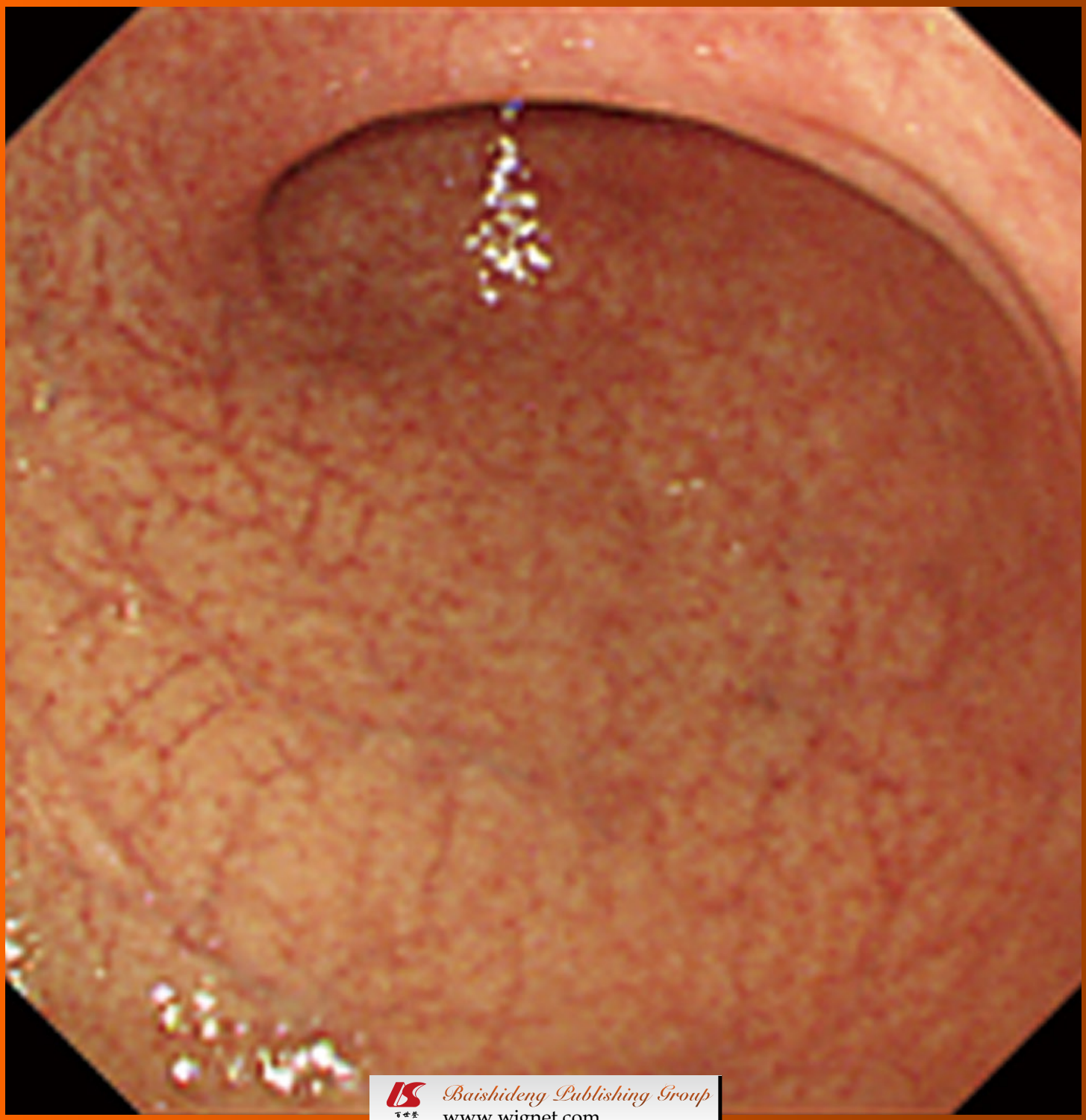
ISSN 1948-5190 (online)

World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2010 December 16; 2(12): 381-416



Baishideng Publishing Group
www.wjgnet.com

WJGE World Journal of Gastrointestinal Endoscopy

A peer-reviewed, online, open-access journal of gastrointestinal endoscopy

Editorial Board

2009-2013

The *World Journal of Gastrointestinal Endoscopy* Editorial Board consists of 400 members, representing a team of worldwide experts in gastrointestinal endoscopy. They are from 45 countries, including Australia (7), Austria (1), Belgium (6), Brazil (7), Canada (5), Chile (2), China (26), Croatia (2), Cuba (1), Czech Republic (3), Denmark (1), Ecuador (1), Egypt (1), Finland (2), France (10), Germany (27), Greece (11), Hungary (4), India (15), Iran (2), Ireland (2), Israel (6), Italy (37), Japan (62), Lebanon (1), Lithuania (1), Malaysia (2), Mexico (1), Netherlands (6), New Zealand (1), Norway (2), Pakistan (2), Poland (2), Portugal (5), Romania (2), Singapore (2), South Africa (1), South Korea (13), Spain (17), Sweden (3), Thailand (5), Turkey (8), United Arab Emirates (1), United Kingdom (15), and United States (69).

Czech Republic

Marcela Kopacova, *Hradec Kralove*
Michal Procke, *Prague*
Miroslav Zavoral, *Prague*

Denmark

Peter Bytzer, *Koege*

Ecuador

Carlos Robles-Medranda, *Portoviejo*

Egypt

Nabil Ali Gad El-Hak, *Mansoura*

Finland

Paulina Salminen, *Turku*
Lars Mikael Victorzon, *Vaasa*

France

Romain Coriat, *Paris*
Bernard G Dallemagne, *Strasbourg*
Gerard Jean Gay, *Vandoeuvre les Nancy*
Lesur Gilles, *Boulogne*
René Lambert, *Lyon*
Sylvain Manfredi, *Rennes*
Barthet Marc, *Marseille Cedex*
JF Rey, *Saint Laurent Du Var Cedex*
José Sahel, *Marseille*
Nathalie Salles, *Pessac*

Germany

Marcel Binnebösel, *Aachen*
P Born, *Munich*
Stefan von Delius, *München*
Dirk Domagk, *Muenster*
Christoph Eisenbach, *Heidelberg*
Ines Gockel, *Mainz*
Arthur Hoffman, *Mainz*
Georg FBA Kähler, *Mannheim*
Günter Kampf, *Hamburg*
Ralf Kiesslich, *Mainz*
Andreas Kirschniak, *Tübingen*
Oliver Pech, *Wiesbaden*
Michael Pietsch, *Mainz*
Andreas Probst, *Augsburg*
Andrea Riphaus, *Bochum*
Raphael Rosch, *Aachen*
Claus Schäfer, *Munich*
Hubert J Scheidbach, *Magdeburg*
Peter Schemmer, *Heidelberg*
Hans Scherübl, *Berlin*
Thomas W Spahn, *Schwerte*
Holger Sudhoff, *Bielefeld*
Jens Tischendorf, *Aachen*
Michael Vieth, *Bayreuth*
Jochen Wedemeyer, *Hannover*
Uwe Will, *Gera*

Greece

Georgios K Anagnostopoulos, *Athens*
Anna Eleftheriadou, *Rethymnon*
Dimitris K Iakovidis, *Lamia*
Dimitrios Kapetanos, *Thessaloniki*
John A Karagiannis, *Athens*
Stefanos Karagiannis, *Kifissia*
Spiros D Ladas, *Athens*
Konstantinos A Papadakis, *Heraklion*
George H Sakorafas, *Athens*
Elias Xirouchakis, *Areos*

Hungary

Pal Demeter, *Budapest*
Lujber László, *Pecs*
Peter Lakatos, *Budapest*
István Rácz, *Gyor*

India

Ramanathan S Bharathi, *Uttar Pradesh*
Devendra C Desai, *Mumbai*
Evan L Fogel, *Indianapolis*
Uday Chand Ghoshal, *Lucknow*
Chittor M Habibullah, *Andhra Pradesh*
Rakesh Kochhar, *Chandigarh*
Rakesh Kumar, *New Delhi*
Sri Prakash Misra, *Allahabad*
Sandeep Nijhawan, *Rajasthan*
Kaushal Kishor Prasad, *Chandigarh*
Surinder Singh Rana, *Chandigarh*
Muthukumaran Rangarajan, *Tamil Nadu*
D Nageshwar Reddy, *Hyderabad*
Omar Javed Shah, *Kashmir*
Virendra Singh, *Chandigarh*

Iran

Tahereh Falsafi, *Tehran*
Mohammad Rahnavardi, *Tehran*

Ireland

Colm Ó'Moráin, *Dublin*
Eamonn M Quigley, *Cork*

Israel

Simon Bar-Meir, *Ramat Gan*
Rami Eliakim, *Haifa*
Zvi Fireman, *Hadea*
Irina Hirsh, *Haifa*
Tiberiu Hershcovici, *Jerusalem*
Jesse Lachter, *Haifa*

Italy

Paola De Angelis, *Rome*
Paolo G Arcidiacono, *Milan*
Alberto Arezzo, *Torino*
Gabrio Bassotti, *San Sisto*
Giampaolo Bresci, *Pisa*
Carlo Calabrese, *Bologna*
Salvatore MA Campo, *Rome*
Federico Carpi, *Pisa*
Livio Cipolletta, *Torre del Greco*
Sandro Contini, *Parma*
Salvatore Cucchiara, *Rome*
Gabriele Curcio, *Palermo*
Luigi Familiari, *Cavalluccio*
Lorenzo Fuccio, *Bologna*
Giuseppe Galloro, *Napoli*
Giovanni B Gasbarrini, *Rome*
Carlo M Girelli, *Busto Arsizio*
Mauro Manno, *Baggiovara di Modena*
Hugo Martines, *Savona*
Gabriele Masselli, *Rome*
Emanuele Meroni, *Milan*
Andrea Moglia, *Pisa*
Raffaele Pezzilli, *Bologna*
Venerino Poletti , *Forlì*
Salvatore Pucciarelli, *Padova*
Franco Radaelli, *Como*
Marmo Riccardo, *Luigi Curto Polla*
Maria Elena Riccioni, *Rome*
Stefania Romano, *Naples*
Emanuele Rondonotti, *Milano*
Gianluca Rotondano, *Torre del Greco*
Vittorio Terruzzi, *Como*
Cristina Trovato, *Milano*
Antonio Tucci, *Bologna*
Maurizio Vecchi, *Milan*
Maurizio Ventrucci, *Bologna*

Japan

Mitsuhiro Asakuma, *Osaka*
Hiroki Endo, *Kanagawa*
Shotaro Enomoto, *Wakayama*
Kuang-I Fu, *Kashiwa*
Makoto Hashizume, *Fukuoka*
Toru Hiyama, *Higashihiroshima*
Akira Hokama, *Okinawa*
Akira Horiuchi, *Komagane*
Kinichi Hotta, *Nagano*
Atsushi Imagawa, *Kagawa*
Hiroo Imazu, *Tokyo*
Haruhiro Inoue, *Yokohama*
Ryu Ishihara, *Osaka*
Naoki Ishii, *Tokyo*
Hajime Isomoto, *Nagasaki*
Takao Itoi, *Tokyo*
Satoru Kakizaki, *Gunma*
Hiroshi Kakutani, *Tokyo*
Terumi Kamisawa, *Tokyo*
Yoshihide Kanno, *Sendai*
Mototsugu Kato, *Sapporo*
Takashi Kawai, *Tokyo*

Hirofumi Kawamoto, *Okayama*
Hiroto Kita, *Saitama*
Koga Komatsu, *Akita*
Hitoshi Kondo, *Sapporo*
Hiroaki Kubo, *Fukuoka*
Keiichiro Kume, *Kitakyusyu*
Iruru Maetani, *Tokyo*
Hiroto Miwa, *Hyogo*
Akihiro Mori, *Aichi*
Akihiro Mori, *Aichi*
Yoshihiro Moriwaki, *Yokohama*
Naoki Muguruma, *Tokushima*
Shinji Nishiwaki, *Gifu*
Ichiro Oda, *Tokyo*
Kazuichi Okazaki, *Osaka*
Yasuhiro Oono, *Chiba*
Taro Osada, *Tokyo*
Yutaka Saito, *Tokyo*
Yuzo Sakai, *Chiba*
Naoto Sakamoto, *Tokyo*
Nobuyuki Sakurazawa, *Tokyo*
Yasushi Sano, *Hyogo*
Tomoyuki Shibata, *Toyoake*
Takashi Shida, *Chiba*
Atsushi Sofuni, *Tokyo*
Kazuki Sumiyama, *Tokyo*
Nobumi Tagaya, *Tochigi*
Hirokazu Takahashi, *Yokohama*
Kyosuke Tanaka, *Mie*
Shinji Tanaka, *Hiroshima*
Gen Tohda, *Fukui*
Tomoyuki Tsujikawa, *Shiga*
Noriya Uedo, *Osaka*
Shuji Yamamoto, *Kyoto*
Takayuki Yamamoto, *Yokkaichi*
Hideo Yanai, *Yamaguchi*
Kenjiro Yasud, *Kyoto*
Naohisa Yoshida, *Kyoto*

Lebanon

Kassem A Barada, *Beirut*

Lithuania

Laimas Virginijus Jonaitis, *Kaunas*

Malaysia

Sanjiv Mahadeva, *Kuala Lumpur*
Sreenivasan Sasidharan, *Pulau Pinang*

Mexico

OT Teramoto-Matsubara, *México*

Netherlands

Marco Bruno, *Rotterdam*
Dirk Joan Gouma, *Amsterdam*
Iris Lansdorp-Vogelaar, *Rotterdam*
Chris JJ Mulder, *Amsterdam*
Vasileios Panteris, *Rotterdam*
Harald Erwin Vonkeman, *Enschede*

New Zealand

Michael PG Schultz, *Dunedin*

Norway

Magdy El-Salhy, *Stord*
Odd Helge Gilja, *Bergen*

Pakistan

Syed H Ali Shah, *Karachi*
Lubna Kamani, *Karachi*

Poland

Stanislaw A Hac, *Gdansk*
Maciej Michalik, *Pomorskie*

Portugal

Miguel T Coimbra, *Porto*
Marie I Cremers, *Setúbal*
Mário Dinis-Ribeiro, *Porto*
Pedro N Figueiredo, *Coimbra*
Rui MA da Silva, *Porto*

Romania

Mihai Ciocirlan, *Bucharest*
Lucian Negreanu, *Bucharest*

Singapore

Zhiwei Huang, *Singapore*
Surendra K Mantoo, *Singapore*

South Africa

Roland N Ndip, *Alice*

South Korea

Young-Tae Bak, *Seoul*
Dong Kyung Chang, *Seoul*
Youn-Seok Cho, *Uijeongbu*
Seong Woo Jeon, *Daegu*
Jong-Man Kang, *Seoul*
Yong Sung Kim, *Gyeonggi-do*
Hang Lak Lee, *Sungdonggu*
Suck-Ho Lee, *Cheonan*
Jong Ho Moon, *Bucheon*
Dong Kyun Park, *Incheon*
Dae Kyung Sohn, *Gyeonggi*
Jaekyu Sung, *Daejeon*
Si-Young Song, *Seoul*

Spain

Jose FN Aguilar, *Palma*
Adolfo P Blanco, *Asturias*
Andres Cardenas, *Barcelona*
Gloria Fernández-Esparrach, *Barcelona*
Jesús García-Cano, *Cuenca*
Angels Gines, *Barcelona*
Angel Lanas, *Zaragoza*
G Payeras Llodrá, *Madrid*
Alfredo José Lucendo, *Tomelloso*
Enrique F Perez-Cuadrado Martinez, *Murcia*
Luis Rabago, *Madrid*
Eduardo Redondo-Cerezo, *Cuenca*
Luis Rodrigo, *Oviedo*
Jaume Boix Valverde, *Badalona*
Josep Llach Vila, *Barcelona*
Santiago Vivas, *León*

Sweden

George Dafnis, *Eskilstuna*
Per-Ola Park, *Borås*
Carlos A Rubio, *Stockholm*

Thailand

Somchai Amornyotin, *Bangkok*
Thawatchai Akaraviputh, *Bangkok*
Udom Kachintorn, *Bangkok*
Varut Lohsiriwat, *Bangkok*
Rungsun Rerknimitr, *Bangkok*

Turkey

Selcuk Disibeyaz, *Nkara*
Mehmet Eken, *Istanbul*
Muammer Kara, *Ankara*
Taylan Kav, *Ankara*
Nevin Oruc, *İzmir*
Burhan Ozdil, *Adana*
Nurdan Ozmeric, *Emek Ankara*
Sema Zer Toros, *Istanbul*

United Arab Emirates

Margit Gabriele Muller, *Abu Dhabi*

United Kingdom

Basil J Ammori, *Manchester*
Simon HC Anderson, *London*
Adam D Farmer, *London*
Annette Fritscher-Ravens, *Landon*
Gianpiero Gravante, *Bristol*
Abdulzahra Hussain, *London*
United KV Kodogiannis, *London*
Seamus J Murphy, *Newry*
Perminder Phull, *Aberdeen*

WJGE World Journal of Gastrointestinal Endoscopy

Contents

Monthly Volume 2 Number 12 December 16, 2010

World Journal of Gastrointestinal Endoscopy
Volume 2 Number 12 December 16, 2010

Contents

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

LAUNCH DATE
October 15, 2009

SPONSOR
Beijing Baishideng BioMed Scientific Co., Ltd.,
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-8538-1892
Fax: +86-10-8538-1893
E-mail: baishideng@wjgnet.com
http://www.wjgnet.com

EDITING
Editorial Board of *World Journal of Gastrointestinal Endoscopy,*
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-5908-0038
Fax: +86-10-8538-1893
E-mail: wjge@wjgnet.com
http://www.wjgnet.com

PUBLISHING
Baishideng Publishing Group Co., Limited,
Room 1701, 17/F, Henan Building,
No.90 Jaffe Road, Wanchai,
Hong Kong, China
Fax: 00852-3115-8812
Telephone: 00852-5804-2046
E-mail: baishideng@wjgnet.com
http://www.wjgnet.com

SUBSCRIPTION
Beijing Baishideng BioMed Scientific Co., Ltd.,
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-8538-1892
Fax: +86-10-8538-1893
E-mail: baishideng@wjgnet.com
http://www.wjgnet.com

ONLINE SUBSCRIPTION
One-Year Price: 216.00 USD

PUBLICATION DATE
December 16, 2010

CSSN
ISSN 1948-5190 (online)

EDITORIAL OFFICE
Hai-Ning Zhang, Director
World Journal of Gastrointestinal Endoscopy
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-5908-0038
Fax: +86-10-8538-1893
E-mail: wjge@wjgnet.com
http://www.wjgnet.com

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/1948-5190/g_info_20100316080002.htm. If you do not have web access please contact the editorial office.

