

WJG 20th Anniversary Special Issues (6): *Helicobacter pylori*

***Helicobacter pylori*-negative, non-steroidal anti-inflammatory drug: Negative idiopathic ulcers in Asia**

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Author contributions: Iijima K substantial contributions to conception and design, interpretation of data, drafting the article, final approval of the version to be published; Kanno T, Koike T and Shimosegawa T acquisition of data, revising it critically for important intellectual content, final approval of the version to be published.

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Received: September 11, 2013 Revised: November 7, 2013

Accepted: December 3, 2013

Published online: January 21, 2014

Abstract

Since the discovery of *Helicobacter pylori* (*H. pylori*) infection in the stomach, the bacteria infection and non-steroidal anti-inflammatory drugs (NSAIDs) use had been considered to be the 2 main causes of peptic ulcers. However, there have been recent reports of an increase in the proportion of peptic ulcers without these known risk factors; these are termed idiopathic peptic ulcers. Such trend was firstly indicated in 1990s from some reports in North America. In Asia, numerous studies reported that idiopathic ulcers accounted for a small percentage of all ulcers in the 1990s, but in the 2000s, multiple studies reported that the proportion of idiopathic ulcers had reached 10%-30%, indicating that the incidence of idiopathic ulcers in Asia has also been rising in recent years. While a decline in *H. pylori* infection rates of general population in Asia is seen as the main reason for the increased incidence of idiopathic ulcers, it is also possible that the absolute number of idiopathic ulcer cases has increased. Advanced age, serious systemic complication, and psychological stress

are considered to be the potential risk factors for idiopathic ulcers. Management of idiopathic ulcers is challenging, at present, because there is no effective preventative measure against recurrence in contrast with cases of *H. pylori*-positive ulcers and NSAIDs-induced ulcers. As it is expected that *H. pylori* infection rates in Asia will decline further in the future, measures to treat idiopathic ulcers will also likely become more important.

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Key words: *Helicobacter pylori*; Non-steroidal anti-inflammatory drugs; Idiopathic peptic ulcer

Core tip: In Asia, numerous studies reported that idiopathic ulcers accounted for a small percentage of all ulcers in the 1990s, but in the 2000s, multiple studies reported that the proportion of idiopathic ulcers had reached 10%-30%, indicating that the incidence of idiopathic ulcers in Asia has also been rising in recent years. As it is expected that *Helicobacter pylori* infection rates in Asia will decline further in the future, measures to treat idiopathic ulcers will also likely become more important.

Iijima K, Kanno T, Koike T, Shimosegawa T. *Helicobacter pylori*-negative, non-steroidal anti-inflammatory drug: Negative idiopathic ulcers in Asia. *World J Gastroenterol* 2014; 20(3): 706-713 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v20/i3/706.htm> DOI: <http://dx.doi.org/10.3748/wjg.v20.i3.706>

INTRODUCTION

After *Helicobacter pylori* (*H. pylori*) was discovered in 1982, it was considered to be the cause of a large number of peptic ulcers (90%-95% of duodenal and 70%-90% of

gastric ulcers)^[1]. *H. pylori*, aspirin, and other non-steroidal anti-inflammatory drugs (NSAIDs) comprise the causes of a large proportion of peptic ulcers. A subsequent rise in global NSAID use and a relative increase in the proportion of NSAID-caused ulcers^[2,3] led to wide acceptance that *H. pylori* infection and NSAID use are the 2 main causes of peptic ulcers^[4]. Other causes include Zollinger-Ellison syndrome, Crohn's disease, and viral infections such as cytomegalovirus and herpes.

