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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 specifcity 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 modifcation, medical therapy and surgical therapy. Lifestyle modifcations 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-refux 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 refux disease.

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

Core tip: Given the high prevalence of gastroesophageal refux 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 refux of gastric contents into the esophagus or beyond, into the oral cavity (including larynx) or lung[1,2]. GERD can be classifed as non-erosive refux disease (NERD) or erosive refux 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

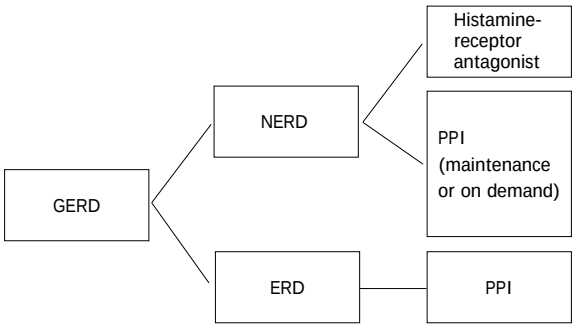

Figure 1 In general, patients with gastroesophageal reflux disease who are found to have evidence of erosive esophagitis on endoscopy should be placed on maintenance proton pump inhibitor due to the high risk of relapse off proton pump inhibitor. However, patients with NERD may achieve symptom control 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].

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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 fstulizing 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; Infammatory 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.

Swaminath A, Taunk R, Lawlor G. Use of methotrexate in infammatory bowel disease in 2014: A User's Guide. *World J Gastrointest Pharmacol Ther* 2014; 5(3): 113-121 Available from: URL: http://www.wjgnet.com/2150-5349/full/v5/i3.113.htm DOI: http://dx.doi.org/10.4292/wjgpt.v5.i3.113

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 efcacy in Infammatory 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 efcacy 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 fstula 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 fstulas 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 fstula, 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 fstulas 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 fstulas.

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	19.9 mg 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 25 mg	Oral *sc*/*im*	68 23	Retrospective	60	25/68 (37%) 7/23 (30%)		N/A

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.

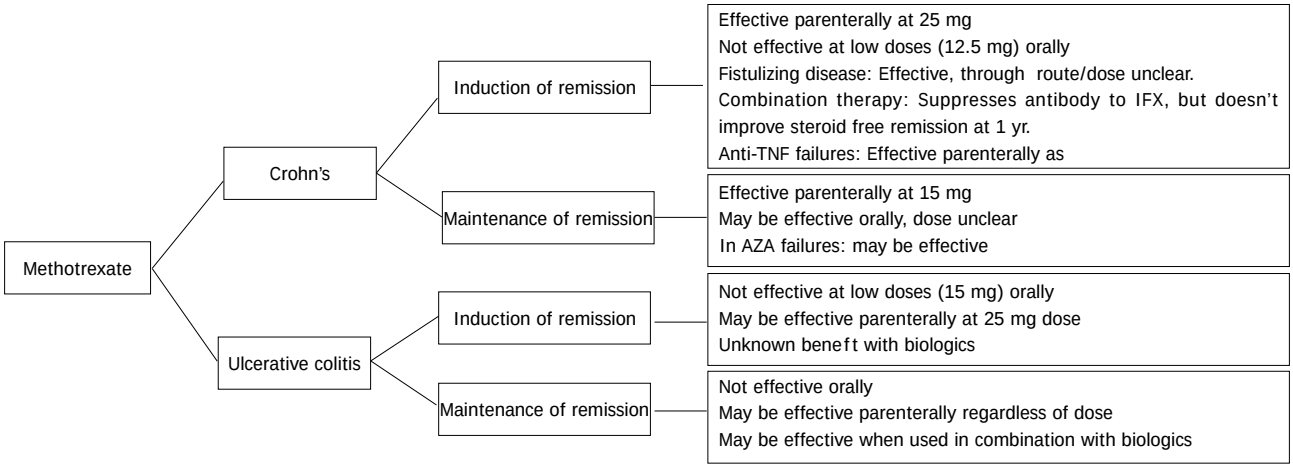

Figure 1 Algorithm for evidence-based use of methotrexate in inflammatory bowel disease. AZA: Azathioprine.

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.

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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 briefy 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 levofoxacin resistance primarily in patients with chronic infectious bronchopneumopathy as they may have already received fuoroquinolones[26]. Structured patient counseling and follow-up might improve the patient compliance and effcacy of the therapy[104] and therefore, assist preventing antibiotic resistance. Secondly, the drug interaction is of signifcant 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 modifcation 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 signifcant 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 specifc characteristics of geriatric population.