ONLINE SUBMISSION
http://www.wjgnet.com/1948-5190office/

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
doi:10.4253/wjge.v2.i12.381

World J Gastrointest Endosc 2010 December 16; 2(12): 381-387
ISSN 1948-5190 (online)

EDITORIAL

Novel risk markers for gastric cancer screening: Present status and future prospects

Shotaro Enomoto, Takao Maekita, Hiroshi Ohata, Kimihiko Yanaoka, Masashi Oka, Masao Ichinose

Shotaro Enomoto, Takao Maekita, Hiroshi Ohata, Kimihiko Yanaoka, Masashi Oka, Masao Ichinose, Second Department of Internal Medicine, Wakayama Medical University, Wakayama 641-0012, Japan
Author contributions: Enomoto S drafted the manuscript; Maekita T, Ohata H, Yanaoka K, Oka M and Ichinose M critically revised the paper; and all the authors read and approved the final manuscript.
Correspondence to: Shotaro Enomoto, MD, PhD, Second Department of Internal Medicine, Wakayama Medical University, 811-1 Kimiidera, Wakayama-city, Wakayama 641-0012, Japan. shoe@orion.ocn.ne.jp
Telephone: +81-73-4471335 Fax: +81-73-4453616
Received: July 15, 2010 Revised: October 21, 2010
Accepted: October 28, 2010
Published online: December 16, 2010

Abstract

Initial identification of populations at high risk of gastric cancer (GC) is important for endoscopic screening of GC. As serum pepsinogen (PG) test-positive subjects with progression of chronic atrophic gastritis (CAG) show a high likelihood of future cancer development, this population warrants careful follow-up observation as a high-risk GC group. By combining the PG test with *Helicobacter pylori* (HP) antibody titers, the HP-related chronic gastritis stage can be classified, thus identifying not only a GC high-risk group but also a low-risk group. Among PG test-negative patients without CAG, those with high serum PG Ⅱ levels and HP antibody titers are thought to have severe gastric mucosal inflammation and the risk of diffuse-type GC is also high. Meanwhile, in gastric mucosae obtained by endoscopic biopsy, HP infection induces aberrant DNA methylation in CpG islands in multiple gene regions and the extent of methylation clearly correlates with GC risk. By quantifying aberrant DNA methylation in suitable gene markers, we can determine the extent of the epigenetic field for cancerization. These novel concepts and risk markers will have many clinical applications in gastrointestinal endoscopy, including more efficient endoscopic GC screening and a strategic approach to metachronous multiple GCs after endoscopic treatment.

Key words: Gastric cancer; Screening; Risk; Pepsinogen; *Helicobacter pylori*; DNA methylation

Peer reviewers: Perminder Phull, MD, FRCP, FRCPE, Gastrointestinal and Liver Service, Room 2.58, Ashgrove House, Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB25 2ZN, United Kingdom; Jiang-Fan Zhu, MD, Professor of Surgery, Department of General Surgery, East Hospital of Tongji University, Pudong 200120, Shanghai, China

Enomoto S, Maekita T, Ohata H, Yanaoka K, Oka M, Ichinose M. Novel risk markers for gastric cancer screening: Present status and future prospects. *World J Gastrointest Endosc* 2010; 2(12): 381-387 Available from: URL: http://www.wjgnet.com/1948-5190/full/v2/i12/381.htm DOI: http://dx.doi.org/10.4253/wjge.v2.i12.381

INTRODUCTION

Owing to the recent advances in minimally invasive and radical endoscopic treatments including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), early gastric cancers (GCs) have been endoscopically resected, especially in Japan[1-3]. Following advances in new endoscopic treatment, early detection and accurate diagnosis of GC has been increasing in importance. In particular, advances in endoscopic equipment and developments in endoscopic image enhancement technology have greatly contributed to improved diagnosis for early GC[4-6]. Furthermore, identifying which populations are at high risk for GC plays a key role in endoscopic GC diagnosis. This not only assists in endoscopic diagnosis but can also contribute greatly to other aspects of endoscopic management of GC, including the current problem of identifying populations who should be targeted for GC

Table 1 Comparison of accuracy of gastric cancer detection by each serum pepsinogen test index

Serum PG test	Our results[25]		Meta-analysis of reported cases[26]	
	Sensitivity (95% CI)	Specificity (95% CI)	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)
PG Ⅰ ≤ 70 and PG Ⅰ/Ⅱ ≤ 3 (PG index 1+)	58.70% (45.6-70.8)	73.40% (72.1-74.6)	77.30% (69.8-83.8)	73.20% (72.8-73.6)
PG Ⅰ ≤ 50 and PG Ⅰ/Ⅱ ≤ 3 (PG index 2+)	49.20% (36.5-62.0)	80.50% (79.4-81.6)	68.40% (59.1-76.8)	69.30% (66.6-70.0)
PG Ⅰ ≤ 30 and PG Ⅰ/Ⅱ ≤ 2 (PG index 3+)	27.00% (16.9-39.9)	92.00% (91.3-92.8)	51.90% (40.3-63.5)	84.40% (83.7-85.0)

PG: pepsinogen.

screening[7] and strategic approaches to metachronous multiple GC after EMR or ESD[8].

Helicobacter pylori (HP) infection is a major risk factor in GC development[9]. However, in countries like Japan with high HP infection rates, the existence of HP infection alone offers inadequate specificity for the assessment of GC risk. Novel risk markers to identify GC high-risk groups based on a detailed natural history of GC have thus long been awaited. In this paper, we discuss the emerging significance of serum pepsinogen (PG) as a GC risk marker for more precise identification of GC high-risk groups. We also discuss our research on DNA methylation in gastric mucosae obtained at endoscopic biopsy as a molecular biological marker to evaluate GC risk.

SERUM PG TEST FOR IDENTIFICATION OF GC HIGH-RISK GROUPS

Theoretical considerations of the serum PG test

PG is the inactive precursor of pepsin, a gastrointestinal enzyme specifically produced in the gastric mucosae[10]. PG is mainly excreted into the stomach lumen but about 1% of the total enters into the blood stream and is measurable as serum PG. Changes in serum PG levels reflects gastric mucosal morphology and exocrine function[11,12]. In an endoscopic study with Congo red staining, an increase in glandular boundary, associated with diagnosed progression of gastric mucosal atrophy, correlated strongly with stepwise reductions in serum PG Ⅰ levels and the PG Ⅰ/Ⅱ ratio[13]. In other words, measuring serum PG Ⅰ and the PG Ⅰ/Ⅱ ratio offers the opportunity to evaluate the progression of chronic atrophic gastritis (CAG), a precursor of GC[14].

As criteria for the serum PG test used for GC screening, the combination of PG Ⅰ ≤ 70 ng/mL and PG Ⅰ/Ⅱ ≤ 3.0 is widely accepted as a reference value (PG index 1+)[14,15]. Low values based on this reference are considered PG test-positive. In addition, to identify more severe CAG progression, criteria of PG Ⅰ ≤ 50 ng/mL and PG Ⅰ/Ⅱ ≤ 3.0 (PG index 2+), and PG Ⅰ ≤ 30 ng/mL and PG Ⅰ/Ⅱ ≤ 2.0 (PG index 3+) are also used. Since 1992, when PG assay kits became commercially available, a number of screening services provided by work place or community health services have adopted this serum test as a filter test[16-22].

Accuracy of GC detection using the serum PG test

We conducted a 10 year follow-up observation study of GC occurrence in a cohort of middle-aged healthy men[23-25]. Based on the results, we evaluated the accuracy of each serum PG test index for detecting GC during the observation period[25]. Table 1 summarizes the accuracy for each PG test index. For the most lenient criteria (PG index 1+), sensitivity was 58.7%, specificity was 73.4% and positive predictive value was 2.6%. Overall, the results showed obviously low sensitivity. Compared to a recently reported meta-analysis of PG test sensitivity[26], these results were clearly poor, particularly in terms of low sensitivity.

One interpretation of these results is that some GCs are easier to detect by barium X-ray and some GCs are easier to detect by the serum PG test[22]. In the above-mentioned meta-analysis, many of the reviewed reports were studies of populations in whom GC was diagnosed over a long period by barium X-rays. Targeting a population with a concentration of GC cases difficult to detect by barium X-ray, or in other words, GC easy to detect by the serum PG test, these studies analyzed results of GC detection just after introduction of the serum PG test and over a short period. On the other hand, in our study, GC cases just after introduction of the serum PG test were excluded and follow-up was continued over a period of 10 years. The results of detecting GC occurring during the observation period were thus examined more rigorously, better depicting the accuracy of GC detection using the serum PG test. Based on these results, the serum PG test has limitations when used alone for GC screening. This shows the need for more in-depth systematic screening, including in PG test-negative GC.

GC risk diagnosis using the serum PG test

Previous studies have examined the accuracy of serum PG as a filter test for endoscopy. Recently, as part of an investigation into the natural history of GC occurrence, we examined GC risk in each population identified using each serum PG test index[25]. The annual incidence of GC was 0.07% in the atrophy-negative group, compared to 0.28% in the atrophy-positive (PG index 1+) group, 0.32% in the PG index 2+ group and 0.42% in the PG index 3+ group. The incidence of GC thus increased in a stepwise and significant manner with CAG progression (Figure 1). These results clearly indicate that PG test-positive subjects are a high-risk GC group, have a higher future likelihood of developing GC and represent a population requiring careful follow-up observation.

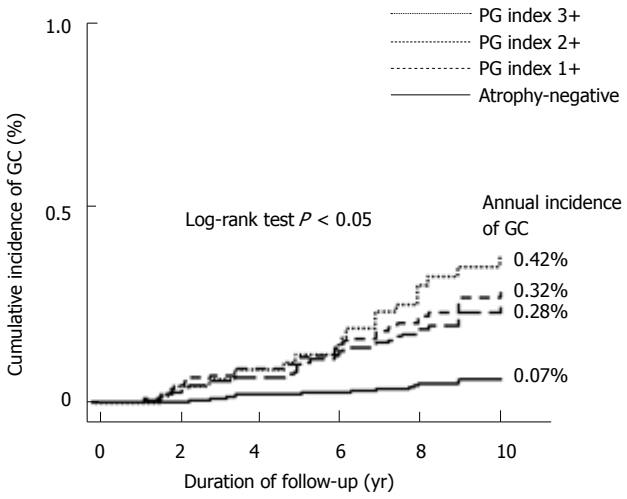


Figure 1 Kaplan-Meier analysis of gastric cancer development in subjects classified using the index of the pepsinogen test (modified from Yanaoka *et al*[25]). This shows the annual incidence of gastric cancer (GC) in each population identified based on serum pepsinogen test index criteria in middle-aged healthy men. With chronic atrophic gastritis progression, incidence of GC increased in a stepwise and significant manner. PG: pepsinogen.

Identification of GC high-risk groups using a combination of the serum PG test and HP infection diagnosis

Next, in the same populations, the relationship between HP infection, a major cause of chronic gastritis, and GC risk was also examined[23,24]. To diagnose HP infection, we used anti-HP antibody titers which, like serum PG, are easily measured using blood samples. The stage of HP-related chronic gastritis was classified into 4 stages based on the combination of both test results: Group A [HP(-), PG(-)]; Group B [HP(+), PG(-)]; Group C [HP(+), PG(+)]; and Group D [HP(-), PG(+)] (Figure 2). Group A comprised of HP non-infected healthy men. Group B showed established HP infection but without CAG. Group C had CAG. Group D had severe intestinal metaplasia due to progression of CAG but HP had been spontaneously eliminated, representing so-called metaplastic gastritis. Annual incidences of GC were: Group A, 0%; Group B, 0.11%; Group C, 0.24%; and Group D, 1.31%. Thus, with HP infection and CAG progression, the rate increased in a stepwise and significant manner. Moreover, in the non-infected healthy Group A, GC did not occur in a single case during 10 years of follow-up observation. Based on the above results, using a combination of the serum PG test and HP infection diagnosis, not only high-risk groups, but also a low-risk group, can theoretically be identified.

Points to consider in the serum PG test-negative GC

The serum PG test is highly useful as a GC risk marker but the occurrence of GC (particularly diffuse-type GC) in the PG test-negative group (Group B in HP-related chronic gastritis stage) cannot be ignored. In our study, even using the most balanced PG test criteria in terms of test accuracy (PG index 1+), about 40% of GCs that occurred represented PG test-negative GC. This point must be clearly kept in mind when assessing GC risk using the serum PG test.

We therefore evaluated the occurrence of GC in the PG test-negative group in further detail. Specifically, we examined the incidence of GC in 3 PG test-negative subgroups: α group (PG Ⅰ $\leqslant$ 70 ng/mL and PG Ⅰ / Ⅱ > 3); β group (PG Ⅰ > 70 ng/mL and PG Ⅰ / Ⅱ > 3); and γ group (PG Ⅰ > 70 ng/mL and PG Ⅰ / Ⅱ $\leqslant$ 3). In the γ group, with a higher serum PG Ⅱ and presumably severe gastric mucosal inflammation, the incidence of GC was 0.2%, thus identifying a new GC high-risk group mainly at risk of developing diffuse-type GC[25]. The rate in the γ group, although not high among the serum PG test-negative group, does indicate a subgroup to which careful attention should be paid. In addition, the group with high HP antibody titers (a marker which, like serum PG Ⅱ levels, reflects the degree of gastric mucosal inflammation) had a higher incidence of GC compared to a group with lower titers[24]. Furthermore, in this group, HP eradication therapy can be highly effective in preventing GC[27].

ABERRANT DNA METHYLATION AND GC RISK

Aberrant DNA methylation in cancers

Epigenetic abnormalities are also important as cancer gene abnormalities in addition to gene structural abnormalities such as mutations and chromosomal deletions. DNA methylation represents one type of epigenetic information. DNA methylation occurs physiologically and is observed at CpG sites where cytosine (C) is located adjacent to guanine (G) in gene sequences. CpG sites occur with low frequency in the genome but areas with a high density of CpG sites are occasionally encountered as so-called CpG islands (CGIs). When a CGI is in a gene promotor region and is entirely methylated, transcription of downstream genes to mRNA is potently inhibited (silencing). DNA methylation together with mutations and chromosomal deletions is a major factor in gene inactivation in many cancers[28-31].

In cancer cells, compared to normal cells, genome-overall hypomethylation and regional hypermethylation are observed. Genome-overall hypomethylation is involved in carcinogenesis by causing chromosomal instability[32]. Regional hypermethylation refers to aberrant methylation of a specific CGI that is normally unmethylated. If hypermethylation is induced in a promotor region CGI of a tumor suppressor gene, gene inactivation occurs. This causes cell cycle abnormalities, growth signaling abnormalities and mutation accumulation, thus playing a role in cancer onset and progression.

In gastrointestinal cancers, including GC, silencing of several important tumor suppressor genes has been reported. In particular, in GC, inactivation of *CDKN2A*, *MLH1* and *CDH1* due to methylation is more frequent than inactivation due mutations or chromosomal deletions[33].

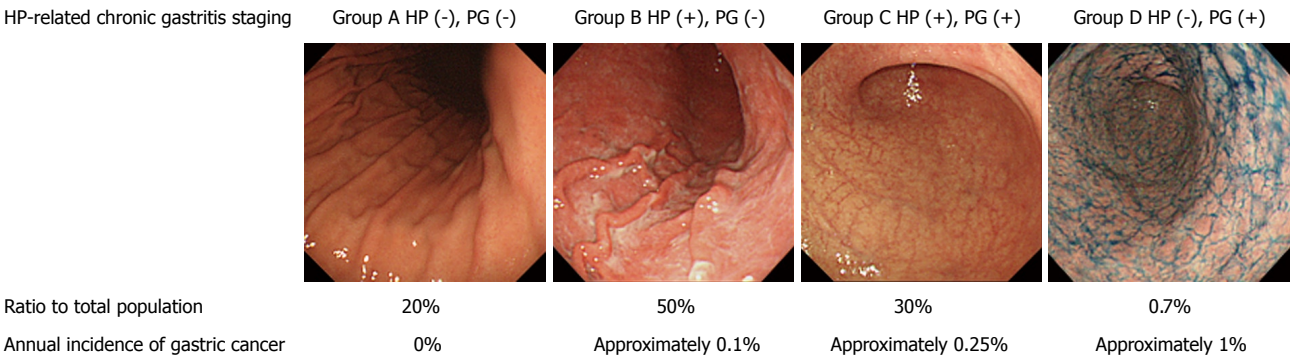


Figure 2 Gastric cancer incidence and *Helicobacter pylori*-related chronic gastritis stage classification based on a combination of the serum pepsinogen test and *helicobacter pylori*-infection diagnosis (modified from Ohata *et al*[23]). This shows percentages in each group, among middle-aged healthy men, based on the serum pepsinogen test and *Helicobacter pylori* (HP) antibody titers. As HP-related chronic gastritis stage progressed from Group A to Group D, annual incidence of gastric cancer increased in a stepwise and significant manner. PG: pepsinogen.

