophagus. *Am J Gastroenterol* 2008; **103**: 788-797 [PMID: 18341497 DOI: 10.1111/j.1572-0241.2008.01835.x]
28 **DeMeester SR**. Letter to the editor regarding "Definition of Barrett's esophagus: time for a rethink-is intestinal metapla-

sia dead?". *Am J Gastroenterol* 2010; **105**: 1201-1202; author reply 1201-1202 [PMID: 20445513]

29 **Bennett C**, Vakil N, Bergman J, Harrison R, Odze R, Vieth M, Sanders S, Gay L, Pech O, Longcroft-Wheaton G, Romero Y, Inadomi J, Tack J, Corley DA, Manner H, Green S, Al Dulaimi D, Ali H, Allum B, Anderson M, Curtis H, Falk G, Fennerty MB, Fullarton G, Krishnadath K, Meltzer SJ, Armstrong D, Ganz R, Cengia G, Going JJ, Goldblum J, Gordon C, Grabsch H, Haigh C, Hongo M, Johnston D, Forbes-Young R, Kay E, Kaye P, Lerut T, Lovat LB, Lundell L, Mairs P, Shimoda T, Spechler S, Sontag S, Malfertheiner P, Murray I, Nanji M, Poller D, Ragunath K, Regula J, Cestari R, Shepherd N, Singh R, Stein HJ, Talley NJ, Galmiche JP, Tham TC, Watson P, Yerian L, Rugge M, Rice TW, Hart J, Gittens S, Hewin D, Hochberger J, Kahrilas P, Preston S, Sampliner R, Sharma P, Stuart R, Wang K, Waxman I, Abley C, Loft D, Penman I, Shaheen NJ, Chak A, Davies G, Dunn L, Falck-Ytter Y, Decaestecker J, Bhandari P, Ell C, Griffin SM, Attwood S, Barr H, Allen J, Ferguson MK, Moayyedi P, Jankowski JA. Consensus statements for management of Barrett's dysplasia and early-stage esophageal adenocarcinoma, based on a Delphi process. *Gastroenterology* 2012; **143**: 336-346 [PMID: 22537613 DOI: 10.1053/j.gastro.2012.04.032]

30 **Lee SH**, Wolf PL, Escudero R, Deutsch R, Jamieson SW, Thistlethwaite PA. Early expression of angiogenesis factors in acute myocardial ischemia and infarction. *N Engl J Med* 2000; **342**: 626-633 [PMID: 10699162 DOI: 10.1056/NEJM200003023420904]

31 **Picardo SL**, Maher SG, O'Sullivan JN, Reynolds JV. Barrett's to oesophageal cancer sequence: a model of inflammatory-driven upper gastrointestinal cancer. *Dig Surg* 2012; **29**: 251-260 [PMID: 22868386 DOI: 10.1159/000341498]

32 **Matsumoto S**, Kishida K, Shimomura I, Maeda N, Nagaretani H, Matsuda M, Nishizawa H, Kihara S, Funahashi T, Matsuzawa Y, Yamada A, Yamashita S, Tamura S, Kawata S. Increased plasma HB-EGF associated with obesity and coronary artery disease. *Biochem Biophys Res Commun* 2002; **292**: 781-786 [PMID: 11922634 DOI: 10.1006/bbrc.2002.6720]

33 **Menke V**, Pot RG, Moons LM, van Zoest KP, Hansen B, van Dekken H, Siersema PD, Kusters JG, Kuipers EJ. Functional single-nucleotide polymorphism of epidermal growth factor is associated with the development of Barrett's esophagus and esophageal adenocarcinoma. *J Hum Genet* 2012; **57**: 26-32 [PMID: 22129558 DOI: 10.1038/jhg.2011.124]

34 **Suchorolski MT**, Paulson TG, Sanchez CA, Hockenbery D, Reid BJ. Warburg and Crabtree effects in premalignant Barrett's esophagus cell lines with active mitochondria. *PLoS One* 2013; **8**: e56884 [PMID: 23460817 DOI: 10.1371/journal.pone.0056884]

35 **Berridge MV**, Herst PM, Tan AS. Metabolic flexibility and cell hierarchy in metastatic cancer. *Mitochondrion* 2010; **10**: 584-588 [PMID: 20709626 DOI: 10.1016/j.mito.2010.08.002]

36 **DE Jonge PJ**, Wolters LM, Steyerberg EW, VAN Dekken H, Kusters JG, Kuipers EJ, Siersema PD. Environmental risk factors in the development of adenocarcinoma of the oesophagus or gastric cardia: a cross-sectional study in a Dutch cohort. *Aliment Pharmacol Ther* 2007; **26**: 31-39 [PMID: 17555419 DOI: 10.1111/j.1365-2036.2007.03344.x]

37 **Solaymani-Dodaran M**, Card TR, West J. Cause-specific mortality of people with Barrett's esophagus compared with the general population: a population-based cohort study. *Gastroenterology* 2013; **144**: 1375-1383, 1383.e1 [PMID: 23583429 DOI: 10.1053/j.gastro.2013.02.050]

38 **Moayyedi P**, Burch N, Akhtar-Danesh N, Enaganti SK, Harrison R, Talley NJ, Jankowski J. Mortality rates in patients with Barrett's oesophagus. *Aliment Pharmacol Ther* 2008; **27**: 316-320 [PMID: 18062791 DOI: 10.1111/j.1365-2036.2007.03582.x]

39 **Kastelein F**, Spaander MC, Biermann K, Steyerberg EW, Kuipers EJ, Bruno MJ. Nonsteroidal anti-inflammatory drugs and statins have chemopreventative effects in patients with Barrett's esophagus. *Gastroenterology* 2011; **141**: 2000-2008; quiz 2000-2008; [PMID: 21878200 DOI: 10.1053/j.gastro.2011.08.036]

40 **Nguyen DM**, Richardson P, El-Serag HB. Medications (NSAIDs, statins, proton pump inhibitors) and the risk of esophageal adenocarcinoma in patients with Barrett's esophagus. *Gastroenterology* 2010; **138**: 2260-2266 [PMID: 20188100 DOI: 10.1053/j.gastro.2010.02.045]

41 **Kantor ED**, Onstad L, Blount PL, Reid BJ, Vaughan TL. Use of statin medications and risk of esophageal adenocarcinoma in persons with Barrett's esophagus. *Cancer Epidemiol Biomarkers Prev* 2012; **21**: 456-461 [PMID: 22241250 DOI: 10.1158/1055-9965.EPI-11-1014]