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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.

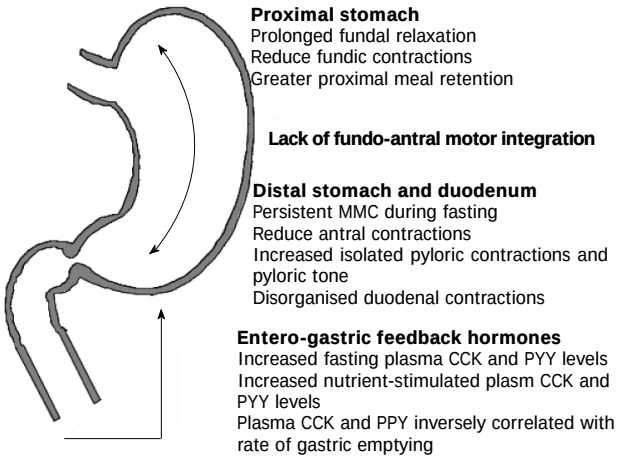

Figure 1 Gastric motor abnormalities reported during critical illness. CCK: Cholecystokinin; PYY: peptide YY.

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

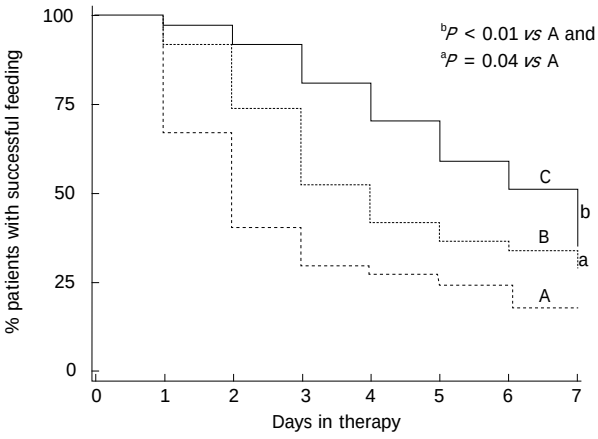

Figure 2 Efficacy of metoclopramide (A), erythromycin (B) and combined erythromycin and metoclopramide (C) in the treatment of feed intolerance of critical illness over 7-d period.

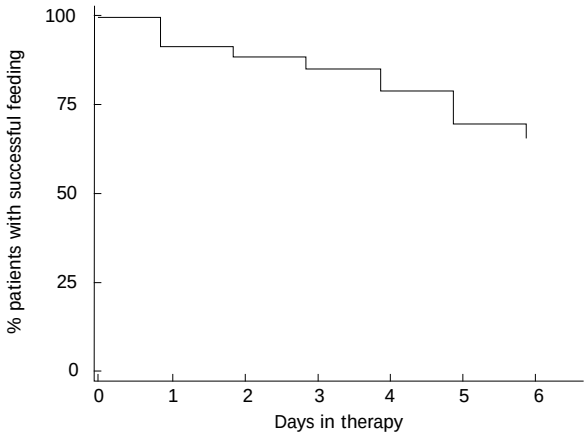

Figure 3 Efficacy of rescue combined metoclopramide and erythromycin in critically ill patients who failed to response to either erythromycin or metoclopramide in the treatment of feed intolerance.

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.

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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 fuid 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 clarifes 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 modifed 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 defned 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 feld

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 signifcant 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 defnitions 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 signifcant 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 $\geqslant$ 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 defnition for acute kidney injury (AKI), a new term for acute renal failure, in order to be identifed earlier patients with worse prognosis. According to AKIN criteria, AKI is defned as an increase in sCr level $\geqslant$ 0.3 mg/dL ($\geqslant$ 26.4 μmol/L) or $\geqslant$ 150% (1.5 fold from baseline) within 48 h from the frst 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 fve 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 $\geqslant$ 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 modifed cirrhosis-AKI classifcation 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 $\leqslant$ 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 modifed classifcation a better risk stratifcation 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 fbrosis and with the GFR better than sCr[35-37], but this has not been confrmed 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: Modifed 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 fltration markers. Particularly for patients with established HRS, a modifcation 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 modifcation, 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 feld), 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 frst which should be excluded by the algorithm of Angeli *et al*[5]. The acute renal function is proposed to be assessed with modifed 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 fuid 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 clarifed 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 fuid 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 fxed 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% fbrosis
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 fbrosis
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 fltration rate; GS: Glomerulosclerosis; MDRD-6: Modifcation 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 fushing, 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.