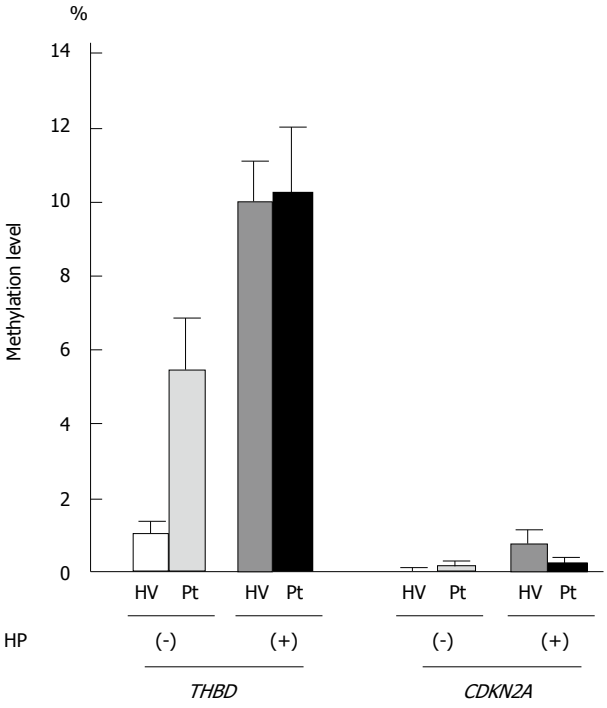


Figure 3 Relationship between gastric mucosae methylation levels and *Helicobacter pylori* infection/gastric cancer (modified from Maekita *et al*[34]). This shows mean methylation levels for the *THBD* and *CDKN2A* genes as measured by quantitative methylation-specific PCR in endoscopically biopsied gastric mucosae. Among *Helicobacter pylori* (HP)-negative cases, non-cancerous gastric mucosae in gastric cancer (GC) patients showed higher methylation levels than gastric mucosa in healthy volunteers. Among HP-positive cases, methylation levels were high regardless of the presence or absence of GC. Methylation susceptibility differed among genes. Compared to *THBD*, *CDKN2A* showed very little induction of methylation. The error bar denotes standard error. HV: healthy volunteers; Pt: patients.

Induction of aberrant DNA methylation in non-cancerous gastric mucosae by HP infection

Aberrant DNA methylation is important in GC but the mechanisms of induction have remained unknown. Using gastric mucosae obtained by endoscopic biopsy from both HP-positive healthy volunteers (individuals without GC) and HP-negative healthy volunteers, we used quantitative methylation-specific PCR (qMSP) to measure the percentage of DNA molecules with aberrant methylation (methylation level, reflecting the percentage of cells with aberrant methylation)[34]. As genes for analysis, we selected CGIs from 8 regions of 7 genes found to be methylated at high frequency in GC[35]. All of the eight regions showed a similar tendency in terms of methylation levels. Among healthy volunteers, methylation levels were 5.4- to 303-fold higher in HP-positive individuals than HP-negative individuals. This suggests that HP infection can potently induce aberrant DNA methylation.

Accumulation of aberrant DNA methylation in gastric mucosa and GC risk

In addition, to correlate the extent of aberrant DNA methylation in the gastric mucosae with GC risk, we analyzed gastric mucosae in healthy volunteers and non-cancerous gastric mucosae in patients with well-differentiated GC. In a comparison among HP-negative cases, methylation levels were 2- to 32-fold higher in non-cancerous gastric mucosae of GC patients than in gastric mucosae of healthy volunteers. We also newly collected non-cancerous gastric mucosae of patients with a single GC and those with multiple GCs and compared methylation levels in the gastric mucosae of patients with multiple GC (very high risk of GC) and patients with single GC. In HP-negative cases, specific gene methylation levels were increased in the order of healthy individual gastric mucosae → single GC patient non-cancerous gastric mucosae → multiple GC patient non-cancerous gastric mucosae[36]. These findings suggested a correlation between gastric mucosae methylation levels and GC risk in HP-negative cases. However, in HP-positive cases, both GC patients and healthy individuals showed potent induction of aberrant DNA methylation with almost no difference in methylation levels.

When evaluated by each gene, mean methylation levels for the tumor suppressor genes *CDKN2A* and *MLH1* were very low, so evaluating the correlation with GC risk was difficult (Figure 3)[34,37]. However, *LOX*, a tumor suppressor gene, showed relatively high methylation levels. Similarly, the microRNA gene, with tumor suppressor activity, also showed high methylation

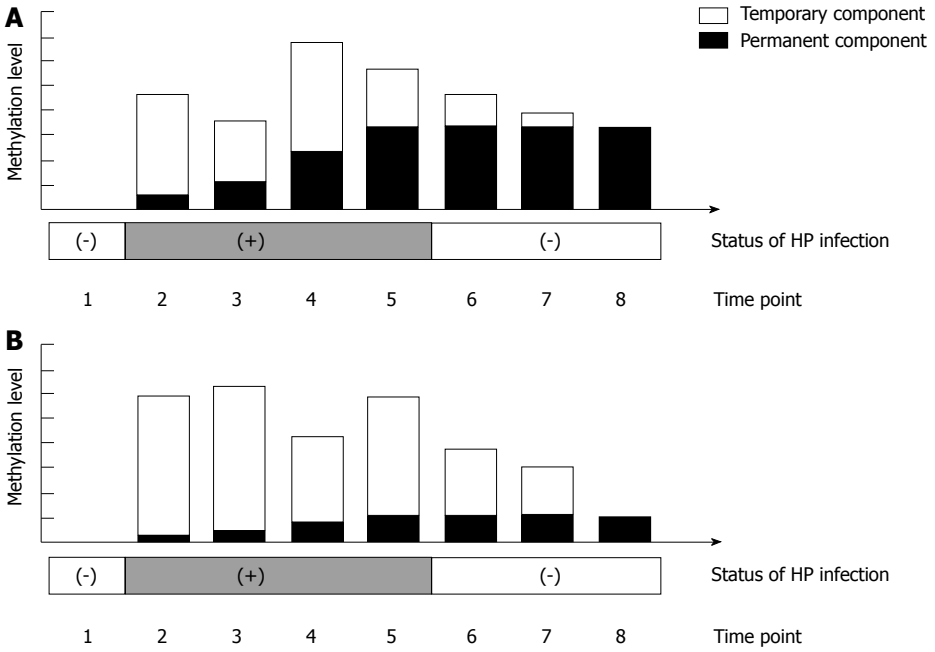


Figure 4 Temporary DNA methylation and permanent DNA methylation of gastric mucosae. DNA methylation includes temporary methylation, which is induced only during *Helicobacter pylori* (HP) infection, and permanent methylation, which persists even after elimination of HP infection. From time points 2 to 5, when HP infection was positive, overall methylation levels changed, with increases in permanent methylation, and increases and decreases in temporary methylation. At this stage, temporary methylation showed large fluctuations, so distinguishing differences in gastric cancer (GC) risk between cases was difficult. However, after spontaneous elimination of HP or HP eradication, at time point 8, at which time only permanent DNA methylation was present, GC risk was clearly higher in Figure 4A.

levels[38]. Methylation of non-tumor suppressor genes like *THBD* was observed in a relatively large number of cells. These levels correlated with GC risk (Figure 3). Genes methylated by HP infection show specificity. With HP infection, resistant genes show no methylation at all while susceptible genes display a high frequency of methylation[39]. Important in this mechanism is a lower expression of methylation-susceptible genes in the gastric mucosae of healthy individuals[39,40]. Thus, with HP infection, gene-specific regional hypermethylation occurs in non-cancerous gastric mucosa. Furthermore, recent study showed that regional (Alu and Sat) hypomethylation is induced in gastric mucosae by HP infection during gastric carcinogenesis[41].

DNA methylation levels after spontaneous elimination and eradication of HP infection

As most patients with intestinal-type GC have a past history of HP infection[42], the following changes in methylation levels are postulated to occur in the natural history of GC development. Firstly, methylation levels in the gastric mucosae are low in HP-non-infected individuals (near 0%). Secondly, with HP infection, DNA methylation of the gastric mucosae is potently induced. Thirdly, with progression of atrophic gastritis, spontaneous elimination of HP infection decreases methylation levels (Figure 4).

In addition, decreased methylation levels after HP eradication have been confirmed in specific genes and different kinetics for each gene have been shown[43,44]. Once methylation has occurred in a cell, it is difficult to conceive that demethylation would again occur in the same region. The decrease in methylation levels observed after HP eradication is thus probably due to cell turnover (temporary methylation). Residual aberrant methylation even after eradication is thought to reflect methylation in gastric gland stem cells (permanent methylation).

Advantages of DNA methylation as a marker of a field for cancerization

Individuals with low residual methylation levels (permanent methylation levels) after HP elimination or eradication have a low risk of GC. Conversely, those with high levels have a higher risk of GC (Figure 4). Using methylation-susceptible genes like *THBD* that are easily methylated at high frequency by HP infection, the GC risk in patients with high methylation levels is 2- to 3-fold higher than that in patients with low methylation levels, if appropriate cut-off values are established. Moreover, in the case of recently discovered genes such as *miR124a-1*, *-2* and *-3*, the GC risk is 5- to 20-fold higher[38].

Aberrant DNA methylation of the gastric mucosae has been strongly suggested to play an important role in the formation of an epigenetic field for cancerization, as the so-called epigenetic field defect[38,45,46]. These have similarly been found for esophageal cancer[47], colon cancer[48], hepatocellular carcinoma[49] and renal cancer[50]. Specific clinical applications of an epigenetic field for cancerization include measurement of methylation levels after HP eradication in healthy individuals to predict the risk of GC and measurement of methylation levels in patients who have undergone endoscopic treatment such as ESD to predict the risk of metachronous multiple GC. Large-scale prospective clinical trials are currently underway to confirm these concepts.

CONCLUSION

In conclusion, we have discussed identifying groups at high risk of developing GC using the serum PG test and predicting GC risk based on the accumulation of aberrant DNA methylation in the gastric mucosae from endoscopically biopsied tissue (Figure 5). Gastrointestinal endoscopists are aiming to improve diagnostic and treatment

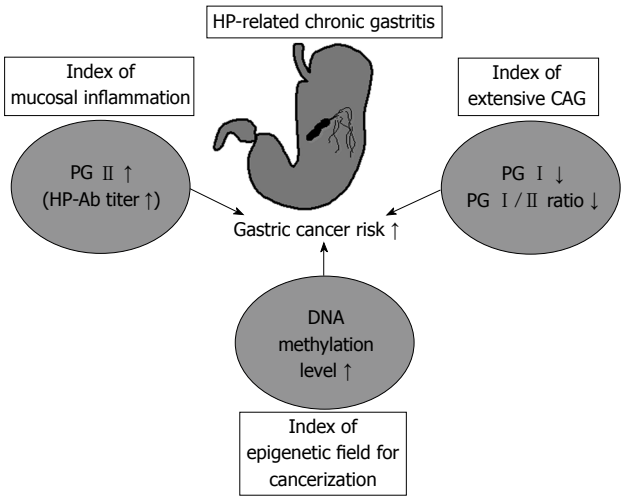


Figure 5 Schematic presentation of novel risk markers for gastric cancer screening. HP: *Helicobacter pylori*; CAG: chronic atrophic gastritis; PG: pepsinogen.

technology in GC but at the same time, as discussed in this paper, a thorough awareness of new concepts and risk markers of GC is also important. This is anticipated to have clinical applications such as in more effective endoscopic GC screening, and in establishing appropriate follow-up intervals for endoscopy based on individual GC risk.

ACKNOWLEDGEMENTS

The authors would like to express their deepest thanks to Ms. Kazu Konishi for her excellent secretarial assistance.

REFERENCES

1 **Kakushima N**, Fujishiro M. Endoscopic submucosal dissection for gastrointestinal neoplasms. *World J Gastroenterol* 2008; **14**: 2962-2967
2 **Yamamoto H**. Technology insight: endoscopic submucosal dissection of gastrointestinal neoplasms. *Nat Clin Pract Gastroenterol Hepatol* 2007; **4**: 511-520
3 **Gotoda T**. Endoscopic resection of early gastric cancer. *Gastric Cancer* 2007; **10**: 1-11
4 **Kodashima S**, Fujishiro M. Novel image-enhanced endoscopy with i-scan technology. *World J Gastroenterol* 2010; **16**: 1043-1049
5 **Curvers WL**, van den Broek FJ, Reitsma JB, Dekker E, Bergman JJ. Systematic review of narrow-band imaging for the detection and differentiation of abnormalities in the esophagus and stomach (with video). *Gastrointest Endosc* 2009; **69**: 307-317
6 **Polkowski M**. Endoscopic diagnosis and treatment of upper gastrointestinal tumors. *Endoscopy* 2008; **40**: 862-867
7 **Mukoubayashi C**, Yanaoka K, Ohata H, Arii K, Tamai H, Oka M, Ichinose M. Serum pepsinogen and gastric cancer screening. *Intern Med* 2007; **46**: 261-266
8 **Nakajima T**, Oda I, Gotoda T, Hamanaka H, Eguchi T, Yokoi C, Saito D. Metachronous gastric cancers after endoscopic resection: how effective is annual endoscopic surveillance? *Gastric Cancer* 2006; **9**: 93-98
9 Organization IafrocWH. Schistosomes, liver flukes and Helicobacter pylori. Lyon: France, 1994: 177-241
10 **Kageyama T**, Ichinose M. Diversity of structure and function of pepsinogens and pepsins. *Rescent Research Developments and Biophysics and Biochemistry* 2003; **3**: 159-178
11 **Hirschowitz BI**. Pepsinogen: its origins, secretion and excretion. *Physiol Rev* 1957; **37**: 475-511
12 **Samloff IM**, Varis K, Ihamaki T, Siurala M, Rotter JI. Relationships among serum pepsinogen I, serum pepsinogen II, and gastric mucosal histology. A study in relatives of patients with pernicious anemia. *Gastroenterology* 1982; **83**: 204-209
13 **Miki K**, Ichinose M, Shimizu A, Huang SC, Oka H, Furihata C, Matsushima T, Takahashi K. Serum pepsinogens as a screening test of extensive chronic gastritis. *Gastroenterol Jpn* 1987; **22**: 133-141
14 **Ichinose M**, Yahagi N, Oka M, Ikeda H, Miki K, Omata M. Screening for gastric cancer in Japan. In: Wu GY, Aziz K, editors. Cancer screening for common malignancies. Totowa, New Jersey: Humana Press, 2001: 87-102
15 **Watanabe Y**, Kurata JH, Mizuno S, Mukai M, Inokuchi H, Miki K, Ozasa K, Kawai K. Helicobacter pylori infection and gastric cancer. A nested case-control study in a rural area of Japan. *Dig Dis Sci* 1997; **42**: 1383-1387
16 **Miki K**, Ichinose M, Ishikawa KB, Yahagi N, Matsushima M, Kakei N, Tsukada S, Kido M, Ishihama S, Shimizu Y. Clinical application of serum pepsinogen I and II levels for mass screening to detect gastric cancer. *Jpn J Cancer Res* 1993; **84**: 1086-1090
17 **Kodoi A**, Yoshihara M, Sumii K, Haruma K, Kajiyama G. Serum pepsinogen in screening for gastric cancer. *J Gastroenterol* 1995; **30**: 452-460
18 **Hattori Y**, Tashiro H, Kawamoto T, Kodama Y. Sensitivity and specificity of mass screening for gastric cancer using the measurment of serum pepsinogens. *Jpn J Cancer Res* 1995; **86**: 1210-1215
19 **Yoshihara M**, Sumii K, Haruma K, Kiyohira K, Hattori N, Tanaka S, Kajiyama G, Shigenobu T. The usefulness of gastric mass screening using serum pepsinogen levels compared with photofluorography. *Hiroshima J Med Sci* 1997; **46**: 81-86
20 **Kitahara F**, Kobayashi K, Sato T, Kojima Y, Araki T, Fujino MA. Accuracy of screening for gastric cancer using serum pepsinogen concentrations. *Gut* 1999; **44**: 693-697
21 **Miki K**, Morita M, Sasajima M, Hoshina R, Kanda E, Urita Y. Usefulness of gastric cancer screening using the serum pepsinogen test method. *Am J Gastroenterol* 2003; **98**: 735-739
22 **Ohata H**, Oka M, Yanaoka K, Shimizu Y, Mukoubayashi C, Mugitani K, Iwane M, Nakamura H, Tamai H, Arii K, Nakata H, Yoshimura N, Takeshita T, Miki K, Mohara O, Ichinose M. Gastric cancer screening of a high-risk population in Japan using serum pepsinogen and barium digital radiography. *Cancer Sci* 2005; **96**: 713-720
23 **Ohata H**, Kitauchi S, Yoshimura N, Mugitani K, Iwane M, Nakamura H, Yoshikawa A, Yanaoka K, Arii K, Tamai H, Shimizu Y, Takeshita T, Mohara O, Ichinose M. Progression of chronic atrophic gastritis associated with Helicobacter pylori infection increases risk of gastric cancer. *Int J Cancer* 2004; **109**: 138-143
24 **Yanaoka K**, Oka M, Yoshimura N, Mukoubayashi C, Enomoto S, Iguchi M, Magari H, Utsunomiya H, Tamai H, Arii K, Yamamichi N, Fujishiro M, Takeshita T, Mohara O, Ichinose M. Risk of gastric cancer in asymptomatic, middle-aged Japanese subjects based on serum pepsinogen and Helicobacter pylori antibody levels. *Int J Cancer* 2008; **123**: 917-926
25 **Yanaoka K**, Oka M, Mukoubayashi C, Yoshimura N, Enomoto S, Iguchi M, Magari H, Utsunomiya H, Tamai H, Arii K, Ohata H, Fujishiro M, Takeshita T, Mohara O, Ichinose M. Cancer high-risk subjects identified by serum pepsinogen tests: outcomes after 10-year follow-up in asymptomatic middle-aged males. *Cancer Epidemiol Biomarkers Prev* 2008; **17**: 838-845
26 **Dinis-Ribeiro M**, Yamaki G, Miki K, Costa-Pereira A, Matsukawa M, Kurihara M. Meta-analysis on the validity of