42 **Beales IL**, Vardi I, Dearman L. Regular statin and aspirin use in patients with Barrett's oesophagus is associated with a reduced incidence of oesophageal adenocarcinoma. *Eur J Gastroenterol Hepatol* 2012; **24**: 917-923 [PMID: 22569083 DOI: 10.1097/MEG.0b013e3283543f01]

43 **Ladanchuk TC**, Johnston BT, Murray LJ, Anderson LA. Risk of Barrett's oesophagus, oesophageal adenocarcinoma and reflux oesophagitis and the use of nitrates and asthma medications. *Scand J Gastroenterol* 2010; **45**: 1397-1403 [PMID: 20626305 DOI: 10.3109/00365521.2010.503968]

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CASE REPORT

Statins and their role in acute pancreatitis: Case report and literature review

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Abstract

Statin induced pancreatitis has historically been considered a diagnosis of exclusion, with literature references typically in the form of case reports and observational studies. Recently, larger studies have challenged the correlations made by earlier case reports, and instead demonstrate a mild protective effect in statin users. We present a case report of likely statin induced pancreatitis in a 58-year-old male (which we have attributed to drug-drug interaction with resulting inhibition of hepatic cytochrome P450 enzymes) and have reviewed the apparent dichotomy in the available literature.

Key words: Statin; Pancreatitis; CYP450; Inflammation; Toxic

Core tip: Statins may reduce the risk of developing an acute episode of pancreatitis through anti-inflammatory perturbation of the systemic inflammatory response pathway. However, it appears that these drugs may also carry a concomitant long-term risk of pancreatitis through a buildup of toxic metabolite/s.

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INTRODUCTION

Drug-induced pancreatitis has historically been considered a relatively uncommon cause of acute pancreatitis, accounting for 1.4%-2% of all cases[1,2]. However, recent studies indicate that the diagnosis of drug-induced pancreatitis may be underestimated[3,4]. Among the many drugs that have been associated with pancreatitis, lipid-lowering agents-in particular, statins-have been increasingly reported as a cause of acute pancreatitis[5]. More recently, a large population based case control study and meta-analysis have called into question the prevailing consensus regarding the role of statins in the development of acute pancreatitis. This apparent dichotomy in the literature warrants that we re-examine what is known about the role of statins in acute pancreatitis. We present a case of a 58-year-old male incidentally found to have acute pancreatitis in the setting of background statin therapy.

CASE REPORT

A 58-year-old Caucasian male with a past medical history of traumatic brain injury at the age of five with a history of complex partial seizures and renal cell cancer status post right partial nephrectomy presented with syncope. His initial complete blood count (CBC) and electrolyte panel were normal. Head computer tomography (CT) was negative for any intracranial processes. The patient was subsequently managed for vaso-vagal syncope secondary to severe coughing spells. On the day of planned discharge the patient complained of vague pain in his right upper quadrant and epigastrium that had been progressively worsening for the past month. Physi-

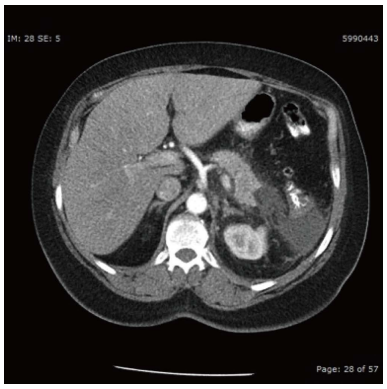

Figure 1 Cross-sectional view of computer tomography abdomen with contrast showing pancreatitis of the body and tail.

cal exam revealed a negative Murphy's sign and labs and imaging were ordered. The ultrasound was negative for gallstone disease, pericholecystic fluid and pericholecystic thickening. Liver function tests (LFTs), white blood cell count, serum creatinine and calcium levels were also within normal limits. Interestingly, lipase and amylase levels were noted to be elevated at 702 units/L (normal values 28-350 units/L) and 417 units/L (normal values 27-117 units/L), respectively. Triglyceride levels were found to be 317 mg/dL, which would unlikely account for an episode of acute pancreatitis (hypertriglyceridemia is typically considered a risk for pancreatitis when levels are > 1000 mg/dL)[6]. In addition, the patient denied any history of alcohol use. He did not have any travel outside of the United States. CT of the abdomen was performed and found to be consistent with an acute episode of pancreatitis without evidence of structural anomaly (Figure 1). After extensive review of his history and the relevant literature, we found that the patient was on three medications [valproic acid (class 1A), omeprazole (class 1B) and simvastatin (class 1A)] that could potentially cause pancreatitis[5]. In this patient's case, venlafaxine (a potent inhibitor of neuronal serotonin and norepinephrine reuptake and weak inhibitor of dopamine reuptake) was started six weeks prior and is extensively metabolized by the same hepatic enzyme (CYP3A4) as simvastatin-which he had been taking for more than 10 years. Omeprazole is extensively metabolized by CYP2C19 with only minor contributions from CYP3A4 while valproic acid is not metabolized by CYP3A4. We accordingly held his simvastatin with subsequent decline in lipase levels and resolution of symptoms in the next 24-48 h.

Notably, the standardized Naranjo Adverse Drug Reaction Probability Scale was used to assess the strength of the suspected link between acute pancreatitis and the above-mentioned drugs (venlafaxine, simvastatin, omeprazole and valproic acid) in this patient. In each case, we deduced the probability to be possible for an adverse drug reaction causing acute pancreatitis[7].

DISCUSSION

Although the mechanism of action of statin induced pancreatitis remains ill defined in the literature, an immune-mediated inflammatory response, direct cellular toxicity and metabolic effect have all been postulated as possible culprits[8]. Three case reports have identified drug-drug interaction as the most likely precipitant. Wong *et al*[9] documented a case of multiple organ toxicity, including acute pancreatitis, which was due to the interaction between lovastatin and erythromycin. Likewise, Abdul-Gaffar and El-Sombaty reported a case of acute pancreatitis with rhabdomyolysis due to the interaction between lovastatin and gemfibrozil[10]. Acute pancreatitis was also reported in the context of interaction between simvastatin and fenofibrate[11]. Interestingly, with regards to combined simvastatin and fenofibrate therapy, Stefanutti *et al*[12] reported no serious adverse effects in 45 patients using this double-drug regimen over a 12 mo period. The above data and previously reported cases of statin-induced pancreatitis during the last 2 decades are reported in Table 1.