However, there have been recent reports of an increase in the proportion of peptic ulcers without these known risk factors; these are termed idiopathic peptic ulcers. By the 1990s, several studies reported that idiopathic ulcers comprised 20%-40% of all peptic ulcers in North America^[5-7]. In this region, 20% of *H. pylori*-positive ulcers recurred after bacterial elimination^[8], a markedly higher percentage than that reported in other areas. This finding indicated that a large number of "bystander" cases existed, wherein a patient is positive for *H. pylori* but the bacteria are not directly involved in causing the ulcer. In the 2000s, increases in the proportion of idiopathic ulcers were also reported in Europe and Asia (Table 1). However, a few studies still report low idiopathic ulcer proportions (4%), including a recent report from Italy^[6].

Detailed reviews of idiopathic ulcers were published in 2002^[37] and 2008^[38]. Here, we examine more recent trends in the incidence of idiopathic ulcers, particularly in Asia.

PRECAUTIONS FOR IDIOPATHIC ULCER DIAGNOSIS

When diagnosing idiopathic ulcers, *H. pylori* infection and history of NSAID use, the 2 main causes of peptic ulcers, must be completely ruled out. Otherwise, one will naturally find a high proportion of idiopathic ulcers.

Various methods are used to diagnose *H. pylori* infection, none of which is 100% accurate alone. Thus, the absence of *H. pylori* can be determined only when several tests are combined and the results of all are found to be negative^[38]. Diagnostic methods that use endoscopic biopsy specimens-histology, culture, and rapid urease tests (RUT)-can show false negatives due to sampling errors caused by non-uniform distribution of *H. pylori* inside the stomach^[39]. Therefore, biopsies must be obtained from several locations. Further, these methods can show false negatives immediately after acute upper digestive tract hemorrhage^[40]. In these situations, other diagnostic methods must be used in combination. The urea breath test (UBT) examines urease activity throughout the stomach due to *H. pylori*, and is used to compensate for sampling errors in tests using biopsy specimens. However, care is needed when using UBT, as false negatives can result when bacterial concentrations decrease during administration of proton pump inhibitors (PPIs)^[41], similar to other tests using biopsies. The serum antibody method is not affected by PPI administration or acute upper digestive tract hemorrhage; therefore, it is useful for diagnosing *H.*

pylori infection in these situations. However, this method continues to show positive results for some time after bacterial elimination^[42], making it difficult to differentiate between current and past infections. Nevertheless, it is a useful test because it provides a precise diagnosis of idiopathic ulcer (as few false negatives as possible). There are several tests for even more precise diagnosis of *H. pylori*-negative patients; although these tests do not directly confirm the presence of *H. pylori*, they eliminate the diagnosis of idiopathic ulcer based on tissue findings associated with infection, such as neutrophil infiltration into the gastric mucosa or atrophy of the gastric mucosa^[28,30].

Another important factor in diagnosing idiopathic ulcers is careful elimination of NSAID users. Aspirin and other NSAIDs can be purchased without a doctor's prescription in many countries. A large number of surreptitious NSAID users likely exist; therefore, patients must be questioned scrupulously about their drug history. Indeed, several previous studies have clarified the existence of surreptitious NSAIDs users. Lanas *et al.*^[43] examined patients with gastrointestinal perforation using platelet cyclooxygenase activity in the blood as an objective marker of aspirin usage. They identified 13% more aspirin users with this method than were found through investigation of medical history. Moreover, based on measurements of blood salicylic acid concentrations, Hirschowitz *et al.*^[44] reported that 50% of intractable peptic ulcer patients who denied using aspirin were in fact aspirin users. These findings underscore the necessity of carefully eliminating NSAID users when diagnosing idiopathic ulcers. Retrospective studies, which can only determine NSAID usage from past medical records, would be inevitably too lenient in eliminating NSAID users. The result would be a tendency to report higher rates of idiopathic ulcers; therefore, care must be taken when interpreting such data.