pepsinogen test for gastric carcinoma, dysplasia or chronic atrophic gastritis screening. *J Med Screen* 2004; **11**: 141-147
27 **Yanaoka K**, Oka M, Ohata H, Yoshimura N, Deguchi H, Mukoubayashi C, Enomoto S, Inoue I, Iguchi M, Maekita T, Ueda K, Utsunomiya H, Tamai H, Fujishiro M, Iwane M, Takeshita T, Mohara O, Ichinose M. Eradication of Helicobacter pylori prevents cancer development in subjects with mild gastric atrophy identified by serum pepsinogen levels. *Int J Cancer* 2009; **125**: 2697-2703
28 **Esteller M**. Epigenetics in cancer. *N Engl J Med* 2008; **358**: 1148-1159
29 **Jones PA**, Baylin SB. The epigenomics of cancer. *Cell* 2007; **128**: 683-692
30 **Ushijima T**. Detection and interpretation of altered methylation patterns in cancer cells. *Nat Rev Cancer* 2005; **5**: 223-231
31 **Ushijima T**, Asada K. Aberrant DNA methylation in contrast with mutations. *Cancer Sci* 2010; **101**: 300-305
32 **Gaudet F**, Hodgson JG, Eden A, Jackson-Grusby L, Dausman J, Gray JW, Leonhardt H, Jaenisch R. Induction of tumors in mice by genomic hypomethylation. *Science* 2003; **300**: 489-492
33 **Ushijima T**, Sasako M. Focus on gastric cancer. *Cancer Cell* 2004; **5**: 121-125
34 **Maekita T**, Nakazawa K, Mihara M, Nakajima T, Yanaoka K, Iguchi M, Arii K, Kaneda A, Tsukamoto T, Tatematsu M, Tamura G, Saito D, Sugimura T, Ichinose M, Ushijima T. High levels of aberrant DNA methylation in Helicobacter pylori-infected gastric mucosae and its possible association with gastric cancer risk. *Clin Cancer Res* 2006; **12**: 989-995
35 **Kaneda A**, Kaminishi M, Yanagihara K, Sugimura T, Ushijima T. Identification of silencing of nine genes in human gastric cancers. *Cancer Res* 2002; **62**: 6645-6650
36 **Nakajima T**, Maekita T, Oda I, Gotoda T, Yamamoto S, Umemura S, Ichinose M, Sugimura T, Ushijima T, Saito D. Higher methylation levels in gastric mucosae significantly correlate with higher risk of gastric cancers. *Cancer Epidemiol Biomarkers Prev* 2006; **15**: 2317-2321
37 **Enomoto S**, Maekita T, Tsukamoto T, Nakajima T, Nakazawa K, Tatematsu M, Ichinose M, Ushijima T. Lack of association between CpG island methylator phenotype in human gastric cancers and methylation in their background non-cancerous gastric mucosae. *Cancer Sci* 2007; **98**: 1853-1861
38 **Ando T**, Yoshida T, Enomoto S, Asada K, Tatematsu M, Ichinose M, Sugiyama T, Ushijima T. DNA methylation of microRNA genes in gastric mucosae of gastric cancer patients: its possible involvement in the formation of epigenetic field defect. *Int J Cancer* 2009; **124**: 2367-2374
39 **Nakajima T**, Yamashita S, Maekita T, Niwa T, Nakazawa K, Ushijima T. The presence of a methylation fingerprint of Helicobacter pylori infection in human gastric mucosae. *Int J Cancer* 2009; **124**: 905-910
40 **Takeshima H**, Ushijima T. Methylation destiny: Moira takes account of histones and RNA polymerase II. *Epigenetics* 2010; **5**: 89-95
41 **Yoshida T**, Yamashita S, Takamura-Enya T, Niwa T, Ando T, Enomoto S, Maekita T, Nakazawa K, Tatematsu M, Ichinose M, Ushijima T. Alu and Sata Hypomethylation in Helicobacter pylori-Infected Gastric Mucosae. *Int J Cancer* 2010; **45**: 37-44
42 **Uemura N**, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, Taniyama K, Sasaki N, Schlemper RJ. Helicobacter pylori infection and the development of gastric cancer. *N Engl J Med* 2001; **345**: 784-789
43 **Niwa T**, Tsukamoto T, Toyoda T, Mori A, Tanaka H, Maekita T, Ichinose M, Tatematsu M, Ushijima T. Inflammatory processes triggered by Helicobacter pylori infection cause aberrant DNA methylation in gastric epithelial cells. *Cancer Res* 2010; **70**: 1430-1440
44 **Nakajima T**, Enomoto S, Yamashita S, Ando T, Nakanishi Y, Nakazawa K, Oda I, Gotoda T, Ushijima T. Persistence of a component of DNA methylation in gastric mucosae after Helicobacter pylori eradication. *J Gastroenterol* 2010; **45**: 37-44
45 **Ushijima T**. Epigenetic field for cancerization. *J Biochem Mol Biol* 2007; **40**: 142-150
46 **Nakajima T**, Enomoto S, Ushijima T. DNA methylation: a marker for carcinogen exposure and cancer risk. *Environ Health Prev Med* 2008; **13**: 8-15
47 **Ishii T**, Murakami J, Notohara K, Cullings HM, Sasamoto H, Kambara T, Shirakawa Y, Naomoto Y, Ouchida M, Shimizu K, Tanaka N, Jass JR, Matsubara N. Oesophageal squamous cell carcinoma may develop within a background of accumulating DNA methylation in normal and dysplastic mucosa. *Gut* 2007; **56**: 13-19
48 **Shen L**, Kondo Y, Rosner GL, Xiao L, Hernandez NS, Vilaythong J, Houlihan PS, Krouse RS, Prasad AR, Einspahr JG, Buckmeier J, Alberts DS, Hamilton SR, Issa JP. MGMT promoter methylation and field defect in sporadic colorectal cancer. *J Natl Cancer Inst* 2005; **97**: 1330-1338
49 **Kondo Y**, Kanai Y, Sakamoto M, Mizokami M, Ueda R, Hirohashi S. Genetic instability and aberrant DNA methylation in chronic hepatitis and cirrhosis--A comprehensive study of loss of heterozygosity and microsatellite instability at 39 loci and DNA hypermethylation on 8 CpG islands in microdissected specimens from patients with hepatocellular carcinoma. *Hepatology* 2000; **32**: 970-979
50 **Arai E**, Kanai Y, Ushijima S, Fujimoto H, Mukai K, Hirohashi S. Regional DNA hypermethylation and DNA methyltransferase (DNMT) 1 protein overexpression in both renal tumors and corresponding nontumorous renal tissues. *Int J Cancer* 2006; **119**: 288-296

S- Editor Zhang HN **L- Editor** Roemmele A **E- Editor** Liu N

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
doi:10.4253/wjge.v2.i12.388

World J Gastrointest Endosc 2010 December 16; 2(12): 388-396
ISSN 1948-5190 (online)

GUIDELINES FOR CLINICAL PRACTICE

Gastroesophageal reflux disease: Important considerations for the older patients

Maxwell M Chait

Maxwell M Chait, Hartsdale Medical Group, Hartsdale, NY 10530, United States
Author contribution: Chait MM contributed solely to this paper.
Correspondence to: Maxwell M Chait, MD FACP, FACG, AGAF, FASGE, 180 East Hartsdale Avenue, Hartsdale, NY 10530, United States. mdgi77@aol.com
Telephone: +1-914-7252010 Fax: +1-914-7256488
Received: October 28, 2010 Revised: November 29, 2010
Accepted: December 6, 2010
Published online: December 16, 2010

Abstract

Gastroesophageal reflux disease (GERD) is the most common upper gastrointestinal disorder seen in the elderly. The worldwide incidence of GERD is increasing as the incidence of *Helicobacter pylori* is decreasing. Although elderly patients with GERD have fewer symptoms, their disease is more often severe. They have more esophageal and extraesophageal complications that may be potentially life threatening. Esophageal complications include erosive esophagitis, esophageal stricture, Barrett's esophagus and adenocarcinoma of the esophagus. Extraesophageal complications include atypical chest pain that can simulate angina pectoris; ear, nose, and throat manifestations such as globus sensation, laryngitis, and dental problems; pulmonary problems such as chronic cough, asthma, and pulmonary aspiration. A more aggressive approach may be warranted in the elderly patient, because of the higher incidence of severe complications. Although the evaluation and management of GERD are generally the same in elderly patients as for all adults, there are specific issues of causation, evaluation and treatment that must be considered when dealing with the elderly.

Key words: Gastroesophageal reflux disease; Older patient; Elderly

Peer reviewers: Shinji Nishiwaki, MD, PhD, Director, Department of Internal Medicine, Nishimino Kosei Hospital, Yorocho, Yoro-gun, Gifu 503-1394, Japan; Kaushal Kishor Prasad, MD, PDCC, Associate Professor, Chief, Division of GE Histopathology, Department of Superspeciality for Gastroenterology, Postgraduate Institute of Medical Education and Research, Sector-12, Chandigarh, UT 160012, India

Chait MM. Gastroesophageal reflux disease: Important considerations for the older patients. *World J Gastrointest Endosc* 2010; 2(12): 388-396 Available from: URL: http://www.wjgnet.com/1948-5190/full/v2/i12/388.htm DOI: http://dx.doi.org/10.4253/wjge.v2.i12.388

INTRODUCTION

Gastroesophageal reflux disease (GERD) is the most common upper gastrointestinal disorder encountered in the elderly patient. It is highly prevalent worldwide with a prevalence of 10%-20% in the western world[1-4]. It is estimated that GERD affects 18.6 million people in the United States[5,6]. The prevalence of weekly symptoms has increased to an annual rate of approximately 5% in North America[4]. In the US adult population, 10%-20% of people have symptoms at least once weekly and 15%-40% of people have symptoms at least once monthly[4]. Among adult patients with GERD who seek medical care, up to 20% have serious complications[7]. There has been an increasing incidence of GERD and its complications, including Barrett's esophagus and adenocarcinoma of the esophagus, throughout the world[8-9]. No causal relationship has been demonstrated between *Helicobacter pylori* (*H. Pylori*) infection and gastroesophageal reflux disease. In fact, there is an inverse relationship of the prevalence of GERD to that of *H. Pylori* infection[10-11].

GERD has direct impact on quality of life, especially in the elderly. GERD patients reported a lower quality of life than unaffected individuals, especially in those with nighttime GERD[12]. In one study, 78% of GERD

patients reported nocturnal symptoms and 63% of those patients reported that sleep was negatively affected[13].

GERD has a significant economic impact. In the US direct costs of medical consultations, testing and treatment total 9.3 billion dollars. In addition, indirect costs in the US of absenteeism and interference with job performance, which is termed presenteeism, total 75 billion dollars[14-15].

Although there is a tendency to reduced symptom frequency of the usual complaints of heartburn and acid regurgitation in older patients, the frequency of GERD complications, such as erosive esophagitis, esophageal stricture, Barrett's esophagus, and esophageal cancer is significantly higher[6]. For example, Collen *et al* found an increase of esophagitis and Barrett's esophagus in patients over 60 years of age compared to those younger, 81% versus 47%[16]. Huang *et al*[17] found more severe gastroesophageal reflux and esophageal lesions in elderly patients, as compared to younger patients. Therefore, elderly patients with GERD are at greater risk than younger patients for developing serious complications of GERD.

PATHOGENESIS

GERD is defined as symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus[18]. A newer definition has been adopted which states that GERD is a condition that develops when reflux of gastric contents causes troublesome symptoms and/or complications[19]. The abnormalities that appear to play a pathogenic role in GERD tend to be more severe in the elderly patient and lead to the increased rate of GERD complications.

Injury to the esophagus is due to reflux of gastric acid and pepsin. However, duodenogastric reflux of bile may also cause esophageal injury[20]. The pathogenic abnormalities causing GERD include a defective antireflux barrier, abnormal esophageal clearance, reduced salivary production, altered esophageal mucosal resistance, and delayed gastric emptying.

The lower esophageal sphincter (LES) is the antireflux barrier[6] GERD most often occurs as a result of transient LES relaxations (tLESRs), where the drop in LES pressure is not accompanied by swallowing. The tLESRs promote acid reflux and the constellation of GERD problems. Incompetence of the LES was shown by Huang *et al*[17] to be more prevalent in the elderly. Furthermore, multiple medications more frequently taken by the elderly for co-morbid illnesses, such as hypertension, cardiovascular disease, and pulmonary disease and depression are well known to decrease LES pressure. These include nitrates, calcium channel blockers, benzodiazepines, anticholinergic agents, and antidepressants. The frequency of hiatal hernia and the loss of the diaphragmatic "pinch" which impairs the function of the LES and the clearance of refluxed acid from the distal esophagus also appear to increase with age[21].

Esophageal acid clearance is impaired in the elderly due to disturbances of esophageal motility and saliva production. In elderly patients, there is a significant decrease in the amplitude of peristaltic contraction and an increase in the frequency of nonpropulsive and repetitive contractions compared to younger individuals, often referred to as presbyesophagus[21]. Salivary production slightly decreases with age and is associated with a significantly decreased salivary bicarbonate response to acid perfusion of the esophagus[22]. Many of the medications noted above taken by elderly patients adversely affect esophageal motility as well as the LES. Many diseases that can negatively affect esophageal motility appear with greater frequency with advancing age, such as Parkinson's disease, cerebrovascular disease, cardiovascular disease, pulmonary disease and diabetes mellitus.

Gastric dysmotility with delayed gastric emptying and duodenogastric reflux of bile plays a significant role in GERD pathogenesis in elderly patients and is an important consideration in elderly patients that poorly respond to acid reducing medication. Delayed gastric emptying and duodenogastric reflux may be a significant cause of non-erosive reflux disease (NERD) and non-ulcer dyspepsia (NUD). Many of the medications taken by elderly patients that adversely affect esophageal motility as well as the LES also negatively affect gastric dysmotility with delayed gastric emptying and duodenogastric reflux[20].

Direct esophageal injury occurs more frequently in the elderly, because of medications given for co-morbid illnesses such as cardiovascular diseases, cerebrovascular disease, arthritis and osteoporosis that can directly injure the esophageal mucosa. These medications include nonsteroidal anti-inflammatory drugs (NSAIDs), potassium tablets, iron supplements and bisphosphonates.

Reduced pain perception can increase the rate of G ERD complications in the elderly, because acid injury can occur without the usual warning symptom significant heartburn and acid reflux symptoms[7]. Gastric acid secretion per se does not decrease with age alone. However, there is a decrease in esophageal pain perception with advancing age[21]. In addition, atrophic gastritis is more common in the elderly[23]. It may be associated with anti-parietal cell antibodies and pernicious anemia. *H. pylori* is also associated with decreased acid production and reduced acid reflux symptoms[10-11].

Lifestyle factors can be associated with increased gastroesophageal reflux and more complications of GE RD[7]. Tobacco smoking, caffeine, alcohol and fatty foods adversely affect GERD. Obesity, sedentary lifestyle and nocturnal gastroesophageal reflux are important mechanisms that are associated with more severe esophageal and extraesophageal complications of GERD in the elderly[12-13]. Obesity is a significant problem which increases acid reflux and thus increases GERD and its complications[24]. Nocturnal effects on GERD are reported by up to 78% of patients, with 75% of patients reporting that it negatively affects their ability to sleep[12]. Nocturnal gastroesophageal reflux and the recumbent, supine position remove the protective effect of gravity in GERD

Table 1 Complications of gastroesophageal reflux disease

Esophageal
Erosive esophagitis
Esophageal stricture
Barrett's esophagus
Esophageal adenocarcinoma
Extraesophageal
Atypical noncardiac chest pain
ENT complications
Globus sensation
Pharyngitis
Sinusitis
Otits media
Dental erosions
Hoarseness
Laryngitis
Vocal cord granulomas
Subglottic stenosis
Laryngeal cancer
Pulmonary complications
Chronic cough
Asthma
Chronic bronchitis
Pulmonary fibrosis
Aspiration pneumonia
Sleep apnea

ENT: ear, nose, and throat.

in the elderly patient[26-27]. Nocturnal GERD allows for more gastroesophageal reflux and further increases esophageal injury and GERD complications, especially in elderly patients who often spend more time in bed due to comorbid illness, such as dementia, Parkinson's disease, cerebrovascular disease, cardiovascular disease, pulmonary disease and diabetes mellitus.

The worldwide variation in incidence of GERD may be inversely related to the prevalence of *H Pylori* infection[11]. Studies have found a negative association between the prevalence of *H. Pylori* infection and GERD that is more marked with the more virulent CagA strains[27]. Additionally, they have shown a negative association of *H. Pylori* status and the complications of GERD including Barrett's esophagus and esophageal adenocarcinoma[27]. A study by Labins revealed a possible protective effect of *H. Pylori* infection in the subgroup analysis of patients with severe esophagitis[10]. In a study from China, a stepwise relationship was found between increasing grade of esophagitis and decreasing prevalence of *H. Pylori*[28]. In a Swedish study, *H. Pylori* was found to be associated with a significantly decreased risk of adenocarcinoma of the esophagus[29]. A subgroup analysis showed that the negative association was only apparent for the CagA positive strains of *H. Pylori*.

CLINICAL PRESENTATION

The most common symptoms of GERD are heartburn and acid regurgitation[30]. Other common symptoms include water brash, belching, and nausea. Important symptoms that herald more severe disease include dysphagia, odynophagia, anemia, unexplained weight loss, and gastrointestinal bleeding[31].

Heartburn is characterized by epigastric and retrosternal burning pain that may radiate to the neck, throat, and back. It often occurs after large meals, exercise, or reclining. Remarkably, the frequency of severe heartburn seems to decline with age, possibly due to a decrease in esophageal pain perception and atrophic gastritis. Dysphagia, difficulty in swallowing, is an important symptom that has been reported in 7% to 22% of the general population. In the frail elderly nursing home patient dysphagia is reported in 40% to 50% of patients[32]. When it occurs in response to both solids and liquids or more to liquids than solids, it is may be related to esophageal dysmotility due to disease states more common in the elderly, such as Parkinson's disease, cerebrovascular disease, dementia and diabetes. However, when it occurs in response to solids more than liquids, it may be structural in nature and due to severe esophagitis, esophageal stricture or esophageal cancer

Other important symptoms that signify more severe disease are odynophagia, anemia, unexplained weight loss, and gastrointestinal bleeding. These may signal problems such as severe esophagitis, esophageal ulcer, esophageal stricture, Barrett's esophagus or esophageal cancer.

Extrasesophageal symptoms occur more commonly in the elderly. They include atypical chest pain that can simulate angina pectoris; ear, nose, and throat (ENT) manifestations such as globus sensation, laryngitis, and dental problems; pulmonary problems such as chronic cough, asthma, and pulmonary aspiration and sleep apnea[33].

COMPLICATIONS

Complications of GERD that are potentially severe are more common in the elderly. Among patients with GERD seeking medical care in the United States, 20% have complications[7]. Complications may be esophageal or extraesophageal in nature and may vary from mild esophagitis to major life threatening problems such as recurrent pulmonary aspiration, Barrett's esophagus, and esophageal cancer[7,9] (Table 1).