These cases are predicated on the inhibitory effect of these drugs on the oxidative metabolism of statins *via* the hepatic cytochrome P450 enzymes, in particular CYP3A4[13]. This is the mechanism that we have postulated in the case above. Venlafaxine is metabolized predominantly by CYP3A4 and was likely the reason that Simvastatin, which was being used for years, had precipitated an episode of acute pancreatitis. Interestingly, fibrates have also been found to inhibit the glucuronidation and non-CYP3A-mediated oxidation of statins[14]. It is important to note that in the case presented above, other more common causes of acute pancreatitis such as alcohol, mechanical ampullary obstruction *via* gallstones, hypercalcemia, hypertriglyceridemia, post-endoscopic retrograde cholangiopancreatography (ERCP) and trauma were initially ruled by history, laboratory tests and gallbladder ultrasound. CT of the abdomen also excluded congenital pancreatic anomaly-which is rather unlikely to have primary occurrence in the 6th decade of life. Initial workup for other less common causes such as autoimmune (IgG4 related) pancreatitis, vasculitis from systemic lupus erythematosis and polyarteritis nodosa was negative.

As an aside, it is noted that the patient above had right partial nephrectomy secondary to a history of renal cell carcinoma. While this has been shown to alter the pharmacokinetics (*e.g.*, decrease in renal metabolism/excretion of drugs) in patients with resultant chronic kidney disease, the above patient did not have evidence of renal impairment and thus this condition was not expected to significantly impact renal drug metabolism[15,16].

Singh and Loke have postulated that there exists differences in the safety profiles of the various statins that may correlate with the degree to which they inhibit cytochrome P450 CYPA4 as well as the degree of their lipophilicity[17]. A subsequent meta-analysis demonstrating a lower incidence of adverse drug reactions with pravastatin (which is the only statin not metabolized by CYP3A4) versus with atorvastatin (which inhibits CYP3A4) gives credence to this idea[18]. Miltiadous *et al*[19] have also documented a case in which acute pancreatitis may have been caused by the interaction between atorvastatin and

Table 1 Previously reported cases of statin-induced pancreatitis

Ref.	Patient (age, yr/gender)	Associated drug/s	Drug rechallenge	Outcome
Abdul-Ghaffar *et al*[10]	55/Female	Lovastatin and gemfibrozil	No	Complete recovery
Wong *et al*[9]	73/Male	Lovastatin and erythromycin	Yes: no recurrence	Complete recovery
Belaïche *et al*[22]	63/Male	Atorvastatin	No	Complete recovery
Tysk *et al*[13]	36/Male	Fluvastatin	Yes: Recurrence	Complete recovery
McDonald *et al*[11]	70/Male	Simvastatin and Fenofibrate	No	Fatal
Miltiadous *et al*[19]	60/Male	Salicylate and Atorvastatin	No	Not available
Anagnostopoulos *et al*[20]	56/Male	Pravastatin	Yes: Recurrence	Complete recovery
Singh *et al*[23]	77/Female	Atorvastatin and Rosuvastatin	Yes; Recurrence with Rosuvastatin	Complete recovery
Antonopoulos *et al*[41]	58/Male	Salicylate and Simvastatin	No	Complete recovery
Tsigrelis*et al*[25]	50/Female	Pravastatin	No	Complete recovery
Chintanaboina*et al*[21]	67/Female	Rosuvastatin	Yes: Recurrence	Complete Recovery
Current report	58/Male	Simvastatin and Venlafaxine	No	Complete Recovery

salicylates, however no possible mechanism of action has been put forward.

Understandably, reintroduction of the likely offending drug following the resolution of symptoms has been largely unfeasible due to the risk of recurrence. As such, their remains a dearth of concrete experimental evidence regarding the precise mechanism of action for the reported cases of statin-induced pancreatitis. Interestingly, the majority of documented instances in which statins have been reintroduced, demonstrate reproducibility of acute pancreatitis and/or symptoms consistent with this diagnosis[8,13,19-21]. However, these findings have not been universal as Belaiche and colleagues have documented a patient who tolerated pravastatin prior to and following an episode of atorvastatin-induced pancreatitis[22]. Furthermore, the latency period from initiation of treatment with a statin to onset of pancreatitis also varies between different statins, ranging from one day to several months[13]. Thus, there is lack of consensus in the literature regarding whether statins exert a class effect or carry distinct and individual risk profiles[13,22,23]. Observations from Singh *et al*[17] however suggest that statin induced pancreatitis rarely occurs early and most commonly occurs months to years after statins have been started. As one would expect, this predilection for later onset favors the buildup of toxic metabolite as an etiologic factor. A more recent cross-sectional study also found that statin use was more frequent among patients with idiopathic acute pancreatitis than in patients with other known etiologies of acute pancreatitis (*e.g.*, alcohol and gallstone-induced). The inherent positive correlation does not however prove causality as it is noted that statin users were more likely to suffer from diabetes, obesity and dyslipidemia-which are all risk factors for acute pancreatitis[24].

A systematic review of observational studies and case reports yielded interesting results as statin-induced pancreatitis was found to have no correlation with the cumulative ingested dose of statins[17]. Analysis of the data revealed that the development of statin-induced pancreatitis was independent of duration of therapy even though it occurred more commonly months to years after treatment with statins. Although statins are generally used more frequently in older individuals, age of the patient was not found to be a major susceptibility factor[17]. It also appears that the majority of cases of statin-induced pancreatitis usually follow a relatively mild course with only a few severe or fatal cases reported[17,25]. This mirrors the natural history of other documented cases of drug-induced pancreatitis[1].

However, as noted above, lack of consensus regarding the precise causal link between statin use and the development of acute pancreatitis still exists. With regards to pathophysiology, acute pancreatitis involves local pancreatic inflammation as well as activation of the systemic inflammatory response system (SIRS)[26]. The latter system is characterized by the activation of multiple cellular processes and humoral cascades which supports the notion that acute pancreatitis results from an imbalance of pro-inflammatory and anti-inflammatory cytokines[27]. Thus, any targeted- intervention should, in theory, be capable of attenuating several arms of the inflammatory cascade. Statins have a diverse range of potent anti-inflammatory properties which are believed to modify the pathogenesis of acute pancreatitis. To this end, Almog *et al*[27] have proposed the following possible effects of statins as it relates to the inflammatory cascade: (1) statins could disrupt ligand receptor interaction step thereby hindering the SIRS cascade; (2) statins could blunt the acute-phase response and its immediate consequences; (3) statins could exert a protective effect on the elegant sequence of endothelial activation, dysfunction; and (4) apoptosis statins may also help create a favorable balance between constitutive nitric oxide synthase and inducible nitric oxide synthase so that maintenance of hemodynamic stability is favored[28-32].