IDIOPATHIC ULCER TRENDS IN ASIA

Six reports of the proportion of idiopathic ulcers in Asia were published in 1999-2003 based on patient data from the 1990s^[19-24], 5 of which reported low rates of 1.3%-4.1%^[19-23]. In 9 studies from 2005-2006 based on patient data from the 2000s^[28-36], almost all reported that the proportion of idiopathic ulcers was 10%-30%, indicating that the proportion of these ulcers among all peptic ulcers in Asia is increasing. A decline in *H. pylori* infection rates among background healthy individuals is likely a cause of this increase. This trend is common among Asian countries^[45], and indicates that recent improvements in sanitation and the increased use of *H. pylori* elimination therapies have decreased the *H. pylori* infection rates in the region. Even if the increase in idiopathic ulcers is merely a relative rise accompanying a decline in *H. pylori*-positive ulcers, or if *H. pylori* has only been coexisting as a bystander in many cases, the decline in *H. pylori* infection rates among the overall population has given prominence to the issue of idiopathic ulcers. Further, it

Table 1 Prevalence of idiopathic ulcers

Ref.	Year	Country	Sampling period	Sampling style	Subjects disease	Subjects number	Prevalence of IPU (%)	Diagnostic method for <i>H. pylori</i>
North America								
Perterson <i>et al</i> ^[5]	1996	United States	Not mentioned	RCT	DU	185	26	Hist/RUT/culture
Jyotheeswaran <i>et al</i> ^[6]	1998	United States	1993-1996	Retrospective	PUD	305	39	Hist/RUT
Ciociola <i>et al</i> ^[7]	1999	United States	1991-1995	6 RCT	DU	2910	27	Hist/RUT/culture
Europe								
McColl <i>et al</i> ^[9]	1993	United Kingdom	Past 5 yr	Cross-sectional	DU	400	1.5	Hist/RUT/UBT/antibody
Gisbert <i>et al</i> ^[10]	1999	Spain	Not mentioned	Prospective	DU	774	0.8	RUT/culture/UBT
Meucci <i>et al</i> ^[11]	2000	Italy	1995-1996	Prospective	PUD	409	4.4	Hist/RUT
Bytzer <i>et al</i> ^[12]	2001	Denmark	1993-1995	RCT	DU	276	8	Hist/culture/antibody
Konturek <i>et al</i> ^[13]	2003	Poland	1996-2000	Prospective	PUD	1898	18.7	UBT
Arents <i>et al</i> ^[14]	2004	Netherland	1991-1998	Retrospective	PUD	405	5	Hist/RUT/culture
Arroyo <i>et al</i> ^[15]	2004	Spain	Not mentioned	Prospective	PUD	830	4.1	Hist/RUT/UBT
Sbrozzi-Vanni <i>et al</i> ^[16]	2010	Italy	2005-2007	Retrospective	PUD	300	4	Hist/UBT
Musumba <i>et al</i> ^[3]	2012	United Kingdom	2005-2010	Retrospective and prospective	PUD	386	12	Hist/RUT/antibody
Australia								
Borody <i>et al</i> ^[17]	1991	Australia	Not mentioned	Prospective	DU	302	0.3	Hist/culture
Xia ^[18]	2000	Australia	Not mentioned	Prospective	PUD	48	40	Hist/RUT/culture
Asia								
Tsuji <i>et al</i> ^[19]	1999	Japan	1995-1997	Prospective	DU and GU	DU: 120, GU: 215	GU:2.3, DU: 0.9	Hist/RUT/culture/antibody
Higuchi <i>et al</i> ^[20]	1999	Japan	Not mentioned	Cross-sectional	DU	338	2.4	Hist/RUT/culture/UBT/antibody
Aoyama <i>et al</i> ^[21]	2000	Japan	1995-1998	Cross-sectional	DU and GU	302	2.6	Hist/culture/antibody
Nishikawa <i>et al</i> ^[22]	2000	Japan	1992-1997	Cross-sectional	PUD	398	1.3	Hist/RUT/antibody
Chan <i>et al</i> ^[23]	2001	Hong Kong	1997-1998	Prospective	hPUD	977	4.1	Hist/RUT
Xia <i>et al</i> ^[24]	2001	Hong Kong	1997-1999	Prospective	DU	599	17.4	Hist/RUT/UBT
Kamada <i>et al</i> ^[25]	2003	Japan	Past 8 yr	Cross-sectional	DU	464	1.3	Hist//UBT/antibody
Chu <i>et al</i> ^[26]	2005	Hong Kong	1996-2002	Prospective	DU	1343	23	Hist/RUT
Yakoob <i>et al</i> ^[27]	2005	Pakistan	1999-2000	Retrospective	DU	217	29	Hist/RUT
Hung <i>et al</i> ^[28]	2005	Hong Kong	2000	Prospective	hPUD	638	18.8	Hist/RUT
Ong <i>et al</i> ^[29]	2006	Singapore	2002-2004	Prospective	PUD	600	8	Hist/RUT
Ootani <i>et al</i> ^[30]	2006	Japan	2000-2002	Prospective	hPUD	116	1.7	RUT/UBT/antibody
Jang <i>et al</i> ^[31]	2008	South Korea	2004-2005	Prospective	PUD	895	22.2	Hist/RUT
Chen <i>et al</i> ^[32]	2010	Taiwan	2003-2004	Prospective	DU	731	8	RUT/UBT
Goenka <i>et al</i> ^[33]	2011	India	2008-2009	Prospective	PUD	142	36.6	RUT/UBT
Chang <i>et al</i> ^[34]	2011	Taiwan	2007-2008	Prospective	PUD	204	17.2	Hist/RUT/UBT
Wong <i>et al</i> ^[35]	2012	Hong Kong	2002-2009	Prospective	hPUD	4827	13.8	Hist/RUT
Kang <i>et al</i> ^[36]	2012	South Korea	2006-2008	Prospective	PUD	173	16.2	Hist/RUT/culture/antibody