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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-specifc 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 (chiefy 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 feld 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.

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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 benefcial role for antiviral therapy in preventing the development of HCC has been diffcult 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 signifcant risk factors for the development of HCC. Although there is substantial geographical variation, the greatest burden

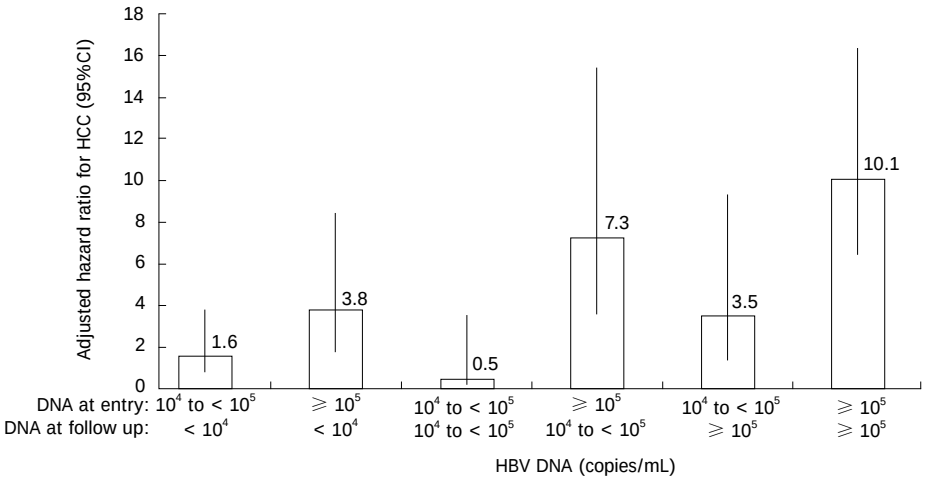

Figure 1 Adjusted hazard ratio for hepatocellular carcinoma by serum hepatitis B virus DNA levels at study entry and last follow-up. Data were adjusted for gender, age, cigarette smoking and alcohol consumption using Cox proportional hazards model. HCC: hepatocellular carcinoma; HBV: Hepatitis B virus.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

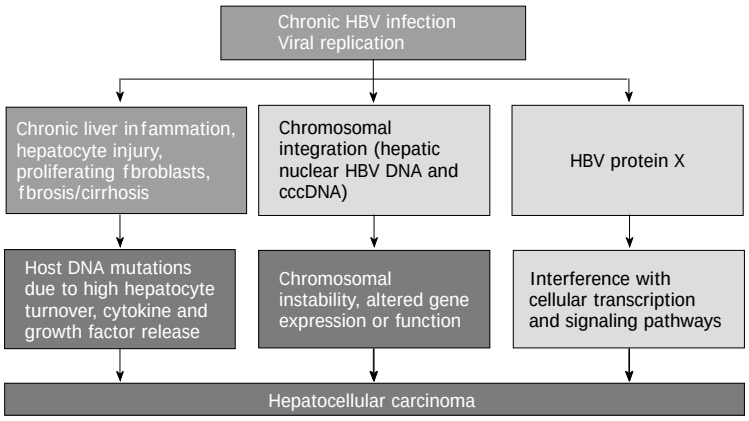

Figure 2 Mechanisms of chronic hepatitis B virus infection-related hepato-carcinogenesis[27-32]. cccDNA: Covalently closed circular DNA. HBV: Hepatitis B virus.

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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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 ref (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 ref (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 ref (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.

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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-

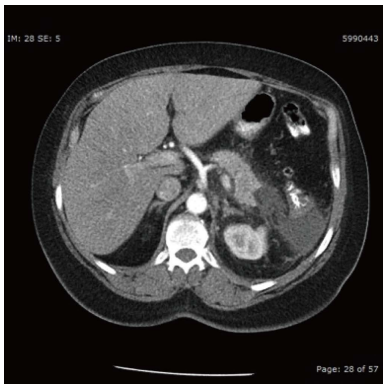

Figure 1 Cross-sectional view of computer tomography abdomen with contrast showing pancreatitis of the body and tail.

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.

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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 (fbrates, 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 benefts 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 frst 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 fuvastatin 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 frst 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.

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Patent (list all authors)

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Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.

Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc*.

Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc*.

Biology: *H. pylori*, *E coli*, *etc*.

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