In addition to the above theoretical benefits, Choi *et al*[33] have demonstrated an increase in Heat Shock Protein (HSP) 60 (HSPs are responsible for maintaining cellular homeostasis and help cells survive stress conditions by repairing damaged proteins)and decrease in the release of inflammatory mediators (*e.g.*, IL-1beta, TNF-alpha and IL-6) when statins were used in rats with cholecystokinin-octapeptide (CCK)-induced pancreatitis. Subsequent animal studies have also demonstrated benefit of statin therapy in acute *via* reduction of IL-10 levels and myeloperoxidase activity[28]. Thus, these studies may indicate an anti-inflammatory role-*via* the modulation of various pro

and anti-inflammatory cytokines-for statins in acute pancreatitis, however no long term protective benefit have been yet demonstrated.

In a population based case-control study involving three Danish counties, Thisted *et al*[34] found no strong causative effect of statins on the risk of developing acute pancreatitis. Instead, they found that former statin users (those patients who used statins greater than ninety days prior to hospital admission for acute pancreatitis) were at increased risk of acute pancreatitis. Furthermore, no increased risk among new users (those patients who filled their first statin prescription 0-90 d prior to hospital admission for acute pancreatitis) was shown, arguing against a direct short-term toxic effect of statins. These authors also cite a possible mild protective effect of statins as their results indicated an inverse relationship between the number of filled statin prescriptions and the risk of acute pancreatitis[34]. This finding does not lend support to the theory of a long-term accumulation of a toxic metabolite and may be mediated by the cholesterol and-to a lesser extent-triglyceride lowering effects of statins (it is noted that statins are not the first line therapy for hypertriglyceridemia)[34,35].

More recently, a meta-analysis conducted by Preiss *et al*[36] demonstrated that statin use was associated with a reduced risk of pancreatitis in patients with normal or mildly elevated triglyceride levels. This study also suggests a possible protective effect of statins, citing both the reduction of bile cholesterol levels and reduced risk of gallstone formation in statin users as corroborating evidence[37,38]. However, this meta-analysis is likely to be effected by multiple issues such as the failure of the trials to include pancreatitis as a primary end point, the lack of standardization when recording episodes of pancreatitis, the inability to examine specific causes of pancreatitis such as gallstones, and lack of access to individual-participant data. In addition, because exclusion criteria in the trials tended to exclude patients with marked hypertriglyceridemia, the findings may not be generalizable to that specific group of patients[36].

In light of the evolving evidence regarding statin induced pancreatitis, we believe that statins may reduce the risk of developing an acute episode of pancreatitis through anti-inflammatory perturbation of the systemic inflammatory response pathway. However, it appears that these drugs may also carry a concomitant long-term risk through a buildup of toxic metabolite/s. That being said, the overall mortality benefit of statin use (*e.g.*, especially in patients with recent acute coronary syndrome and established coronary artery disease) clearly outweighs the risk of developing acute pancreatitis based on current evidence[39,40]. Further prospective double blinded trials with statin challenge and re-challenge are necessary to clarify the precise relationship between statin use and the development of acute pancreatitis.

COMMENTS

Case characteristics

A 58 years old male with presenting with sudden onset abdominal pain.

Clinical diagnosis

Characteristic epigastric abdominal pain and tenderness radiating to the back.

Differential diagnosis

Includes acute cholecystitis, gastroesophageal reflux disease, peptic ulcer disease and abdominal aortic dissection.

Laboratory diagnosis

Lipase and amylase levels were elevated at 702 units/L (normal values 28-350 units/L) and 417 units/L (normal values 27-117 units/L), respectively.

Imaging diagnosis

Computer tomography of the abdomen with contrast demonstrated inflammation of the body and tail of the pancreatitis highly suggestive of acute pancreatitis.

Treatment

The offending agent, which in this case was simvastatin, was discontinued in addition to bowel rest and pain control.

Related reports

Please refer to Table 1 for previously reported cases of statin-induced pancreatitis during the last 2 decades.

Experiences and lessons

Careful examination of drug profile and drug-drug interactions is necessary when other more common causes (*e.g.*, gallstone disease, alcohol, *etc.*) of pancreatitis have been excluded.

Peer review

The authors report a case of pancreatitis during treatment with statin, quickly improved after stopping statin intake, and review literature concerning this topic. The manuscript is of sufficient interest, considering the limited knowledge currently available on the possible correlation between use of statins and pancreatitis.

REFERENCES

1 **Lankisch PG**, Dröge M, Gottesleben F. Drug induced acute pancreatitis: incidence and severity. *Gut* 1995; **37**: 565-567 [PMID: 7489946 DOI: 10.1136/gut.37.4.565]

2 **Eland IA**, van Puijenbroek EP, Sturkenboom MJ, Wilson JH, Stricker BH. Drug-associated acute pancreatitis: twenty-one years of spontaneous reporting in The Netherlands. *Am J Gastroenterol* 1999; **94**: 2417-2422 [PMID: 10484002 DOI: 10.1111/j.1572-0241.1999.01367.x]

3 **Vinklerová I**, Procházka M, Procházka V, Urbánek K. Incidence, severity, and etiology of drug-induced acute pancreatitis. *Dig Dis Sci* 2010; **55**: 2977-2981 [PMID: 20499176 DOI: 10.1007/s10620-010-1277-3]

4 **Grendell JH**. Editorial: drug-induced acute pancreatitis: uncommon or commonplace? *Am J Gastroenterol* 2011; **106**: 2189-2191 [PMID: 22138943 DOI: 10.1038/ajg.2011.307]

5 **Badalov N**, Baradarian R, Iswara K, Li J, Steinberg W, Tenner S. Drug-induced acute pancreatitis: an evidence-based review. *Clin Gastroenterol Hepatol* 2007; **5**: 648-661; quiz 644 [PMID: 17395548]

6 **Berglund L**, Brunzell JD, Goldberg AC, Goldberg IJ, Sacks F, Murad MH, Stalenhoef AF. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2012; **97**: 2969-2989 [PMID: 22962670 DOI: 10.1210/jc.2011-3213]

7 **Naranjo CA**, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; **30**: 239-245 [PMID: 7249508 DOI: 10.1038/clpt.1981.154]

8 **Johnson JL**, Loomis IB. A case of simvastatin-associated pancreatitis and review of statin-associated pancreatitis. *Pharmacotherapy* 2006; **26**: 414-422 [PMID: 16503723 DOI: 10.1592/phco.26.3.414]

9 **Wong PW**, Dillard TA, Kroenke K. Multiple organ toxicity from addition of erythromycin to long-term lovastatin therapy. *South Med J* 1998; **91**: 202-205 [PMID: 9496876 DOI: 10.1097/00007611-199802000-00015]

10 **Abdul-Ghaffar NU**, el-Sonbaty MR. Pancreatitis and rhabdomyolysis associated with lovastatin-gemfibrozil therapy.