RCT: Randomized controlled trial; RUT: Rapid urease test; UBT: Urea breath test; PUD: Peptic ulcer diseases; DU: Duodenal ulcers; GU: Gastric ulcers; hPUD: Hemorrhagic peptic ulcer diseases; *H. pylori*: *Helicobacter pylori*.

has been reported that not only the proportion of idiopathic ulcers has increased but also the actual number of cases has been increasing annually^[28]. This trend suggests the existence of not just a relative cause but also some other direct factor that is contributing to the incidence of idiopathic ulcers. Next, we will examine the incidence of idiopathic ulcers in various Asian countries in detail.

Hong Kong

Hong Kong has been the most active region in conducting clinical studies on idiopathic ulcers; these studies have provided valuable data for understanding trends in idiopathic ulcer incidence. Two studies on the proportion of idiopathic ulcers based on patient data from the 1990s reported somewhat scattered results of 4% and 17%^[23,24]. However, 3 studies based on data from the 2000s reported relatively high and consistent values of 14%-23%^[26,28,34]. In particular, a recent major study on

approximately 5000 peptic ulcer patients from 2002-2009 reported a 13.8% proportion of idiopathic ulcers^[34], again showing that these ulcers are not rare in Hong Kong. A study on yearly changes in the proportion of idiopathic ulcers in the same institution reported a rise from 1997-1998 to 2000 of 4.1% to 18.8%^[28], with other reports also showed an increase in the proportion of idiopathic ulcers over time^[26]. While this rise in idiopathic ulcer rates reflects a relative increase accompanying a decline in *H. pylori*-positive ulcers due to the increased use of bacterial elimination therapy or decline of *H. pylori* infection rate among background healthy population^[46], yearly data also suggest that the actual number of idiopathic ulcer patients is increasing^[28].