Esophageal complications

As in younger patients, the most common complication of GERD in the elderly is esophagitis. This may progress from non-erosive esophagitis (NERD) to severe esophageal erosions, ulcerations and hemorrhage[33]. Esophageal stricture occurs in up to 10% of patients who have reflux esophagitis, especially in elderly men. Esophageal strictures are often associated with the use of NSAIDs. Treatment with esophageal dilatation and aggressive antireflux therapy is usually effective.

An important and increasingly common esophageal complication is Barrett's esophagus, in which columnar epithelium replaces squamous epithelium in the distal esophagus[34]. Barrett's esophagus is a premalignant condition highly associated with the development of adenocarcino-

ma of the esophagus and the gastric cardia. It is found in approximately 10%-15% of patients with GERD symptoms who undergo endoscopic examinations. It is more common in elderly Caucasian men over the age of 60[9]. Although its pathogenesis remains uncertain, acid reflux appears to injure the squamous epithelium and promote epithelial repair by columnar metaplasia of the esophageal mucosa. Because of the frequency and importance of Barrett's esophagus, upper GI endoscopy should be considered in all elderly patients with recurrent reflux symptoms. Patients with Barrett's esophagus must be evaluated with multiple biopsies to look for the presence of dysplasia, which is the precursor of invasive cancer. Continued endoscopic surveillance and aggressive measures, especially in high-grade dysplasia, are warranted to prevent adenocarcinoma of the esophagus. These measures include endoscopic ablative techniques such as endoscopic mucosal resection, electrocautery fulguration, laser photoablation, photodynamic therapy. Surgical esophagectomy in good operative risk patients with severe dysplasia is warranted[9].

Adenocarcinoma of the esophagus is among the fastest growing carcinomas by incidence in the United States where it has become the most common form of esophageal cancer[9]. The incidence of adenocarcinoma in patients with Barrett's esophagus is approximately 1% per year. Patients with esophageal cancer typically present in the seventh or eighth decade of life with weight loss and dysphagia. Although the overall survival rate of patients with adenocarcinoma of the esophagus is less than 10%, those with early stage cancer identified in surveillance programs usually have a higher survival rate[35].

Extraesophageal complications

Extraesophageal complications of GERD are more common in the elderly[33]. These include atypical noncardiac chest pain; ear, nose, and throat (ENT) manifestations, such as globus sensation, laryngitis, otitis media, sinusitis, pharyngitis, hoarseness, vocal cord granulomas, subglottal stenosis, laryngeal cancer, dental erosions; pulmonary problems, such as asthma, chronic cough, chronic bronchitis, pulmonary fibrosis, aspiration pneumonia and sleep apnea.

Atypical noncardiac chest pain has been related to GERD in up to 60% of cases. In 50% of cases symptoms are related directly to reflux injury and in 10% symptoms are related to esophageal dysmotility. Atypical noncardiac chest pain due to GERD may often be indistinguishable from angina pectoris[36]. Therefore, a cardiac evaluation is indicated in these elderly patients before ascribing symptoms to GERD alone.

Ear, nose, and throat (ENT) complications of GERD are frequent in the elderly with laryngitis being the most common. In up to 10% of patients with hoarseness, acid peptic injury from reflux is the cause. Acid injury can also cause globus sensation, otitis media, sinusitis, pharyngitis, hoarseness, dental erosions, vocal cord granulomas, subglottal stenosis and laryngeal cancer. Prolonged antireflux therapy may be necessary and is often effective in these patients. However, prompt relapses occur when therapy is discontinued[37].

Pulmonary complications of GERD are common in the elderly. Conditions include asthma, chronic cough, chronic bronchitis, pulmonary fibrosis, aspiration pneumonia and sleep apnea are all seen more frequently in the elderly. In up to 21% of patients with chronic cough, GERD is the cause[38]. Remarkably, chronic cough can be the only symptom of GERD is some patients. The mechanism for the development of pulmonary complications is not only pulmonary aspiration of refluxed material but also involves a neurally mediated reflex bronchoconstriction due to esophageal irritation by acid[38]. As with ENT manifestations, antireflux therapy is often helpful with a prompt recurrence occurring upon discontinuation of therapy.

EVALUATION

Diagnostic testing in older patients is essentially the same as for younger patients with GERD[39]. However, because of the higher incidence of complications in the elderly that may be severe and life threatening, an aggressive approach with prompt evaluation is warranted[7]. Barium swallow upper GI series and upper GI endoscopy are used to evaluate dysphagia and mucosal injury. Endoscopy is superior to the barium swallow exam, but must be used with caution in the elderly frail patient. Capsule endoscopy is evolving as a modality to evaluate the upper GI tract. It is less invasive than routine upper GI endoscopy and may be an alternative in the elderly patient. In patients with atypical symptoms or when quantification of reflux is required, ambulatory pH monitoring is helpful, but may be difficult to perform in the elderly patient. Wireless probes may improve compliance[40]. Multichannel intraluminal impedance measurement with a pH sensor allows the detection of pH episodes irrespective of their pH values (acid and nonacid reflux). This is useful in the postprandial period, in patients with persistent symptoms while on therapy and in those patients with atypical symptoms[41]. Esophageal manometry is often used in patients with markedly atypical symptoms, for locating the LES for pH testing, and in those for whom surgery is contemplated. However, it is not useful for the evaluation of GERD in the majority of patients.

The proton pump inhibitor (PPI) test has become a useful noninvasive test in elderly GERD patients for the evaluation atypical chest pain. Patients are given a course of high dose PPI agent, such as omeprazole 60 mg per day for 7 d, and observed for improvement in their clinical response[42]. However, this does not supplant the use of endoscopy in patients with significant symptoms, such as odynophagia and dysphagia.

Diagnostic testing should be performed in patients in whom the diagnosis remains uncertain; in patients with atypical symptoms such as chest pain, ENT problems, or pulmonary complications; in patients with significant

Table 2 Noninvasive treatment of gastroesophageal reflux disease[1]

Lifestyle modification
Elevation of head of bed
Avoid eating within 3 h of bedtime
Avoid tobacco, alcohol, caffeine, fatty food, peppermint
Avoid harmful medications if possible, such as NSAIDs, beta blockers
Calcium-channel blockers, theophylline, potassium tablets, bisphosphonate
Medications
Antacids
Motility agents:
Metoclopramide, erythromycin, bethanechol, cisapride, GABA B-receptor agonists
H_2 receptor antagonists:
Cimetidine, famotidine, nizatidine, ranitidine
PPI agents[1]:
Esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, dexlansoprazole

GABA: Gamma-aminobutyric acid B-receptor agonist; NSAIDS: non-steroidal anti-inflammatory drugs; H_2: histamine$_2$; PPI: proton pump inhibitor; [1]Most often successful.

symptoms that are often associated with complications such as dysphagia, odynophagia, unexplained weight loss, GI hemorrhage, and anemia; in patients who have an inadequate response to therapy, whether medical or surgical; in patients with recurrent symptoms; and in patients prior to consideration of antireflux surgery[43].

There are important considerations relating to diagnostic and treatment methods in elderly patients[44]. In cognitively impaired patients, a Mini-Mental State Examination may be indicated. Informed consent to procedures may be difficult to obtain in patients who suffer from cognitive dysfunction. With the exception of a true life-threatening emergency, every attempt should be made to obtain consent for testing procedures from the patient, if competent, or the surrogate. In cases where a guardian cannot be reached, administrative consent should be obtained. Timing of tests and type of intervention should be tailored, especially for the frail elderly patient, depending upon functional status, its impact on outcome, and the available diagnostic strategies. However, intervention should not be withheld because of age alone.

Older patients are more likely to have pacemakers with or without defibrillators. Recommendations for management of patients who require endoscopy and have pacemakers and internal defibrillators are not well defined. Cardiology consultation may often be indicated. If required, alternative means of tissue removal, destruction, or hemostasis should be considered to simplify management of patients. For example, to control hemorrhage in the bleeding patient with a defibrillator one may need to use such methods as hemo-clips, ligation devices, and injection of epinephrine and sclerosing agents. The general principle of geriatric pharmacology of starting with low doses of medication and slowly advancing to larger doses is an important dictum in conscious sedation of the elderly patient during endoscopy. Initial dosages should be lower and titration should be more gradual[44]. Deeper sedation that requires an anesthesiologist may be warranted in difficult cases.

In contrast to younger patients, endoscopy should be considered as the initial diagnostic test in elderly patients with heartburn, regardless of the severity or duration of complaints. This aggressive approach is warranted because of the higher incidence of cumulative acid injury over time and the higher incidence of complications of Barrett's esophagus and esophageal cancer in the elderly[16].

TREATMENT

Treatment of GERD in the elderly patient is essentially the same as in all adults with GERD[33]. However, a more aggressive approach to treatment is necessary in the elderly patient, because of the higher incidence of complications[16]. This aggressive approach must be balanced with the constraints of dealing with an older often frailer patient with comorbidities. The treatment goals, as in all patients with GERD, are elimination of symptoms, healing of esophagitis, managing or preventing complications, and maintaining remission[43]. The vast majority of patients can be treated successfully with the noninvasive methods of lifestyle modification and medication[43] (Table 2).

Although lifestyle modification remains a cornerstone of initial therapy in GERD, it may not be sufficient to control symptoms in the majority of patients, especially in those with complications. However, patients should try to loose weight, be more active, elevate the head of their bed before going to sleep, avoid eating within three hours of bedtime, stop tobacco smoking, decrease dietary fat and volume of meals and avoid dietary irritants such as alcohol, peppermint, onion, citrus juice, coffee, and tomatoes.

Potentially harmful medications that can aggravate the symptoms and effects of GERD in the elderly, such as NSAIDs, potassium tablets, bisphosphonates, beta blockers, theophylline and calcium-channel blockers should be avoided if possible. If these agents must be continued because of comorbid illness, the regimen should be modified on an individual basis, such as switching potassium tablets to an elixir or using an alternative medication or dosing frequency in the osteoporotic patient on biphosphonates. All medications should be given with 6-8 ounces of water in an upright position.

Over-the-counter antacids, histamine (H_2) blockers and PPI agents on an as-needed basis may be helpful for those individuals who have mild disease. However, for the majority of patients, and certainly for those patients with complications, one must use prescription agents for more effective therapy[7].

Motility agents, such as cisapride, metoclopramide, erythromycin, bethanechol and the gamma-amino butyric acid B-receptor (GABA) agonist Baclofen have helped to improve LES tone and esophagogastric motility in selected patients[44]. However, their success is limited in patients with more severe disease. For patients with diabetes, cisapride and metoclopramide have been used with moderate success in improving gastric emptying and re-

Table 3 Potential effects of prolonged acid suppression with histamine$_2$ receptor antagonists and PPI agents

Reduced absorption of nutrients and calcium
B_{12}, iron, calcium
Osteoporosis
Bacterial proliferation
Community acquired pneumonia
Clostridium difficile
Drug metabolism interference
Acid effects on drug absorption
PPI Effects on CYP2C19 pathway interference
Clopidogrel
Histamine$_2$ receptor antagonists effects on cytochrome P-450 3A4 system
Warfarin, phenytoin, benzodiazepines, theophylline
Drug side effects
Delirium, especially cimetidine
Neurorologic
Antiandrogen
Cardiac side effects
Hematologic

PPI: proton pump inhibitor.

ducing GERD symptoms. However, cisapride is only available on a restricted-use basis due to potentially fatal cardiac arrhythmias. Metoclopramide must be used with caution in the elderly, because it can cause side effects, such as muscle tremors, spasms, agitation, insomnia, drowsiness, and tardive dyskinesia, in up to one-third of patients. Erythromycin use is limited by its side effects and tachyphylaxis. Bethanechol has not proved useful in GERD. Gamma-amino butyric acid B-receptor (GABA) agonists, such as Baclofen, reduce tLESRs and improve gastric emptying. However, side effects that are more common in the elderly, such as somnolence, confusion, dizziness, lightheadedness, weakness and trembling, limit their use in the older patient. Newer agents are under investigation[45].

Histamine H-2 receptor antagonists, including cimetidine, ranitidine, famotidine, and nizatidine, are helpful in patients with GERD, by providing good acid suppression and symptom relief. These drugs are remarkably similar in their action and equally effective at equivalent doses. However, high doses of up to four times daily may be necessary in some patients with severe symptoms. Reducing dosage because of renal insufficiency, which is more common in the elderly, is often necessary. In addition, all these agents, especially cimetidine, can cause delirium in the older patient. Drug-drug interactions with histamine H-2 receptor antagonists through metabolism of the hepatic cytochrome P-450 3A4 system may be potentially harmful in elderly patients who use medications such as warfarin, phenytoin, benzodiazepines, and theophylline. Side effects of these agents, especially cimetidine, are more common in the elderly and in those with comorbid illnesses. Side effects include central nervous system side effects, such as mental confusion, delirium, headache, and dizziness; antiandrogen side effects of gynecomastia and impotence; cardiac side effects of sinus bradycardia, atrioventricular block, and prolongation of the QT interval; and hematological side effects of anemia, neutropenia, and thrombocytopenia. However, most side effects are reversible with dosage reduction or withdrawal of the offending agent[7].

Proton pump inhibitors (PPIs), such as esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, and dexlansoprazole are the most effective medical therapeutic agents for the treatment of GERD. Proton pump inhibitors provide excellent acid suppression and effective symptom relief[43]. These agents are particularly useful in elderly persons who often require more acid suppression due to more severe disease and complications. In older patients who are unable to swallow pills, capsules may be opened and the granules mixed in water or juice or sprinkled on applesauce or yogurt. For example, lansoprazole is available as an orally dissolving tablet and both lansoprazole and omeprazole powder are available as oral suspensions, which may be useful for those with swallowing disorders or those who require tube feedings.

Maintenance therapy is most often required, because relapses are common in elderly patients with GERD, especially those with associated complications. Long-term treatment with adequate doses of medication is the key to effective care in the elderly. For the majority of patients with esophageal strictures, the use of acid suppression and esophageal dilatation are effective. Aggressive acid suppression is effective in the majority of patients with GERD-related atypical chest pain. ENT complications, such as hoarseness, show dramatic response to these agents when adequate doses are used for prolonged periods. In patients with GERD-mediated asthma, significant improvement will occur with acid suppression by H_2 blockers and PPIs. Maintenance therapy is required in all of these patients because relapses occur very soon after cessation of therapy. In patients with Barrett's esophagus, chronic medical therapy is warranted, although its success remains controversial[45].

POTENTIAL EFFECTS OF PROLONGED ACID SUPPRESSION

Prolonged acid suppression by Histamine H-2 receptor antagonists and PPI agents may potentially affect nutrient and calcium absorption, bacterial proliferation, and drug metabolism in the older patient. However, with adequate monitoring, long term maintenance with PPI agents remains quite safe in the elderly population[46] (Table 3).

Vitamin B12, iron and calcium absorption can be affected. The effect on B12 and iron absorption appears to be insignificant, but periodic monitoring for anemia and reduced B12 and iron stores may be warranted[47].

Reduction of calcium absorption and the potential development or worsening of osteoporosis and resultant bone fracture is a significant but controversial issue. Reduction in bone density and increased incidence of hip fractures has been reported with both PPI agents and Histamine H-2 receptor antagonists[48]. If these agents are used for maintenance therapy, patients should be monitored for

Table 4 Invasive treatment of gastroesophageal reflux disease endoscopic therapy

Evolving techniques
Non-biodegradable polymer
Radiofrequency treatment of the gastroesophageal junction
Endoscopic suturing
Implantable gastric electrodes
Botulinum injection of the pyloris
Ablative techniques for Barrett's esophagus
Endoscopic mucosal resection
Electrocautery fulguration
Laser photoablation
Photodynamic therapy
Surgery
Laparoscopic fundoplication

osteoporosis as per recommended guidelines and given adequate intake of calcium and vitamin D. If osteoporosis is detected, treatment with appropriate agents, such as bisphosphanates should be offered. Withdrawal of acid suppression agents with worsening bone health in elderly patients must be considered.

Bacterial proliferation with an increased incidence of community acquired pneumonia and the development of gastrointestinal infection, such as *Clostridium difficile* associated colitis, has been reported and is important, although a controversial issue in the elderly patient. These patients have a higher incidence of comorbities and more often are in hospitals or long term care facilities. This would predispose them to frequent and more serious infections. Restriction of acid suppressant use in this regard remains controversial[49-50].

Interference of acid suppressant agents with drug metabolism is an issue. Acid inhibition may affect absorption of some drugs. Recently, interference with drug metabolism has become an issue with clopidogrel, which is often used for anticoagulation in the elderly. Omeprazole competitively interferes with conversion of clopidogrel to its active metabolite through the CYP2C19 pathway. The significance of this interference remains controversial, but switching to another PPI that may not significantly use this pathway, such as pantoprazole, lansoprazole or rabeprazole or switching to a Histamine H-2 receptor antagonist may be warranted[51].

Histamine H-2 receptor antagonists, especially cimetidine, can cause delirium in the older patient. Drug-drug interactions with histamine H-2 receptor antagonists through metabolism of the hepatic cytochrome P-450 3A4 system may be potentially harmful in elderly patients who use medications such as warfarin, phenytoin, benzodiazepines, and theophylline. Side effects of these agents, especially cimetidine, are more common in the elderly and in those with comorbid illnesses. Side effects include central nervous system side effects, such as mental confusion, delirium, headache, and dizziness; antiandrogen side effects of gynecomastia and impotency; cardiac side effects of sinus bradycardia, atrioventricular block, and prolongation of the QT interval; and hematological side effects of anemia, neutropenia, and thrombocytopenia. However, most side effects are reversible with dosage reduction or withdrawal of the offending agent[7].

Although the vast majority of elderly patients with complications associated with GERD can be successfully managed with medical therapy, invasive methods of surgery and endoscopic treatment may be warranted in some cases. Surgery is an option for some patients with GERD[52] and is now more frequently considered because of the ability to perform antireflux surgery laparoscopically. It is indicated in patients with intractable GERD, difficult-to-manage strictures, severe bleeding, nonhealing ulcers, recurrent aspiration, and GERD requiring large maintenance doses of PPI agents or H-2 receptor antagonists. Barrett's esophagus alone is not an indication for surgery. However, surgery is warranted for high grade dysplasia and esophageal adenocarcinoma. Given that there appears to be no greater increase in postoperative morbidity or mortality in the elderly with this type of surgery, healthy elderly patients should not be denied surgery on the basis of age alone[53]. Careful patient selection with complete preoperative evaluation, including upper GI endoscopy, esophageal manometry, pH testing, and gastric emptying studies, should be done prior to surgery.