J Clin Gastroenterol 1995; **21**: 340-341 [PMID: 8583121 DOI: 10.1097/00004836-199512000-00027]
11 **McDonald KB**, Garber BG, Perreault MM. Pancreatitis associated with simvastatin plus fenofibrate. *Ann Pharmacother* 2002; **36**: 275-279 [PMID: 11847949 DOI: 10.1345/aph.1A180]
12 **Stefanutti C**, Bucci A, Di Giacomo S, Fraone N, Pace A, Mareri M, Musca A, Mammarella A. Efficacy, safety and tolerability of combined low-dose simvastatin-fenofibrate treatment in primary mixed hyperlipidaemia. *Clin Drug Investig* 2004; **24**: 465-477 [PMID: 17523707 DOI: 10.2165/00044011-200424080-00005]
13 **Tysk C**, Al-Eryani AY, Shawabkeh AA. Acute pancreatitis induced by fluvastatin therapy. *J Clin Gastroenterol* ; **35**: 406-408 [PMID: 12394230 DOI: 10.1097/00004836-200211000-00010]
14 **Prueksaritanont T**, Tang C, Qiu Y, Mu L, Subramanian R, Lin JH. Effects of fibrates on metabolism of statins in human hepatocytes. *Drug Metab Dispos* 2002; **30**: 1280-1287 [PMID: 12386136 DOI: 10.1124/dmd.30.11.1280]
15 **Meyer JP**, Delves GH, Sullivan ME, Keoghane SR. The effect of nephroureterectomy on glomerular filtration rate. *BJU Int* 2006; **98**: 845-848 [PMID: 16978282 DOI: 10.1111/j.1464-410X.2006.06373.x]
16 **Shirasaki Y**, Tsushima T, Nasu Y, Kumon H. Long-term consequence of renal function following nephrectomy for renal cell cancer. *Int J Urol* 2004; **11**: 704-708 [PMID: 15379932 DOI: 10.1111/j.1442-2042.2004.00879.x]
17 **Singh S**, Loke YK. Statins and pancreatitis: a systematic review of observational studies and spontaneous case reports. *Drug Saf* 2006; **29**: 1123-1132 [PMID: 17147459 DOI: 10.2165/00002018-200629120-00004]
18 **Silva MA**, Swanson AC, Gandhi PJ, Tataronis GR. Statin-related adverse events: a meta-analysis. *Clin Ther* 2006; **28**: 26-35 [PMID: 16490577 DOI: 10.1016/j.clinthera.2006.01.005]
19 **Miltiadous G**, Anthopoulou A, Elisaf M. Acute pancreatitis possibly associated with combined salicylate and atorvastatin therapy. *JOP* 2003; **4**: 20-21 [PMID: 12555012]
20 **Anagnostopoulos GK**, Tsiakos S, Margantinis G, Kostopoulos P, Arvanitidis D. Acute pancreatitis due to pravastatin therapy. *JOP* 2003; **4**: 129-132 [PMID: 12743419]
21 **Chintanaboina J**, Gopavaram D. Recurrent acute pancreatitis probably induced by rosuvastatin therapy: a case report. *Case Rep Med* 2012; **2012**: 973279 [PMID: 22536267]
22 **Belaïche G**, Ley G, Slama JL. [Acute pancreatitis associated with atorvastatine therapy]. *Gastroenterol Clin Biol* 2000; **24**: 471-472 [PMID: 10844297]
23 **Singh S**, Nautiyal A, Dolan JG. Recurrent acute pancreatitis possibly induced by atorvastatin and rosuvastatin. Is statin induced pancreatitis a class effect? *JOP* 2004; **5**: 502-504 [PMID: 15536291]
24 **Pulkkinen J**, Kastarinen H, Kiviniemi V, Jyrkkä J, Juvonen P, Räty S, Paajanen H. Statin use in patients with acute pancreatitis and symptomatic gallstone disease. *Pancreas* 2014; **43**: 638-641 [PMID: 24632548 DOI: 10.1097/MPA.0000000000000068]
25 **Tsigrelis C**, Pitchumoni CS. Pravastatin: a potential cause for acute pancreatitis. *World J Gastroenterol* 2006; **12**: 7055-7057 [PMID: 17109506]
26 **Bhatia M**, Wong FL, Cao Y, Lau HY, Huang J, Puneet P, Chevali L. Pathophysiology of acute pancreatitis. *Pancreatology* 2005; **5**: 132-144 [PMID: 15849484 DOI: 10.1159/000085265]
27 **Almog Y**. Statins, inflammation, and sepsis: hypothesis. *Chest* 2003; **124**: 740-743 [PMID: 12907568 DOI: 10.1378/chest.124.2.740]
28 **Almeida JL**, Sampietre SN, Mendonça Coelho AM, Trindade Molan NA, Machado MC, Monteiro da Cunha JE, Jukemura J. Statin pretreatment in experimental acute pancreatitis. *JOP* 2008; **9**: 431-439 [PMID: 18648134]
29 **Blanco-Colio LM**, Tuñón J, Martín-Ventura JL, Egido J. Anti-inflammatory and immunomodulatory effects of statins. *Kidney Int* 2003; **63**: 12-23 [PMID: 12472764 DOI: 10.1046/j.1523-1755.2003.00744.x]
30 **Kwak BR**, Mach F. Statins inhibit leukocyte recruitment: new evidence for their anti-inflammatory properties. *Arterioscler Thromb Vasc Biol* 2001; **21**: 1256-1258 [PMID: 11498448]
31 **Willerson JT**, Ridker PM. Inflammation as a cardiovascular risk factor. *Circulation* 2004; **109**: II2-I10 [PMID: 15173056]
32 **Liappis AP**, Kan VL, Rochester CG, Simon GL. The effect of statins on mortality in patients with bacteremia. *Clin Infect Dis* 2001; **33**: 1352-1357 [PMID: 11565076 DOI: 10.1086/323334]
33 **Choi OS**, Park SJ, Seo SW, Park CS, Cho JJ, Ahn HJ. The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, lovastatin (statin) ameliorates CCK-induced acute pancreatitis in rats. *Biol Pharm Bull* 2005; **28**: 1394-1397 [PMID: 16079481 DOI: 10.1248/bpb.28.1394]
34 **Thisted H**, Jacobsen J, Munk EM, Nørgaard B, Friis S, McLaughlin JK, Sørensen HT, Johnsen SP. Statins and the risk of acute pancreatitis: a population-based case-control study. *Aliment Pharmacol Ther* 2006; **23**: 185-190 [PMID: 16393296 DOI: 10.1111/j.1365-2036.2006.02728.x]
35 **Stein EA**, Lane M, Laskarzewski P. Comparison of statins in hypertriglyceridemia. *Am J Cardiol* 1998; **81**: 66B-69B [PMID: 9526817 DOI: 10.1016/S0002-9149(98)00041-1]
36 **Preiss D**, Tikkanen MJ, Welsh P, Ford I, Lovato LC, Elam MB, LaRosa JC, DeMicco DA, Colhoun HM, Goldenberg I, Murphy MJ, MacDonald TM, Pedersen TR, Keech AC, Ridker PM, Kjekshus J, Sattar N, McMurray JJ. Lipid-modifying therapies and risk of pancreatitis: a meta-analysis. *JAMA* 2012; **308**: 804-811 [PMID: 22910758 DOI: 10.1001/jama.2012.8439]
37 **Duane WC**, Hunninghake DB, Freeman ML, Pooler PA, Schlasner LA, Gebhard RL. Simvastatin, a competitive inhibitor of HMG-CoA reductase, lowers cholesterol saturation index of gallbladder bile. *Hepatology* 1988; **8**: 1147-1150 [PMID: 3047037 DOI: 10.1002/hep.1840080531]
38 **Bodmer M**, Brauchli YB, Krähenbühl S, Jick SS, Meier CR. Statin use and risk of gallstone disease followed by cholecystectomy. *JAMA* 2009; **302**: 2001-2007 [PMID: 19903921 DOI: 10.1001/jama.2009.1601]
39 **Cannon CP**, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004; **350**: 1495-1504 [PMID: 15007110 DOI: 10.1056/NEJMoa040583]
40 **Kjekshus J**, Pedersen TR. Reducing the risk of coronary events: evidence from the Scandinavian Simvastatin Survival Study (4S). *Am J Cardiol* 1995; **76**: 64C-68C [PMID: 7572690 DOI: 10.1016/S0002-9149(99)80473-1]
41 **Antonopoulos S**, Mikros S, Kokkoris S, Protopsaltis J, Filioti K, Karamanolis D, Giannoulis G. A case of acute pancreatitis possibly associated with combined salicylate and simvastatin treatment. *JOP* 2005; **6**: 264-268 [PMID: 15883478]