Japan

Five studies of the frequency of idiopathic ulcers in Japan based on 1990s patient data reported very low rates

of 0.9%-2.6%^[19-22,24]. In addition, a 2000-2002 investigation of hemorrhagic ulcer patients found that 11% were *H. pylori*-negative and NSAID-negative^[30]. However, after eliminating cases with a possible history of *H. pylori* infection based on histological atrophy of the gastric mucosa, the final proportion of cases with idiopathic ulcers was 1.7%^[30]. There have since been no further studies on the frequency of idiopathic ulcers in Japan. Recently, there has been a marked decline in *H. pylori* infection rates among the general Japanese population^[47], and it is possible there has been an accompanying rise in the proportion of idiopathic ulcers, as has occurred in other Asian countries. Sugiyama *et al.*^[48] found a similarly low proportion of idiopathic ulcers in Japanese ulcer patients divided into 2 age groups, which showed major differences in *H. pylori* infection rates. Based on this finding, they surmised that the proportion of idiopathic ulcers does not vary according to *H. pylori* infection rates. Considering the extremely low proportion of idiopathic ulcers in Japan in the 1990s, information on recent trends would be of great interest.

South Korea

There are two reports from South Korea on the frequency of idiopathic ulcers based on patient data from the 2000s. One of them, based on 2004-2005 data, reported a high (22%) proportion of idiopathic ulcers^[31]. However, the diagnosis of *H. pylori* infection in this study was based on only a single RUT and histological examination. Therefore, it is unclear whether the diagnosis of *H. pylori* negativity was sufficiently precise. The more recent study, based on 2006-2008 data, employed a strict definition of *H. pylori* negativity using a urease test, histological examination, culture, and the serum antibody method. This report confirmed a high proportion of idiopathic ulcers (16.2%)^[36]. No reports from South Korea are based on patient data from the 1990s; therefore, comparisons with past data cannot be performed. However, it can be surmised that idiopathic ulcers are not rare in South Korea, similar to Europe and the United States. The recent decline in *H. pylori* infection rates among the general South Korean population^[49,50] can be considered as the cause of the increase in the proportion of idiopathic ulcers unrelated to *H. pylori*.

Taiwan

A study from Taiwan based on data from 2003-2004 reported an idiopathic ulcer frequency of 8%^[32]. Another report based on 2007-2008 data reported a 17% frequency^[34], indicating that the proportion of idiopathic ulcers has been rising in recent years. The cause of this trend is also thought to be a decline in *H. pylori* infection rates in Taiwan^[33].

Other Asian countries

A study of 1999-2000 patient data from Pakistan reported that 29% of ulcers were idiopathic^[27]. Although this developing country was thought to have a high *H.*

pylori infection rate at the time^[51], the study reported a large proportion of idiopathic ulcers. However, problems with the methods used to diagnose *H. pylori* infection and issues with the retrospective study design, which did not allow a precise idiopathic ulcer diagnosis, possibly led to this apparently high proportion.

A study of 2002-2004 patient data from Singapore reported an 11% proportion of idiopathic ulcers^[29]. However, data on serum thromboxane B2 concentrations suggested that 1/3 of these cases were surreptitious NSAID users, resulting in a true proportion of idiopathic ulcers of 8%^[29]. Singapore is a multi-ethnic country and is known to have relatively lower rates of *H. pylori* infection than other Asian nations^[52]. Nevertheless, this final proportion of idiopathic ulcers is relatively low. This study showed the importance of eliminating surreptitious NSAID users through blood tests, as well as through interviews.

Patient data from India from 2008-2009 showed an extremely high proportion of idiopathic ulcers at 37%^[33], on par with rates in North America. This study diagnosed *H. pylori* using RUT and UBT, thus having a certain level of precision. Although the *H. pylori* infection rates in India have traditionally been high^[53,54], recent studies have reported a decline in infection rates^[55], and the high frequency of idiopathic ulcers may be a reflection of this. However, since this study involved only a single institution and a relatively small number of ulcer patients, further investigation is needed.

RISK FACTORS OF IDIOPATHIC ULCERS

Although a clear cause of idiopathic ulcers hasn't yet to be shown, several factors related to the condition have been proposed.