Endoscopic therapy of GERD has had little success. Implantation of a biocompatible, non-biodegradable polymer (Enteryx) into the gastric cardia and radiofrequency energy delivery to the gastroesophageal junction, the Stretta Procedure, are available for the treatment of GERD on an investigational basis only[54-55]. Endoscopic suturing below the gastroesophageal junction is possible and has been used with some success to treat GERD[56]. However, further investigation and perfection of this technique is warranted. Pyloric injections of botulinum toxin in patients with refractory GERD and gastroparesis has had limited short term success. Endoscopic ablative techniques for treatment of Barrett's esophagus are evolving. They include endoscopic mucosal resection, electrocautery fulguration, laser photoablation and photodynamic therapy. Implantable gastric electrodes and botulinum injection of the pylorus to improve gastric emptying are further techniques being evaluated to reduce gastroesophageal reflux. Additional evaluation of these therapeutic techniques is warranted[57] (Table 4).

CONCLUSION

GERD and its associated complications are common in the older patient. The elderly tend to have fewer symptoms with more severe complications that may be life threatening. There are important considerations regarding causation, evaluation and treatment in the older as compared to the younger patient. However, with appropriate management, GERD and its associated complications can be treated successfully in majority of elderly patients.

REFERENCES

1 **Shaheen NJ**, Hansen RA, Morgan DR, Gangarosa LM, Ringel

Y, Thiny MT, Russo MW, Sandler RS. The burden of gastrointestinal and liver diseases, 2006. *Am J Gastroenterol* 2006; **101**: 2128-2138
2 **Fujiwara Y**, Higuchi K, Watanabe Y, Shiba M, Watanabe T, Tominaga K, Oshitani N, Matsumoto T, Nishikawa H, Arakawa T. Prevalence of gastroesophageal reflux disease and gastroesophageal reflux disease symptoms in Japan. *J Gastroenterol Hepatol* 2005; **20**: 26-29
3 **Wong WM**, Lai KC, Lam KF, Hui WM, Hu WH, Lam CL, Xia HH, Huang JQ, Chan CK, Lam SK, Wong BC. Prevalence, clinical spectrum and health care utilization of gastro-oesophageal reflux disease in a Chinese population: a population-based study. *Aliment Pharmacol Ther* 2003; **18**: 595-604
4 **El-Serag HB**. Time trends of gastroesophageal reflux disease: a systematic review. *Clin Gastroenterol Hepatol* 2007; **5**: 17-26
5 **Sandler RS**, Everhart JE, Donowitz M, Adams E, Cronin K, Goodman C, Gemmen E, Shah S, Avdic A, Rubin R. The burden of selected digestive diseases in the United States. *Gastroenterology* 2002; **122**: 1500-1511
6 **Johnson DA**, Fennerty MB. Heartburn severity underestimates erosive esophagitis severity in elderly patients with gastroesophageal reflux disease. *Gastroenterology* 2004; **126**: 660-664
7 **Chait MM**. Complications of gastroesophageal reflux disease in the elderly. *Annals of Long Term Care* 2005; **13**: 8-32
8 **Robertson D**, Aldersley M, Shepherd H, Smith CL. Patterns of acid reflux in complicated oesophagitis. *Gut* 1987; **28**: 1484-1488
9 **Lagergren J**, Bergström R, Lindgren A, Nyrén O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med* 1999; **340**: 825-831
10 **Labenz J**, Jaspersen D, Kulig M, Leodolter A, Lind T, Meyer-Sabellek W, Stolte M, Vieth M, Willich S, Malfertheiner P. Risk factors for erosive esophagitis: a multivariate analysis based on the ProGERD study initiative. *Am J Gastroenterol* 2004; **99**: 1652-1656
11 **Chait MM**. The association and clinical implications of gastroesophageal reflux disease and H pylori. *Practical Gastroenterology* 2006; **30**: 40-48
12 **Farup C**, Kleinman L, Sloan S, Ganoczy D, Chee E, Lee C, Revicki D. The impact of nocturnal symptoms associated with gastroesophageal reflux disease on health-related quality of life. *Arch Intern Med* 2001; **161**: 45-52
13 **Shaker R**, Castell DO, Schoenfeld PS, Spechler SJ. Nighttime heartburn is an under-appreciated clinical problem that impacts sleep and daytime function: the results of a Gallup survey conducted on behalf of the American Gastroenterological Association. *Am J Gatroenterol* 2003; **98**: 1487-1493
14 American Gastroenterological Association (AGA). The burden of gastrointestinal disease. Bethesda, Md: AGA, 2001
15 **Brook RA**, Wahlqvist P, Kleinman NL, Wallender MA, Campbell SM, Smeeding JE. Cost of gastroesophageal reflux disease to the employer: a perspective from the United States. *Alim Pharmacol Ther* 2007; **26**: 889-898
16 **Collen MJ**, Abdulian JD, Chen YK. Gastroesophageal reflux disease in the elderly: more severe disease that requires aggressive therapy. *Am J Gastroenterol* 1995; **90**: 1053-1057
17 **Huang X**, Zhu HM, Deng CZ, Porro GB, Sangaletti O, Pace F. Gastroesophageal reflux: the features in elderly patients. *World J Gastroenterol* 1999; **5**: 421-423
18 **DeVault KR**, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. *Am J Gastroenterol* 2005; **100**: 190-200
19 **Vakil N**, van Zanten SV, Kahrilas P, Dent J, Jones R. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol* 2006; **101**: 1900-1920; quiz 1943
20 **Ferriolli E**, Oliveira RB, Matsuda NM, Braga FJ, Dantas RO. Aging, esophageal motility, and gastroesophageal reflux. *J Am Geriatr Soc* 1998; **46**: 1534-1547
21 **Fass R**, Pulliam G, Johnson C, Garewal HS, Sampliner RE. Symptom severity and oesophageal chemosensitivity to acid in older and young patients with gastro-oesophageal reflux. *Age Ageing* 2000; **29**: 125-130
22 **Sonnenberg A**, Steinkamp U, Weise A, Berges W, Wienbeck M, Rohner HG, Peter P. Salivary secretion in reflux esophagitis. *Gastroenterology* 1982; **83**: 889-895
23 **Hurwitz A**, Brady DA, Schaal SE, Samloff IM, Dedon J, Ruhl CE. Gastric acidity in older adults. *JAMA* 1997; **278**: 659-662
24 **Jacobson BC**, Somers SC, Fuchs CS, Kelly CP, Camargo CA Jr. Body-mass index and symptoms of gastroesophageal reflux in women. *N Engl J Med* 2006; **354**: 2340-2348
25 **Orr WC**. Reflux events and sleep: are we vulnerable? *Curr Gastroenterol Rep* 2006; **8**: 202-207
26 **Mody R**, Bolge SC, Kannan H, Fass R. Effects of gastroesophageal reflux disease on sleep and outcomes. *Clin Gastroenterol Hepatol* 2009; **7**: 953-959
27 **Sharma P**. Recent advances in Barrett's esophagus: short-segment Barrett's esophagus and cardia intestinal metaplasia. *Semin Gastrointest* Dis 1999; **10**: 93-102
28 **Zhang J**, Chen XL, Wang KM, Guo XD, Zuo AL, Gong J. Relationship of gastric Helicobacter pylori infection to Barrett's esophagus and gastro-esophageal reflux disease in Chinese. *World J Gastroenterol* 2004; **10**: 672-675
29 **Ye W**, Held M, Lagergren J, Engstrand L, Blot WJ, McLaughlin JK, Nyrén O. Helicobacter pylori infection and gastric atrophy: risk of adenocarcinoma and squamous-cell carcinoma of the esophagus and adenocarcinoma of the gastric cardia. *J Natl Cancer Inst* 2004; **96**: 388-396
30 **Traube M**. The spectrum of the symptoms and presentations of gastroesophageal reflux disease. *Gastroenterol Clin North Am* 1990; **19**: 609-616
31 **Räihä IJ**, Impivaara O, Seppälä M, Sourander LB. Prevalence and characteristics of symptomatic gastroesophageal reflux disease in the elderly. *J Am Geriatr Soc* 1992; **40**: 1209-1211
32 **Chait MM**, Saffel D. Gastroesophageal reflux disease in the elderly. Pharmacy Times, 2006: 101-107
33 **Richter JE**. Gastroesophageal reflux disease in the older patient: presentation, treatment, and complications. *Am J Gastroenterol* 2000; **95**: 368-373
34 **Spechler SJ**. Barrett's esophagus. *Semin Oncol* 1994; **21**: 431-437
35 **van der Burgh A**, Dees J, Hop WC, van Blankenstein M. Oesophageal cancer is an uncommon cause of death in patients with Barrett's oesophagus. *Gut* 1996; **39**: 5-8
36 **Ruigómez A**, García Rodríguez LA, Wallander MA, Johansson S, Graffner H, Dent J. Natural history of gastro-oesophageal reflux disease diagnosed in general practice. *Aliment Pharmacol Ther* 2004; **20**: 751-760
37 **Wong RK**, Hanson DG, Waring PJ, Shaw G. ENT manifestations of gastroesophageal reflux. *Am J Gastroenterol* 2000; **95**: S15-S22
38 **Irwin RS**, French CL, Curley FJ, Zawacki JK, Bennett FM. Chronic cough due to gastroesophageal reflux. Clinical, diagnostic, and pathogenetic aspects. 1993. *Chest* 2009; **136**: e30
39 **Wong WM**, Wong BC. Definition and diagnosis of gastroesophageal reflux disease. *J Gastroenterol Hepatol* 2004; **19** Suppl 3: S26-S32
40 **Pandolfino JE**, Bianchi LK, Lee TJ, Hirano I, Kahrilas PJ. Esophagogastric junction morphology predicts susceptibility to exercise-induced reflux. *Am J Gastroenterol* 2004; **99**: 1430-1466
41 **Hong SK**, Vaezi MF. Gastroesophageal reflux monitoring: pH (catheter and capsule) and impedance. *Gastrointest Endosc Clin N Am* 2009; **19**: 1-22
42 **Fennerty MB**. Use of a therapeutic trial as a diagnostic test for GERD. *Practical Gastroenterology*. 2004; **28**: 45-50
43 **Kahrilas PJ**. Clinical practice. Gastroesophageal reflux disease. *N Engl J Med* 2008; **359**: 1700-1707
44 **Chait MM**. Lower gastrointestinal bleeding in the elderly. *World J Gastrointest Endosc* 2010; **2**: 147-154

45 **Boeckxstaens GE**, Beaumont H, Mertens V, Denison H, Ruth M, Adler J, Silberg DG, Sifrim D. Effects of lesogaberan on reflux and lower esophageal sphincter function in patients with gastroesophageal reflux disease. *Gastroenterology* 2010; **139**: 409-417

46 **Laine L**, Ahnen D, McClain C, Solcia E, Walsh JH. Review article: potential gastrointestinal effects of long-term acid suppression with proton pump inhibitors. *Aliment Pharmacol Ther* 2000; **14**: 651-668

47 **McColl KEI**. Effect of proton pump inhibitors on vitamins and iron. *Am J Gastroenterol* 2009; **104**: S5-S9

48 **Laine L**. Proton pump inhibitors and bone fractures? *Am J Gastroenterol* 2009; **104**: S21-S26

49 **Dial MS**. Proton pump inhibitor use and enteric infections. *Am J Gastroenterol* 2009; **104**: S17-S20

50 **Vakil N**. Acid inhibition and infections outside the gastrointestinal tract. *Am J Gastroenterol* 2009; **104**: S10-S16

51 **Ray WA**, Murray KT, Griffin MR, Chung CP, Smalley WE, Hall K, Daugherty JR, Kaltenbach LA, Stein CM. Outcomes with concurrent use of clopidogrel and proton-pump inhibitors: a cohort study. *Ann Intern Med* 2010; **152**: 337-345

52 **Spechler SJ**. Comparison of medical and surgical therapy for complicated gastroesophageal reflux disease in veterans. The Department of Veterans Affairs Gastroesophageal Reflux Disease Study Group. *N Engl J Med* 1992; **326**: 786-792

53 **Trus TL**, Laycock WS, Wo JM, Waring JP, Branum GD, Mauren SJ, Katz EM, Hunter JG. Laparoscopic antireflux surgery in the elderly. *Am J Gastroenterol* 1998; **93**: 351-353

54 **Johnson DA**, Ganz R, Aisenberg J, Cohen LB, Deviere J, Foley TR, Haber GB, Peters JH, Lehman GA. Endoscopic, deep mural implantation of Enteryx for the treatment of GERD: 6-month follow-up of a multicenter trial. *Am J Gastroenterol* 2003; **98**: 250-258

55 **Triadafilopoulos G**, DiBaise JK, Nostrant TT, Stollman NH, Anderson PK, Wolfe MM, Rothstein RI, Wo JM, Corley DA, Patti MG, Antignano LV, Goff JS, Edmundowicz SA, Castell DO, Rabine JC, Kim MS, Utley DS. The Stretta procedure for the treatment of GERD: 6 and 12 month follow-up of the U.S. open label trial. *Gastrointest Endosc* 2002; **55**: 149-156

56 **Mahmood Z**, McMahon BP, Arfin Q, Byrne PJ, Reynolds JV, Murphy EM, Weir DG. Endocinch therapy for gastro-oesophageal reflux disease: a one year prospective follow up. *Gut* 2003; **52**: 34-39

57 **Dellon ES**, Shaheen NJ. Persistent reflux symptoms in the proton pump era: the changing face of gastroesophageal reflux disease. *Gastroenterology* 2010; **139**: 7-13

S- Editor Zhang HN **L- Editor** Hughes D **E- Editor** Liu N

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
doi:10.4253/wjge.v2.i12.397

World J Gastrointest Endosc 2010 December 16; 2(12): 397-403
ISSN 1948-5190 (online)

Dietary approaches following endoscopic retrograde cholangiopancreatography: A survey of selected endoscopists

Lincoln EVVC Ferreira, Mark D Topazian, William S Harmsen, Alan R Zinsmeister, Todd H Baron

Lincoln EVVC Ferreira, Department of Medicine, Digestive Endoscopy Unit Hospital Universitario da Universidade Federal de Juiz de For a, Juiz de Fora, MG 36036247, Brasil
Mark D Topazian, Todd H Baron, Department of Medicine, Division of Gastroenterology and Hepatology, Rochester, MN 55905, United States
William S Harmsen, Alan R Zinsmeister, Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN 55905, United States
Author contributions: Ferreira LEVVC, Baron TH and Topazian MD were responsible for the idea, the development of the survey and the manuscript; and Harmsen WS and Zinsmeister AR were responsible for the formatting of the survey and statistical analysis.
Correspondence to: Todd H Baron, MD, Department of Medicine, Division of Gastroenterology and Hepatology, 200 1st Street SW, Rochester, MN 55905, United States. baron.todd@mayo.edu
Telephone: +1-507-2842174
Received: July 14, 2010 Revised: November 25, 2010
Accepted: December 2, 2010
Published online: December 16, 2010

Abstract

AIM: To describe the dietary recommendations of experienced endoscopists for patients who have undergone endoscopic retrograde cholangiopancreatography ERCP and the factors that influence these recommendations.

METHODS: Selected U.S. endoscopists with endoscopic retrograde cholangiopancreatography (ERCP) experience were surveyed by e-mail. A questionnaire with three hypothetical ERCP cases of patients at low, medium and high risk for development of post-ERCP pancreatitis (PEP) was shown. For each scenario, respondents were asked to recommend a post-procedure diet and time to first oral intake. Respondents were also asked about the effect of various clinical factors on their recommendations, including risk of PEP.

RESULTS: 97/187 selected ASGE members (51.9%) responded. When risk of PEP was either low, medium or high, 53%, 88% and 96% recommended a diet of clear liquids/NPO respectively, and 2%, 5% and 18% recommended delaying first oral intake until the following day. About 88% of respondents gave the same type of diet to patients at high as those with moderate-risk of PEP (P = 0.04). However, 37% and 43% of respondents gave different types of diet to patients at low *vs* moderate-risk and low-risk *vs* high-risk of PEP respectively (P < 0.001). No statistically significant associations were found regarding the effect of other clinical factors or respondent demographics.

CONCLUSION: Most experienced endoscopists limit diet to NPO/clear liquids after ERCP for patients at high or moderate risk of post-ERCP pancreatitis. About half allow a low-fat or regular diet in patients at low risk.

Key words: Cholangiopancreatography; Endoscopic retrograde; Diet; Pancreatitis; Survey; Postoperative care

Peer reviewers: Wai-Keung Chow, Visiting Staff, Division of Gastroenterology, Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan, China; Majid Abdulrahman Almadi, MD, FRCPC, Department of Gastroenterology Division, McGill University Health Center, Montreal, H3A 1A1, Canada; J Enrique Dominguez-Munoz, MD, Director of the Department of Gastroenterology, University Hospital of Santiago de Compostela, Spain

Ferreira LEVVC, Topazian MD, Harmsen WS, Zinsmesiter AR, Baron TH. Dietary approaches following endoscopic retrograde cholangiopancreatography: A survey of selected endoscopists. *World J Gastrointest Endosc* 2010; 2(12): 397-403 Available from: URL: http://www.wjgnet.com/1948-5190/full/v2/i12/397.htm DOI: http://dx.doi.org/10.4253/wjge.v2.i12.397

INTRODUCTION

Since the first report of endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy in 1974[1,2], there have been numerous advances in ERCP technique. Despite these advances, ERCP still causes significant morbidity[3]. Following ERCP, complications occur at rates of 5%-30%[3-7]. Pancreatitis, perforation, cholangitis and post-sphincterotomy bleeding are the most common complications. Most of these adverse events are diagnosed during the first 24 h after the procedure. Abdominal pain is common after ERCP and is not considered a complication; however pain may be a symptom of other post-ERCP complications.

The decision about when and how to feed patients after ERCP, although empirical, is likely based on the presence of risk factors for complications as well as post-ERCP symptoms. There may be a reluctance to begin feeding early after ERCP because of fear of precipitating post-ERCP pancreatitis or when abdominal pain occurs in the post-procedure recovery area.