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CASE REPORT

Rhabdomyolysis after midazolam administration in a cirrhotic patient treated with atorvastatin

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Abstract

The administration of statins in patients with liver disease is not an absolute contraindication. Hepatotoxicity is a rare and often dose-related event and in the literature there are only a few described cases of fatal rhabdomyolysis in patients with chronic liver disease after statin administration. During treatment with 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, the factors responsible for myopathy may either be related to the patient, or due to interactions with other medications that are metabolic substrates of the same isozymes and therefore able to increase blood statin concentration. The most important side effects consist of increased transaminase levels, abdominal pain or muscle weakness, increased serum levels of creatine kinase and rhabdomyolysis. In this article we report a case of fatal rhabdomyolysis with acute renal failure after gastric endoscopy, where midazolam was used as a sedation agent in a patient with chronic liver disease treated with a high dose of atorvastatin. Therefore, we suggest paying particular attention to the potential risks of associating atorvastatin and midazolam in patients with chronic liver disease who need to undergo gastric endoscopy.

Key words: Rhabdomyolysis; Chronic liver disease; Statins; Midazolam; Alcoholic liver cirrhosis

Core tip: When dealing with alcoholic liver disease, clinicians need to pay particular attention to the administration of drugs, their dosage, interactions and metabolism to avoid severe adverse reactions. Cirrhotic patients on treatment with statins (particularly atorvastatin) are at high risk of developing fatal rhabdomyolysis and acute renal failure when midazolam is used to allow gastric endoscopy.

Gigante A, Di Lazzaro Giraldi G, Gasperini ML, Barbano B, Liberatori M, Sardo L, Di Mario F, Giorgi A, Rossi-Fanelli F, Amoroso A. Rhabdomyolysis after midazolam administration in a cirrhotic patient treated with atorvastatin. *World J Gastrointest Pharmacol Ther* 2014; 5(3): 196-199 Available from: URL: http://www.wjgnet.com/2150-5349/full/v5/i3.196.htm DOI: http://dx.doi.org/10.4292/wjgpt.v5.i3.196

INTRODUCTION

Statins are widely used to treat hypercholesterolemia, therefore reducing cardiovascular risk. Currently, there are no trials on the safety of statins in chronic liver disease. Although hepatotoxicity represents a rare event (< 2%) and is often dose-dependent, adverse effects or even death have been described in patients suffering from liver disease.