Age

Numerous studies in Europe, the United States, and Asia have shown that idiopathic ulcer patients are significantly older than those with simple *H. pylori* ulcers or *H. pylori*/NSAID ulcers^[11,23,24,28,29,56], although older age may be a mere confounder of the following risk factors such as systemic complications or psychological stress. Aging has been shown to be accompanied by a decline in the defense functions of the gastric mucosa owing to a variety of mechanisms, particularly a lower prostaglandin concentration in the gastric mucosa as a person ages^[57], which may be a potential cause for gastric ulcers but not for duodenal ulcers. Prostaglandin plays a central role in the gastric mucosa defense structure by increasing gastric mucus secretions, bicarbonate secretions, and blood flow^[58]. Thus, the diminished prostaglandin concentration in elderly individuals renders the gastric mucosa more fragile, creating an environment in which ulcers are more likely to occur.

Systemic complications

Many studies, primarily from Asia, have reported that a wide variety^[22,24,26,29] of serious^[35] systemic complications

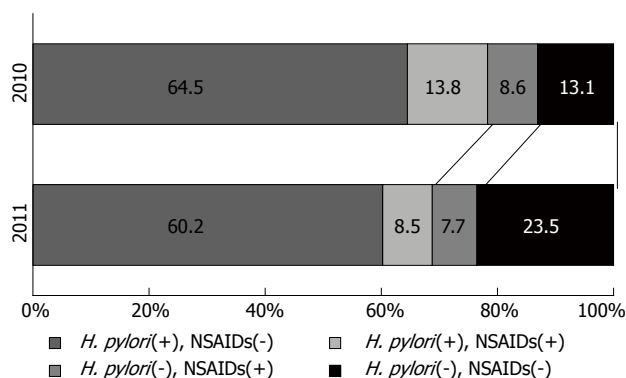


Figure 1 Changing pattern of the etiology of peptic ulcers before (2010) and after (2011) the Great East Japan earthquake. In the analysis of etiologic factors of the ulcers, cases from each year were classified into four groups according to the *Helicobacter pylori* (*H. pylori*) status and non-steroidal anti-inflammatory drugs (NSAIDs) intake. The proportion of *H. pylori*-negative non-NSAIDs takers among PU patients after the earthquake (2011) was significantly higher than in the previous year (13% in 2010 vs 24% in 2011, $P < 0.05$). The date available from reference^[67].

are risk factors for idiopathic ulcers. This finding is possibly related to reports stating that peptic ulcers that occur in intensive care units or against a background of serious underlying disease are unrelated to *H. pylori* infection^[59,60]. Physical or psychological (see below) stress caused by an underlying disease might be related to ulcer incidence.

Several recent studies have reported the relationship between hepatocirrhosis and hemorrhagic peptic ulcers^[61-63]. In particular, decompensated hepatocirrhosis was demonstrated to be a risk factor for hemorrhagic peptic ulcer, independent of *H. pylori* infection^[61-63]. Thus, hepatocirrhosis is an important cause of idiopathic ulcers. Although the pathology by which hepatocirrhosis leads to a peptic ulcer is complex, portal hypertension is likely involved. Visceral congestion from portal hypertension might be linked to ulcer incidence, as it damages the gastroduodenal mucosal blood flow and inhibits the process of mucosal repair^[63-65]. In addition, decreased gastric prostaglandin synthesis observed in hepatocirrhosis patients may be involved in the hepatocirrhosis-related gastric mucosal injury^[62,63].