There are no guidelines about timing and type of diet that should be prescribed after ERCP. The only randomized prospective study published about this issue concluded that in the absence of any perforation or severe acute pancreatitis, feeding could be initiated early[8]. However, it is not known what post-ERCP dietary practices are used in the U.S. and what factors influence these practices. Therefore, we undertook a survey of selected endoscopists with the U.S. who are ASGE members to better understand these practices.

MATERIALS AND METHODS

A total of three e-mail surveys comprised of three hypothetical cases of ERCP were sent to 187 physicians identified from the ASGE directory that were known or believed to perform ERCP as a substantial part of their practice. The first e-mail included a notice about the upcoming survey. The second e-mail contained the survey itself and the third e-mail was sent as a reminder to complete the survey.

The hypothetical cases contained within the survey were outpatients who underwent ERCP and were designed to be at low, medium, and high risk for post-ERCP pancreatitis based on previously defined criteria[9-12]. The high-risk scenario described a 21 year old woman with suspected sphincter of Oddi dysfunction who underwent multiple pancreatic duct injections, biliary sphincterotomy and placement of a prophylactic pancreatic stent. The moderate-risk scenario described a 56 year old woman who underwent biliary sphincterotomy and removal of a bile duct stone with one minimal pancreatic duct injection. The low-risk scenario described an 86 year old man with painless jaundice due to pancreatic cancer who underwent biliary metal stent placement with no pancreatic duct injection. The three cases were sent in randomized order to reduce bias. The physicians were not specifically alerted to the risk of pancreatitis nor that was this risk hypothesized to be a major factor in timing and type of diet prescribed.

For each scenario, respondents were asked to recommend a type of post-procedure diet (clear liquids until the next morning, low fat diet until the next morning, regular diet or other) and time to first oral intake after discharge (4, 6, 12 or 24 h). Questions were also asked about physician demographic data and the respondent's opinion regarding the importance of five clinical factors when recommending a post-ERCP diet (1) risk of post-ERCP pancreatitis; (2) risk of other post-ERCP complications; (3) post-ERCP symptoms; (4) patient's co-morbid medical illnesses; and (5) inpatient versus outpatient status).

Statistical analysis

Since each physician respondent answered the same questions for each of three scenarios, the data were considered paired. For statistical comparisons the recommended diet was grouped as: NPO/clear liquids versus low-fat/normal diet. Similarly, timing of the recommended diet was also grouped as: begin immediately/4 h later/6 h later *vs* 12 h later/24 h later. The three pair-wise comparisons of recommended diets (high-risk *vs* moderate-risk, high-risk *vs* low-risk and moderate-risk *vs* low-risk) were done using McNemar's test for paired contingency tables. The percentage of discordant recommendations in these contingency tables is also reported, i.e. the off-diagonal cells in the tables.

The associations of physician factors with discordant diet recommendations for pairs of patients were examined (in the 2 × 2 contingency table cross-tabulating the recommendations, the number of discordant pairs is the sum of the off-diagonal cells). The associations between physician factors: years of ERCP experience ($\leqslant$ 15 years *vs* > 15 years), number of ERCPs done per year ($\leqslant$ 250 *vs* > 250), physician age (< 45 years *vs* 45-54 years *vs* $\geqslant$ 55 years), and physician's practice location within the United States (northeast *vs* southeast *vs* southwest *vs* northwest) with diet recommendations for a pair of patients (categorized as discordant *vs* concordant) were examined using a Chi-square or Fisher exact test as appropriate.

In the same way as physician factors were examined for association with discordant *vs* concordant recommendations in patient pairs, the importance of patient factors in making diet recommendations was examined with regard to the 5 factors listed previously in the methods section. Possible responses to each of these questions was "very important", "somewhat important", "neither important nor unimportant", "somewhat important" and "very important". For analysis purposes these responses were grouped as important if answered either "very important" or "somewhat important" and not important otherwise.

The significance level was set at 0.05 for statistical significance. Because of the exploratory nature of the analysis, all *P*-values reported in the manuscript are not adjusted for multiple comparisons.

RESULTS

Ninety-seven of 187 physicians (51.9%) answered the survey. Table 1 shows the demographics of the respon-

Table 1 Physicians demographics and endoscopic retrograde cholangiopancreatography experience

Age group (y)	⩽ 39	40-49	50-59	⩾ 60	Missed
n (%)	12 (12.4)	43 (44.3)	31 (31.9)	11 (11.4)	0 (0)
ERCP/year	0	< 50	51-250	> 250	Missed
n (%)	3 (3.1)	8 (8.3)	37 (38.1)	49 (50.5)	0 (0)
Location	Northeast	Southeast	Southwest	Northwest	Missed
n (%)	47 (48.5)	13 (13.4)	13 (13.4)	21 (21.6)	3 (3.1)
NYP ERCP	< 5 yr	5-10 yr	11-15 yr	> 15 yr	Missed
n (%)	10 (10.3)	12 (12.4)	14 (14.4)	60 (61.8)	1 (1.1)

NYP ERCP: Number of years performing endoscopic retrograde cholangiopancreatography.

Table 2 Type of diet prescribed after endoscopic retrograde cholangiopancreatography

Type of diet	Risk of pancreatitis				
	NPO *n* (%)	CL *n* (%)	Low-fat *n* (%)	Normal *n* (%)	Total *n* (%)
Low	0 (0)	51 (52.6)	17 (17.5)	29 (29.9)	97 (100)
Medium	4 (4.1)	81 (83.5)	5 (5.2)	7 (7.2)	97 (100)
High	24 (24.7)	69 (71.1)	2 (2.1)	2 (2.1)	97 (100)

CL: clear liquids; NPO: nil per os.

ders, number of ERCPs performed per year, practice location in the United States and number of years they have performed ERCP. Regarding type of practice, 25 responders (25.8%) work in private practice, 64 (66%) work as fulltime academics and 8 (8.2%) physicians did not respond to this question.

Tables 2 and 3 show overall results regarding type of diet and time to first oral intake recommended by respondents in relation to the risk of post-ERCP pancreatitis. When risk of post-ERCP pancreatitis was either low, medium or high, 53%, 88% and 96% recommended a diet of clear liquids/NPO respectively and 2%, 5% and 18% recommended delaying first oral intake until the following day.

Tables 4 and 5 show data analysis based on the paired nature of the study data. Table 4 shows how often individual respondents changed their recommended diet type based on differences in the patient scenarios. About 88% of respondents gave the same type of diet to patients at high *vs* moderate-risk of post-ERCP pancreatitis ($P = 0.04$). However, 37% and 43% of respondents gave different types of diet to patients at low *vs* moderate-risk and low-risk *vs* high-risk of post-ERCP pancreatitis respectively ($P < 0.001$). This shows that respondents tended to prescribe the same diet (usually NPO or clear liquids) to patients at high and moderate-risk but were more apt to prescribe a solid diet for patients at low-risk of post-ERCP pancreatis.

Table 5 shows how often individual respondents changed their recommended time to first oral intake based on differences in the patient scenarios. This shows that most respondents did not vary their recommendations

Table 3 Timing to resumption of oral intake after endoscopic retrograde cholangiopancreatography

Resume oral intake	Risk of pancreatitis					
	Immediately *n* (%)	4 h later *n* (%)	6 h later *n* (%)	12 h later *n* (%)	24 h later *n* (%)	Total *n* (%)
Low	71 (73.2)	21 (21.6)	2 (2.1)	1 (1.0)	2 (2.1)	97 (100)
Medium	56 (57.7)	29 (29.9)	4 (4.1)	3 (3.1)	5 (5.2)	97 (100)
High	49 (50.5)	18 (18.5)	7 (7.2)	6 (6.2)	17 (17.6)	97 (100)

regarding timing of first oral intake between scenarios. Approximately 20% of physicians did change their recommendations based on patient scenario, in most cases delaying oral intake in patients at high-risk of post-ERCP pancreatitis but not in patients at low or moderate risk.

An analysis was done to examine whether physicians were more likely to change their diet type or timing recommendations based on their age, practice location, number of ERCPs they perform per year or years of ERCP experience (Tables 6 and 7). No statistically significant associations were observed. Additionally, an analysis was done to evaluate whether changes in diet type and timing recommendations were attributable to a physician's views on the importance of various clinical factors, including risk of post-ERCP pancreatitis, risk of other post-ERCP complications, post-ERCP symptoms, patient co-morbid medical illnesses and inpatient *vs* outpatient status (Tables 8 and 9). No statistically significant associations were observed.

DISCUSSION

The endoscopists' decision as to when and how to begin oral intake after a seemingly uncomplicated ERCP is largely based upon training and personal experience. There are theoretical considerations but essentially no empirical data to provide guidance. We believe that there are several clinical factors that affect dietary recommendations after ERCP. In this survey, we sought to determine practice patterns of selected American endoscopists regarding type and timing of diet after ERCP. Although we did not specifically cite the risk of post-ERCP pancreatitis in the individual scenarios given in the survey, patients were described who were at high, moderate and low risk.

We found that about 88% of physicians recommended that patients at moderate and high risk of developing post-ERCP pancreatitis should be kept NPO or given clear liquids. In patients at high-risk of post-ERCP pancreatitis, approximately 20% of physicians recommend delaying time to first oral intake for at least 12 h after discharge. On the other hand, for patients who were at low risk of post-ERCP pancreatitis, about 40% of physicians varied their recommended type of post-procedure diet. In this scenario a solid diet was recommended more frequently and only 3% delayed first oral intake for at least 12 h.

We were unable to demonstrate that respondents'

Table 4 Paired diet recommendations by patient scenario

				Significance[1]	% who changed recommendation based on scenario
		Moderate risk			
		NPO/CL	L-F/Normal		
High risk	NPO/CL	83	10	0.04	12/97 (12%)
	L-F/Normal	2	2		
		Low risk			
High risk	NPO/Clears	51	42	< 0.001	42/97 (43%)
	L-F/Normal	0	4		
		Low risk			
Mod risk	NPO/CL	50	35	< 0.001	36/97 (37%)
	L-F/Normal	1	11		

[1]McNemar test; CL: clear liquids; L-F: low-fat; NPO: nil per os.

Table 5 Paired time to first oral intake recommendations by patient scenario

				Significance[1]	% who changed recommendation based on scenario
		Moderate risk			
		Not delayed	Delayed		
High risk	Not delayed	73	1	< 0.001	17/97 (18%)
	Delayed	16	7		
		Low risk			
High risk	Not delayed	74	0	< 0.001	20/97 (21%)
	Delayed	20	3		
		Low risk			
Mod risk	Not delayed	88	1	0.125	7/97 (7%)
	Delayed	6	2		

[1]McNemar test.

Table 6 Diet type recommended based on age, practice location, number of endoscopic retrograde cholangiopancreatographys performed per year and years of endoscopic retrograde cholangiopancreatography experience of respondents

Physician characteristic			Risk of post-ERCP pancreatitis					
			High *vs* medium		High *vs* low		Medium *vs* low	
		Total number of pairs	Number with different recommendations[b]		Number with different recommendations[b]		Number with different recommendations[b]	
			n (%)	*P*-value[a]	*n* (%)	*P*-value[a]	*n* (%)	*P*-value[a]
ERCP experience[1]	≤ 15 yr	36	4 (11)		17 (47)		17 (47)	
	> 15 yr	60	8 (13)	1.00	24 (40)	0.49	18 (30)	0.09
Number of ERCPs/year	≤ 250	48	6 (12)		21 (44)		15 (31)	
	> 250	49	6 (12)	0.97	21 (43)	0.93	21 (43)	0.24
Age of physician	< 45	30	4 (13)		15 (50)		15 (50)	
	45-54	49	5 (10)		19 (39)		16 (33)	
	≥ 55	18	3 (17)	0.78	8 (44)	0.62	5 (28)	0.20
Residency of physician[2]	NE	47	5 (11)		23 (49)		22 (47)	
	SE	13	2 (15)		5 (38)		3 (23)	
	SW	13	3 (23)		8 (62)		5 (38)	
	NW	21	2 (10)	0.63	6 (29)	0.24	6 (29)	0.36

[a]Significance of the association between physician variable and recommendation of different diets assessed using a Chi-square or Fisher's exact test as appropriate; [b]Recommended diet dichotomized as: NPO/Clears *vs* Low-Fat/Normal, to define "Different Recommendation"; [1]Not completed for 1 physician; [2]Not completed for 3 physicians; ERCP: endoscopic retrograde cholangiopancreatography.

changes in dietary recommendations were based on their general views regarding the importance of various clinical factors; however, this was probably because the great majority of respondents indicated that the risk of post-ERCP pancreatitis was an important determinant of post-procedure diet, regardless of whether they changed their recommendations from scenario to scenario. No statistically significant associations were found between recom-

Table 7 Timing of resumption of diet recommended based on age, practice location, number of endoscopic retrograde cholangiopancreatographys performed per year and years of endoscopic retrograde cholangiopancreatography experience of respondents

Physician characteristic			Risk of post-ERCP pancreatitis					
			High *vs* medium		High *vs* low		Medium *vs* low	
		Total number of pairs	Different timing recommendation		Different timing recommendation		Different timing recommendation	
			n (%)	*P*-value[a]	*n* (%)	*P*-value[a]	*n* (%)	*P*-value[a]
ERCP experience[1]	≤ 15 yr	36	8 (22)		9 (25)		1 (3)	
	> 15 yr	60	9 (15)	0.37	11 (18)	0.44	6 (10)	0.09
Number of ERCPs/year	≤ 250	48	7 (15)		8 (17)		1 (2)	
	> 250	49	10 (20)	0.45	12 (24)	0.34	6 (12)	0.11
Age of physician	< 45	30	6 (20)		6 (20)		0 (0)	
	45-54	49	8 (16)		12 (24)		6 (12)	
	≥ 55	18	3 (17)	0.91	2 (11)	0.48	1 (6)	0.12
Residency of physician[2]	NE	47	11 (23)		14 (30)		5 (11)	
	SE	13	2 (15)		3 (23)		1 (8)	
	SW	13	2 (15)		2 (15)		0 (0)	
	NW	21	2 (21)	0.59	1 (5)	0.11	1 (5)	0.79

[a]Significance of the association between physician variable and recommendation of different timing for the recommended diets assessed using a Chi-square or Fisher's exact test as appropriate. Timing dichotomized as: Immediate/4h/6h *vs* 12h/24h, to define "Different Timing Recommended"; [1]Not completed for 1 physician; [2]Not completed for 3 physicians; ERCP: endoscopic retrograde cholangiopancreatography.

Table 8 Diet type recommended based on clinical factors considered important or not by the respondents

Clinical factors			Risk of post-ERCP pancreatitis					
			High *vs* medium		High *vs* low		Medium *vs* low	
		Total number of pairs	Number with different recommendations[b]		Number with different recommendations[b]		Number with different recommendations[b]	
			n (%)	*P*-value[a]	*n* (%)	*P*-value[a]	*n* (%)	*P*-value[a]
Risk of post-ERCP pancreatitis[1]	Important	12	2 (17)		4 (33)		2 (17)	
	Unimportant	84	10 (12)	0.64	38 (45)	0.44	34 (40)	0.20
Risk other post-ERCP complication[1]	Important	29	3 (10)		12 (41)		9 (31)	
	Unimportant	67	9 (13)	1.00	30 (45)	0.76	27 (40)	0.39
Post-ERCP symptoms[1]	Important	11	1 (9)		2 (18)		3 (27)	
	Unimportant	85	11 (13)	1.00	40 (47)	0.11	33 (39)	0.53
Patient co-morbid medical illnesses[2]	Important	60	9 (15)		27 (45)		24 (40)	
	Unimportant	35	3 (9)	0.53	15 (43)	0.84	12 (34)	0.58
Inpatient/outpatient status[3]	Important	60	6 (10)		26 (43)		24 (40)	
	Unimportant	34	5 (15)	0.52	15 (44)	0.94	12 (35)	0.65

[a]Significance of the association between physician importance answers and recommendation of different diets assessed using a Chi-square or Fisher's exact test as appropriate. [b]Recommended diet dichotomized as NPO/Clears *vs* Low-Fat/Normal to define "Different Recommendation" importance dichotomized as: Very/Somewhat Important → "Important *vs* Neither/Somewhat/Very Unimportant → "Unimportant"; [1]Not completed for 1 physician; [2]Not completed for physicians; [3]Not completed for 3 physicians; ERCP: endoscopic retrograde cholangiopancreatography.

mendations and respondents' ERCP experience, age or practice location.

In a study designed to address dietary intake after ERCP, Barthet *et al*[8] randomized patients to early refeeding (4 h after ES - group 1) and later refeeding (24 h after procedure - group 2). Unfortunately, the type of diet prescribed in this study was not given. Abdominal pain was less prevalent in group 1 (11% *vs* 37%) while abdominal pain associated with oral intake was observed with higher frequency in group 2 (6.8% *vs* 17.8%). Finally, the mean hospital stay was significantly shorter in the early refeeding group. The authors conclude that in the absence of perforation or severe acute pancreatitis, early refeeding would be recommended.

When deciding about timing and type of diet to give patients after ERCP, physicians likely consider the patient's risk of complications (especially post-ERCP pancreatitis), how well the procedure went (difficult cannulation, pancreatic injection *etc*), the complexity and risk of interventions (such as ampullectomy) and whether the patient has symptoms following the procedure. Since more than 2/3 of patients develop symptoms during the first 6 h post-procedure and the presence of symptoms is a poor predictor of complications, the presence or absence of symptoms is not adequate to guide dietary recommendations[13]. When the risk of complications is high, limiting diet to clear liquids on the day of the procedure was recommended by the majority of respondents in this

Table 9 Timing of resume diet recommended based on clinical factors considered important or not by the respondents

Clinical factors		Total number of pairs	Risk of post-ERCP pancreatitis					
			High *vs* medium		High *vs* low		Medium *vs* low	
			Number with different recommendations[b]		Number with different recommendations[b]		Number with different recommendations[b]	
			n (%)	*P*-value[a]	*n* (%)	*P*-value[a]	*n* (%)	*P*-value[a]
Risk of post-ERCP pancreatitis[2]	Important	14	1 (7)		1 (7)		0 (0)	
	Unimportant	81	16 (20)	0.45	19(23)	0.29	7 (9)	0.59
Risk other post-ERCP complication[1]	Important	26	4 (15)		4 (15)		2 (8)	
	Unimportant	70	13 (19)	1.00	16 (23)	0.42	5 (7)	1.00
Post-ERCP symptoms[1]	Important	12	1 (8)		0 (0)		1 (8)	
	Unimportant	84	16 (19)	0.69	20 (24)	0.07	6 (7)	1.00
Patient co-morbid medical illnesses[1]	Important	65	11 (17)		12 (18)		5 (8)	
	Unimportant	31	6 (19)	0.77	8 (26)	0.41	2 (6)	1.00
Inpatient/outpatient status[2]	Important	65	8 (12)		11 (17)		5 (8)	
	Unimportant	30	9 (30)	0.04	9 (30)	0.15	2 (7)	1.00

[a]Significance of the association between physician importance answers and recommendation of different diets assessed using a Chi-square or Fisher's exact test as appropriate. [b]Recommended diet dichotomized as NPO/Clears *vs* Low-Fat/Normal to define "Different Recommendation" importance dichotomized as: Very/Somewhat Important → "Important *vs* Neither/Somewhat/Very Unimportant → "Unimportant"; [1]Not completed for 1 physician; [2]Not completed for physicians; ERCP: endoscopic retrograde cholangiopancreatography.

study. Prospective, controlled studies comparing post-ERCP dietary strategies are warranted.