The concomitant use of other drugs that are metabolic substrates of the same isoenzymes, as cytochrome P-450 and isoenzyme CYP3A4, can increase statin concentration and consequently elevate the risk of myopathy. The most important side effects consist of increased transaminase levels, abdominal pain or muscle weakness,

Table 1 Biochemical analysis on different days

	ER	Before EGDS	1st day after EGDS	2nd day after EGDS	6th day after EGDS	ICU
ALT (UI/L)	146	52	70	130	207	827
AST (UI/L)	125	117	191	240	927	2075
Total bilirubin (mg/dL)	1.2	2.73	3.39	4.51	6.1	7.44
Direct bilirubin (mg/dL)	0.2	1.86	2.12	3.01	3.8	5.87
INR	1.75	1.7	1.58	1.6	1.68	6.11
Fibrinogen (g/L)	3.52	-	-	-	-	0.58
Platelets (mm^3)	115	54	49	45	70	40
D-dimer (ng/mL)	2557	-	-	-	-	9000
ATⅢ (%)	-	-	-	-	-	20
Myoglobine (ng/mL)	175	198	22.899	25.981	> 30.000	> 30.000
CK (U/L)	81	95	3.298	5.876	38.289	89
CK-MB (ng/mL)	4.2	4.1	14.01	25.03	73.59	68.72
Troponin T HS (mg/L)	0.022	0.025	0.061	0.043	0.189	1.53
LDH (UI/L)	240	286	358	470	1603	2084
Creatinine (mg/dL)	1.1	1.3	1.3	1.3	3.14	3.8
BUN (mg/dL)	45	60	61	59	161	78
Calcium (mg/dL)	8.8	8.4	-	-	6.7	4.4
Diuresis (cc)	-	2000	1300	1000	150	300
BP (mmHg)	90/50	115/60	105/55	95/60	75/50	60/40

EGDS: Esophagogastroduodenoscopy; ICU: Intensive care unit; ALT: Alanine transaminase; AST: Aspartate aminotransferase; ATⅢ: Antithrombin Ⅲ; CK: Creatine kinase; INR: International normalized ratio; Troponin T HS: High sensitivity troponin T; LDH: Lactate dehydrogenase; BUN: Blood urea nitrogen; BP: Blood pressure; ER: Emergency room.

increased levels of creatine kinase and rhabdomyolysis[1,2].

CASE REPORT

A 67-year-old man was admitted to an internal medicine ward at our hospital for syncope. In the emergency room (ER) the patient was oriented, apyretic and had pale skin. His blood pressure was 90/50 mmHg, and he had arrhythmia (80 bpm), swollen abdomen and peristalsis.

Laboratory findings demonstrated abnormal alanine transaminase (146 IU/L), aspartate aminotransferase (125 IU/L), D-dimer (2557), creatine kinase-MB (4.2 ng/mL), platelets (115 × 10^3/μL), glucose (195 mg/dL), myoglobin (175 ng/mL), international normalized ratio (1.75), and high sensitivity troponin T (0.022 mg/L) values (Table 1).

Chest X-ray and brain computed tomography (CT) scans were performed, which showed no notable findings. The patient was admitted to our department for further investigation and treatment. This patient had a history of hospitalization for myocardial infarction three months earlier (treated by percutaneous transluminal coronary angioplasty with implantation of two drug-eluting stents), arterial hypertension, type Ⅱ diabetes mellitus (diagnosed about 7 years earlier) and a more recent diagnosis of chronic atrial fibrillation (AF). Patient's medications included carvedilol 50 mg/d, digoxin 0.125 mg, ramipril 10 mg, duoplavin 75/100 mg, furosemide 25 mg, canrenon 100 mg, pantoprazole 40 mg, insulin, and atorvastatin 40 mg. Our examination revealed that the patient presented with low blood pressure, and physiological anamnesis outlined a history of alcohol abuse (about 2 L of wine for the last 30 years). Electrocardiogram (ECG) showed AF at a frequency of 73 bpm, and a Holter monitor confirmed AF. Ambulatory blood pressure monitoring showed recurrent episodes of hypotension. Carotid ultrasonography and electroencephalography showed no abnormalities consistent with syncope. For this reason, we reduced the dosage of antihypertensive medications (ramipril 5 mg, carvedilol 25 mg) and treated the patient with intravenous fluid administration. During hospitalization, because of persistently elevated transaminase levels, the patient underwent hepatobiliary ultrasonography, which showed increased liver size with heterogeneous echogenicity, irregular surface, but no focal lesions. The average velocity in the portal vein was 8.2 cm/s (normal values ⩾ 14 cm/s). Spleen size was increased, and mild ascites was present.

Therefore markers for viral hepatitis were sought and found to be negative, and thus the patient was diagnosed with alcoholic liver cirrhosis.

During his second day of hospitalization, the patient reported localized muscle pain in the lower limbs associated with intense weakness. Since statin-induced myopathy was suspected, muscular enzymes were assayed and the results were within reference intervals. Nonetheless, atorvastatin administration was discontinued. The next day the patient underwent esophagogastroduodenoscopy (EGDS) under sedation with midazolam (at a dose of 2 mg), which revealed congestive gastropathy in absence of esophageal varices. The day after the examination the patient complained of a further increase in muscle pain with extension to the upper limbs: muscular enzymes levels increased, as showed in Table 1. In the following days, despite the discontinuation of the statin, muscle pain did not regress, and neither did muscle enzymes levels return within reference values (Table 1).

Suspecting a possible drug interaction, digoxin was

suspended too, which is a known common substrate of atorvastin cytochrome (CYP 3A4). However laboratory test values and the patient's condition did not improve. Moreover, six days after EGDS, clinical findings of myoglobinuria, oligo-anuria, acute kidney injury and elevated levels of muscle enzymes (Table 1) suggested the diagnosis of rhabdomyolysis, with the indication to begin hemodialysis (HD).

The patient underwent HD treatment for 5 consecutive days with worsening of pain and persistently elevated muscle enzymes. The condition eventually deteriorated into disseminated intravascular coagulation (DIC). ECG showed a new-onset diffuse ST and T wave changes, and prolonged Q-T interval (0.54 s) associated with severe metabolic acidosis.

The patient was transferred to the intensive care unit (ICU). Biochemical values are reported in Table 1. The patient died the next day, 9 d from the diagnosis of rhabdomyolysis.

DISCUSSION

The use of statins in patients with chronic liver disease is not an absolute contraindication: recommendations suggest to start with low doses, making sure that the patient does not consume alcohol and does not suffer from acute hepatitis. In the literature there are only a few described cases of fatal rhabdomyolysis in patients with liver disease treated with statins[3]. Recent studies suggest that even in liver disease patients, especially those suffering from non-alcoholic steatohepatitis, the indication to use statins stands strong because of the increased cardiovascular risk in these subjects[4].

During treatment with statins, the factors responsible for myopathy may be related to the patient (age, female sex, alcoholism, hypothyroidism, systemic diseases, family history of myopathy, high consumption of grapefruit juice, large physical activity, major surgery, *etc.*) or to interaction with other medications (fibrates, cyclosporine, antifungals, macrolides, protease inhibitors, nefazodone, amiodarone, verapamil, *etc.*)[1]. In our case, we assume that the development of rhabdomyolysis was related to several contributing factors such as the high dose of atorvastatin in a patient with undiagnosed chronic liver disease.