Psychological stress

A link between psychological stress and peptic ulcers has long been suggested^[65], but once *H. pylori* infection and damage from NSAID use were identified as the 2 main causes of peptic ulcers, it became unclear whether psychological stress should be considered an independent cause of peptic ulcer^[4,21]. However, there have been reports of ulcer formation in the victims of the Great East Japan Earthquake that struck in 2011^[67,68]. Kanno *et al.*^[67] compared the ulcer incidence 3 mo after the disaster with the ulcer incidence in the same period during the previous year; they found a 1.5-fold rise in ulcer cases after the disaster. Further, the proportion of *H. pylori*- and NSAID-negative (that is, idiopathic) ulcers rose sig-

nificantly from 13% in 2010 to 24% after the disaster in 2011 (Figure 1)^[67]. This study excluded cases complicated by severe trauma due to the disaster, showing indirectly that psychological stress can be an independent cause of peptic ulcers among disaster victims. Interestingly, the *H. pylori*-, NSAID-negative ulcers that arose after the disaster were in patients who were significantly older than those with other ulcer types^[67]; this finding is consistent with the characteristic of idiopathic ulcers described above.

MANAGEMENT OF IDIOPATHIC ULCERS

Bacterial elimination therapy is often effective for preventing the recurrence of *H. pylori*-positive ulcers and does not require subsequent maintenance therapy with acid-suppressive agents^[4]. In NSAID-induced ulcers, changing therapy to COX-2-selective NSAIDs or other alternative medications that do not cause as much damage to the gastrointestinal mucosa can be expected to suppress recurrences^[4]. However, for idiopathic ulcers, although acid-suppressive agents can produce temporary relief, they are not an effective preventative measure against recurrence. It has been shown that recurrence rates are high when patients remain unmedicated after such temporary cures. A study from Denmark observed 32 unmedicated patients with *H. pylori*-negative duodenal ulcers for 2 years, and reported a 35% recurrence rate^[12]. Additionally, a prospective study from Hong Kong that observed unmedicated patients with idiopathic, hemorrhagic gastroduodenal ulcers for 7 years found that 42% experienced a relapse of ulcer hemorrhage. This is 4 times the percentage found while observing patients with *H. pylori*-positive ulcers who were unmedicated after bacterial elimination^[69]. Further, a recent report from South Korea found that compared to *H. pylori*-positive ulcers and NSAID-induced ulcers, idiopathic ulcers showed more recurrences, which led to increased medical costs^[36].

Although it has been shown that recurrences can easily occur when patients with idiopathic ulcer are not treated, there is no consensus on whether maintenance therapy with acid-suppressive agents can effectively prevent these recurrences. In the aforementioned study from Denmark, PPI administration was found to have an effect on preventing the recurrence of *H. pylori*-negative duodenal ulcers^[12]. However, a recent major follow-up study from Hong Kong that examined 663 patients with idiopathic hemorrhagic gastroduodenal ulcers did not find H₂-blocker or PPI administration to be effective in preventing ulcer hemorrhage relapse^[35]. Around 50% of the cases in the Hong Kong study were gastric ulcers^[35], and it was found that gastric ulcers, even idiopathic cases, might show different reactivity to acid-suppressive agents than duodenal ulcers. Until it is determined which medications can effectively prevent the recurrence of idiopathic ulcers, the most realistic choice appears to be continuous PPI therapy.

CONCLUSION

Numerous studies reported that idiopathic ulcers in Asia accounted for a small percentage of all ulcers in the 1990s, but in the 2000s, multiple studies reported that the proportion of idiopathic ulcers had reached 10%-30%. Despite limitations such as difficulties in precise diagnosis of *H. pylori* infection and identification of surreptitious NSAID users, it is clear that the incidence of idiopathic ulcers in Asia has been rising in recent years. While a decline in *H. pylori* infection rates in Asia is seen as the main reason for the increased incidence of idiopathic ulcers, it is also possible that the absolute number of idiopathic ulcer cases has increased. As it is expected that *H. pylori* infection rates in Asia will decline further in the future, measures to treat idiopathic ulcers will also likely become more important. Further multicenter studies from many different countries, with the same protocol, are necessary to investigate the real incidence of idiopathic ulcers and the real causes.

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P- Reviewers: Abulezz T, Savopoulos CGG, Yasuda H
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ISSN 1007-9327



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