The benefits associated with the use of statins in lowering cholesterol levels and preventing cardiovascular disease still remain superior to their potential risk of hepatotoxicity in patients with chronic liver disease. However, in the course of acute viral or alcoholic hepatitis, HMG-CoA reductase inhibitors should be avoided until liver function is restored[5]. In fact, although major trials have excluded patients with a history of active liver disease, other studies recommended to start with low doses of statins, making sure that the patient does not take alcohol, and to check serum transaminase levels after the first two weeks of therapy, and then each month for three months, eventually reducing the interval to four times a year. If serum transaminase levels are doubled or tripled compared to reference, therapy should be discontinued until normalization of liver enzymes, and then the use of another statin is reconsidered[1,2].

In our case, the trigger for the onset of rhabdomyolysis followed by overt DIC and multi organ failure may have been the use of midazolam, metabolized by the same isoenzyme that is responsible for the metabolism of atorvastatin.

Statins are inhibitors of HMG-CoA reductase undergoing first-pass hepatic metabolism. Excluding pravastatin, other molecules of this class are subject to phase 1 hepatic metabolism mediated by CYP 450 isoenzymes. Isoenzyme CYP3A4 is responsible for atorvastatin, lovastatin and simvastatin metabolism, while fluvastatin and rosuvastatin are metabolized mainly by CYP2C9 isozyme.

Although serum levels of atorvastatin and midazolam were not checked, we assume that the concomitant use of drugs that are substrates of the same CYP isoenzymes, as midazolam and atorvastatin, can dangerously increase statin concentration in the blood and consequently the risk of myopathy.

There are some reports of rhabdomyolysis caused by propofol[6] and its interaction with other statins[7], but this is the first case report documenting rhabdomyolysis after atorvastatin and midazolam administration.

Furthermore, patients with alcohol use disorders (AUD) are at high risk for rhabdomyolysis secondary to toxic effects of ethanol in the muscle, metabolic disturbances, alcohol withdrawal syndrome and sepsis.

In this case report, the fatal outcome of drug-induced rhabdomyolysis may have been promoted by the presence of pre-DIC condition due to liver cirrhosis: the association of both conditions escalated to multiple organ failure.

In conclusion, particular attention must be paid to the potential risks of associating statins, such as atorvastatin, with other drugs especially in patients with AUD and chronic liver disease. The use of midazolam as a sedation agent should be avoided in patients needing EGDS while treated with statins.

COMMENTS

Case characteristics

The patient complained of muscle pain in the lower and upper limbs associated with intense weakness.

Clinical diagnosis

Clinical findings included elevated transaminases and muscle enzymes, myoglobinuria, oligo-anuria, acute kidney injury, disseminated intravascular coagulation, prolonged Q-T interval (0.54 s) and severe metabolic acidosis.

Differential diagnosis

Rhabdomyolysis in the presence of pre-disseminated intravascular coagulation (pre-DIC) condition due to secondary toxic effects of ethanol in the muscle, metabolic disturbances, alcohol withdrawal syndrome and sepsis.

Laboratory diagnosis

Findings demonstrated elevated transaminases, muscle enzymes, serum creatinine, myoglobinuria, and disseminated intravascular coagulation.

Imaging diagnosis

Hepatobiliary ultrasonography showed increased liver size with heterogeneous echogenicity and irregular surface, and the average velocity in the portal vein

was low. Increased spleen size and mild ascites were also present.

Treatment

Atorvastatin and other drugs metabolized by the same cytochrome isozyme were discontinued; fluid IV administration and hemodialysis were given.

Related reports

The concomitant use of substrates of the same isozymes (CYP3A4), such as midazolam and atorvastatin, can increase statin blood concentration and consequently the risk of myopathy.

Experiences and lessons

The indication for the use of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors in cirrhotic patients must be evaluated by physicians on the basis of clinical necessity. It is correct to start with low-dose drug administration while monitoring transaminases. Finally, it is appropriate to evaluate simultaneous administration of other drugs metabolized by the same cytochrome, therefore reducing the risk of moderate and severe interactions.

Peer review

It was a nicely written case report. It suggests that rhabdomyolysis may have been related to the simultaneous administration of atorvastatin and midazolam in a patient with alcoholic liver disease.

REFERENCES

1 **Joy TR**, Hegele RA. Narrative review: statin-related myopathy. *Ann Intern Med* 2009; **150**: 858-868 [PMID: 19528564 DOI: 10.7326/0003-4819-150-12-200906160-00009]

2 **Needham M**, Mastaglia FL. Statin myotoxicity: a review of genetic susceptibility factors. *Neuromuscul Disord* 2014; **24**: 4-15 [PMID: 24176465 DOI: 10.1016/j.nmd.2013.09.011]

3 **Baek SD**, Jang SJ, Park SE, Ok TJ, Leem J, Lee HS, Park SJ, Kim TH. Fatal rhabdomyolysis in a patient with liver cirrhosis after switching from simvastatin to fluvastatin. *J Korean Med Sci* 2011; **26**: 1634-1637 [PMID: 22148003 DOI: 10.3346/jkms.2011.26.12.1634]

4 **Tandra S**, Vuppalanchi R. Use of statins in patients with liver disease. *Curr Treat Options Cardiovasc Med* 2009; **11**: 272-278 [PMID: 19627660 DOI: 10.1007/s11936-009-0028-2]

5 **Russo MW**, Jacobson IM. How to use statins in patients with chronic liver disease. *Cleve Clin J Med* 2004; **71**: 58-62 [PMID: 14740969 DOI: 10.3949/ccjm.71.1.58]

6 **Casserly B**, O'Mahony E, Timm EG, Haqqie S, Eisele G, Urizar R. Propofol infusion syndrome: an unusual cause of renal failure. *Am J Kidney Dis* 2004; **44**: e98-101 [PMID: 15558515 DOI: 10.1053/j.ajkd.2004.08.036]

7 **Francis L**, Bonilla E, Soforo E, Neupane H, Nakhla H, Fuller C, Perl A. Fatal toxic myopathy attributed to propofol, methylprednisolone, and cyclosporine after prior exposure to colchicine and simvastatin. *Clin Rheumatol* 2008; **27**: 129-131 [PMID: 17628739 DOI: 10.1007/s10067-007-0696-9]

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In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

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Books

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Chapter in a book (list all authors)

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Conference proceedings

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Conference paper

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Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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