COMMENTS

Background

Pancreatitis is a complication that occurs in up to 20% of patients following endoscopic retrograde cholangiopancreatography (ERCP). ERCP is a procedure that is used to diagnose and treat disorders of the bile and pancreatic ducts. Pancreatitis is an inflammation of the pancreas. It can range from mild to severe. It is unknown if the type of diet and when it is started after ERCP influences the risk of post-ERCP pancreatitis. It is assumed that a low-fat diet may be preferable in high-risk patients because fat causes stimulation of the pancreas.

Research frontiers

There is relatively little information in the literature about post-ERCP pancreatitis and diet. A previous study randomly assigned patients who underwent ERCP to begin eating either 4 h or 24 h after the procedure. There was no difference in the overall complication rate between the two groups.

Innovations and breakthroughs

This article is unique because the authors created a survey from experienced endoscopists on when and what to feed patients after ERCP. In the survey three fictional patients were presented. The three patients had differing risks of post-ERCP pancreatitis. One was at low risk, one was at high risk and one was at medium risk. They found that most endoscopists recommend a clear liquid diet or low-fat diet at 12-24 h (no intake until then) in patients at high risk for post-ERCP pancreatitis and a regular diet sooner for patients at low risk. Although the survey did not inform the physicians that we were asking for their opinion based upon the risk of pancreatitis, most responders admitted that the risk of pancreatitis played a major factor in choice of diet.

Applications

The authors believe that physicians who are less experienced will read this article and change their practice based upon what experts in the field recommend. They also believe that this article will lead to other studies on the effect that diet has on post-ERCP pancreatitis, especially in high risk patients.

Terminology

The readers need to understand what ERCP is and what causes pancreatitis after the procedure. The also need to know what pancreatitis is and how the severity of the disease varies.

Peer reviews

This is a very well written paper focused on a relevant topic that has never been properly investigated. In my opinion, this article will promote future investigations on how to feed patients after ERCP and deserves publication.

REFERENCES

1 **Classen M**, Demling L. [Endoscopic sphincterotomy of the papilla of vater and extraction of stones from the choledochal duct (author's transl)]. *Dtsch Med Wochenschr* 1974; **99**: 496-497

2 **Kawai K**, Akasaka Y, Murakami K, Tada M, Koli Y. Endoscopic sphincterotomy of the ampulla of Vater. *Gastrointest Endosc* 1974; **20**: 148-151

3 **Andriulli A**, Loperfido S, Napolitano G, Niro G, Valvano MR, Spirito F, Pilotto A, Forlano R. Incidence rates of post-ERCP complications: a systematic survey of prospective studies. *Am J Gastroenterol* 2007; **102**: 1781-1788

4 **Freeman ML**, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, Moore JP, Fennerty MB, Ryan ME, Shaw MJ, Lande JD, Pheley AM. Complications of endoscopic biliary sphincterotomy. *N Engl J Med* 1996; **335**: 909-918

5 **Freeman ML**, DiSario JA, Nelson DB, Fennerty MB, Lee JG, Bjorkman DJ, Overby CS, Aas J, Ryan ME, Bochna GS, Shaw MJ, Snady HW, Erickson RV, Moore JP, Roel JP. Risk factors for post-ERCP pancreatitis: a prospective, multicenter study. *Gastrointest Endosc* 2001; **54**: 425-434

6 **Masci E**, Toti G, Mariani A, Curioni S, Lomazzi A, Dinelli M, Minoli G, Crosta C, Comin U, Fertitta A, Prada A, Passoni GR, Testoni PA. Complications of diagnostic and therapeutic ERCP: a prospective multicenter study. *Am J Gastroenterol* 2001; **96**: 417-423

7 **Vandervoort J**, Soetikno RM, Tham TC, Wong RC, Ferrari AP Jr, Montes H, Roston AD, Slivka A, Lichtenstein DR, Ruymann FW, Van Dam J, Hughes M, Carr-Locke DL. Risk factors for complications after performance of ERCP. *Gastrointest Endosc* 2002; **56**: 652-656

8 **Barthet M**, Desjeux A, Gasmi M, Bellon P, Hoi MT, Salducci J, Grimaud JC. Early refeeding after endoscopic biliary or pancreatic sphincterotomy: a randomized prospective study. *Endoscopy* 2002; **34**: 546-550

9 **Cheng CL**, Sherman S, Watkins JL, Barnett J, Freeman M, Geenen J, Ryan M, Parker H, Frakes JT, Fogel EL, Silverman WB, Dua KS, Aliperti G, Yakshe P, Uzer M, Jones W, Goff J, Lazzell-Pannell L, Rashdan A, Temkit M, Lehman GA. Risk factors for post-ERCP pancreatitis: a prospective multicenter study. *Am J Gastroenterol* 2006; **101**: 139-147

10 **Williams EJ**, Taylor S, Fairclough P, Hamlyn A, Logan RF, Martin D, Riley SA, Veitch P, Wilkinson ML, Williamson PR,

Lombard M. Risk factors for complication following ERCP; results of a large-scale, prospective multicenter study. *Endoscopy* 2007; **39**: 793-801
11 **Freeman ML**, Guda NM. Prevention of post-ERCP pancreatitis: a comprehensive review. *Gastrointest Endosc* 2004; **59**: 845-864
12 **Cooper ST**, Slivka A. Incidence, risk factors, and prevention of post-ERCP pancreatitis. *Gastroenterol Clin North Am* 2007; **36**: 259-276, vii-viii
13 **Freeman ML**, Nelson DB, Sherman S, Haber GB, Fennerty MB, DiSario JA, Ryan ME, Kortan PP, Dorsher PJ, Shaw MJ, Herman ME, Cunningham JT, Moore JP, Silverman WB, Imperial JC, Mackie RD, Jamidar PA, Yakshe PN, Logan GM, Pheley AM. Same-day discharge after endoscopic biliary sphincterotomy: observations from a prospective multicenter complication study. The Multicenter Endoscopic Sphincterotomy (MESH) Study Group. *Gastrointest Endosc* 1999; **49**: 580-586

S- Editor Zhang HN **L- Editor** Roemmele A **E- Editor** Liu N

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
doi:10.4253/wjge.v2.i12.404

World J Gastrointest Endosc 2010 December 16; 2(12): 404-407
ISSN 1948-5190 (online)

CASE REPORT

Use of endoscopic ultrasound for diagnosis of cholangiocarcinoma in auto-immune hepatitis

Nathaniel S Rial, Jeff T Henderson, Achyut K Bhattacharyya, Abdul Nadir, John T Cunningham

Nathaniel S Rial, Department of Internal Medicine, College of Medicine, Arizona Cancer Center and Mel & Enid College of Public Health, The University of Arizona, Tucson, AZ 85724 United States
Jeff T Henderson, Arizona Digestive Health Pathology Laboratory, AZ 85006 United States
Achyut K Bhattacharyya, Director Surgical Pathology, Professor and Head Department of Pathology, College of Medicine, The University of Arizona, Tucson, AZ 85724 United States
Abdul Nadir, John T Cunningham, Department of Gastroenterology, College of Medicine, The University of Arizona, Tucson, AZ 85724 United States
Author contributions: Rial NS wrote the manuscript; Nadir A and Cunningham JT were responsible for acquisition of tissue samples by ERCP; and Henderson JT and Bhattacharyya AK provided supportive work, materials and technology.
Correspondence to: Nathaniel S Rial, MD, PhD, CPH, Department of Internal Medicine, College of Medicine, The University of Arizona, Tucson, AZ 85724,
United States. nsrial@email.arizona.edu
Telephone: +1-520-6262761 Fax: +1-520-6266020
Received: August 9, 2010 Revised: October 26, 2010
Accepted: November 2, 2010
Published online: December 16, 2010

Key words: Cholangiocarcinoma; Endoscopic ultrasound; Autoimmune hepatits

Peer reviewers: Vasileios Panteris, MD, FEBG, Department of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands; David J Desilets, MD, PhD, Chief, Division of Gastroenterology, Springfield Bldg, Rm S2606, Department of Medicine; Assistant Professor of Clinical Medicine, Tufts University School of Medicine, Springfield Campus, Baystate Medical Center, Springfield, MA 01199, United States; Mohammad Al-Haddad, MD, Assistant Professor of Clinical Medicine, Director, Endoscopic Ultrasound Fellowship Program, Indiana University School of Medicine, 550 N. University Blvd, Suite 4100, Indianapolis, IN 46202, United States

Rial NS, Henderson JT, Bhattacharyya AK, Nadir A, Cunningham JT. Use of endoscopic ultrasound for diagnosis of cholangiocarcinoma in auto-immune hepatitis. *World J Gastrointest Endosc* 2010; 2(12): 404-407 Available from: URL: http://www.wjgnet.com/1948-5190/full/v2/i12/404.htm
DOI: http://dx.doi.org/10.4253/wjge.v2.i12.404

Abstract

In this report, a patient was exposed to an herbal remedy for hypercholesterolemia. She became acutely jaundiced while taking the remedy and presented for medical care. Endoscopic ultrasound was utilized, and found a distal common bile duct mass. Endoscopic retrograde cholangiopancreatography guided bile duct biopsies revealed that the mass was cholangiocarcinoma (CCA). This case highlights a unique association between autoimmune hepatitis and CCA. It also highlights that EUS can be safely used in patients with cirrhosis to spare invasive evaluation such as exploratory laporotomy for diagnosis and staging of cholangiocarcinoma.

INTRODUCTION

Cholangiocarcinoma (CCA) is an adenocarcinoma arising from the epithelial tissue of the intra-hepatic (10%), hepatic hilar (25%) or extrahepatic (65%) bile ducts[1]. Among gastrointestinal (GI) cancers, CCA is the most difficult to detect and diagnose with a 5 year survival of less than 5%[2]. Recently, endoscopic ultrasound (EUS) has emerged as an important modality in the diagnosis of CCA[3]. EUS guided fine needle aspirate (FNA) has a specificity of 100%, and a sensitivity of 43%-86% depending upon the location of the cholangiocarcinoma[4]. The negative predictive value for EUS-FNA for cholangiocarcinoma is reported at 29%[5]. The additional benefit of EUS-FNA is to sample regional lymph nodes to stage the disease particularly in the context of liver transplant evaluation[4].

Herein a unique case of autoimmune hepatitis that presents with jaundice is described. Here we report that in a cirrhotic patient, EUS was extremely helpful in making the diagnosis of CCA through identification of suspected lesions. EUS and subsequent endoscopic retrograde cholangiopancreatography (ERCP) spared the patient an exploratory laprotomy which has inherent risks related to general anesthesia, intubation, abdominal insufflation and biopsy of masses. EUS is especially helpful in noting differences in echogenicity among normal tissue, lymph nodes and neoplasms. This distinction makes EUS a selective tool for subsequent biopsy. In this way, the pretest probability is higher compared to gross visualization during an exploratory laprotomy.

CASE REPORT

A 64-year-old Caucasian female was referred to University Medical Center (UMC) following a diagnosis of autoimmune hepatitis and cirrhosis that was made at an outside hospital. She had used an over-the-counter herbal remedy "CholestOff" for six months. Prior to using CholesOff, her liver function tests (LFTs) were normal, as documented by her primary care physician (PCP). During her six months of CholestOff therapy, LFTs were evaluated showing a total bilirubin of 1.2 g/dL (0.2-1.0), alkaline phosphatase of 272 IU/L (38-126), aspartate aminotransferase (AST) of 310 IU/L (7-40), and alanine aminotransferase (ALT) of 223 IU/L (7-40). CholestOff therapy was ceased and over a period of two months her LFTs showed a downward trend with an alkaline phosphatase of 167 IU/L, an AST of 207 IU/L, and ALT of 145 IU/L. Four months later, her LFTs were repeated again and showed an alkaline phosphatase of 272 IU/L, AST of 496 IU/L, and ALT of 420 IU/L and bilirubin of 0.8 mg/dL.

Two weeks later, the patient presented to an outside hospital with painless jaundice. Her laboratory results showed an alkaline phosphatase of 357 IU/L, AST of 1464 IU/L, ALT of 1090 IU/L, total bilirubin of 4.6 mg/dL, international normalized ratio (INR) greater than 9.4 and albumin of 2.9 g/dL (3.5-5.5). She tested positive for anti-nuclear antibody (ANA) and antimitochondrial antibody (AMA) at 11.4 (0.0-0.9) and 0.2 (< 0.1) respectively. The antismooth muscle antibody was negative. Her gamma globulins were elevated at 2.4 g/dL (0.6-1.6) while her acute hepatitis panel was negative. Further investigation lead to a transjugular liver biopsy. The results indicated portal inflammation with mixed infiltrate comprising of predominantly lymphocytes, readily identifiable plasma cells and cirrhosis. Bile duct injury and bile duct proliferation were also noted.

A Computed tomography (CT) scan was performed and showed mild intrahepatic and extrahepatic ductal dilation with a nodular contour of the liver. Multiple prominent aortocaval, retrocrural and portacaval nodes as well as hypodensity of the distal common bile duct were also noted. An ERCP was performed and showed a subtle, two centimeter common bile duct (CBD) stricture. Cytol-

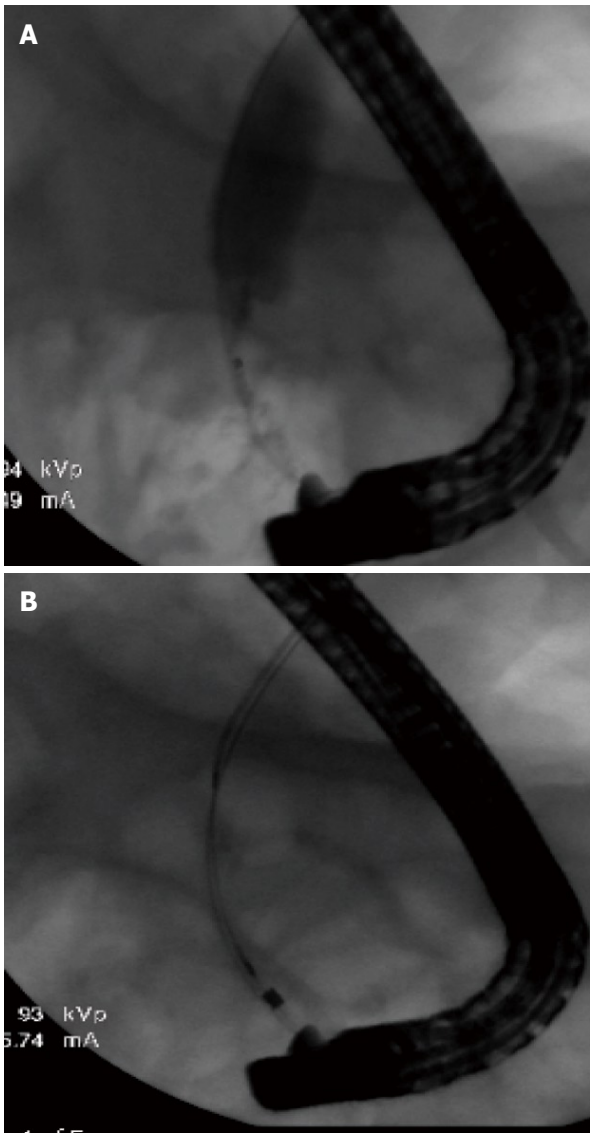


Figure 1 Endoscopic retrograde cholangiopancreatography of mass. A: Endoscopic retrograde cholangiopancreatography (ERCP) of 15 mm hypoechoic mass in the distal common bile duct (CBD); B: ERCP with biliary brushings of the distal CBD mass.

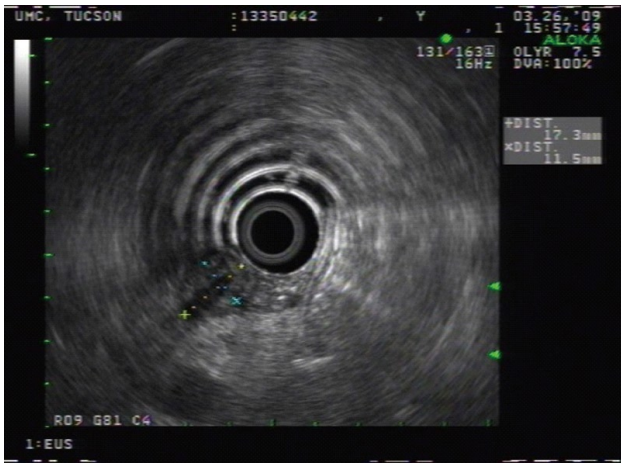


Figure 2 Endoscopic ultrasound of mass. Common bile duct mass was very apparent on endoscopic ultrasound.

ogy sampling was followed by biliary sphincterotomy and placement of a 7 cm/10 Fr. biliary stent. The cytological analysis did not identify malignant cells. The patient was placed on a combination of prednisone and azathioprine therapy with resolution of her jaundice.

Three months later the patient underwent further evaluation at UMC with an EUS examination. At that time a 15 mm hypoechoic mass in the distal CBD (Figure 1A) was identified. Multiple biopsies followed by biliary brushings of the distal CBD mass were accomplished during an ERCP (Figure 1B). The CBD biopsy demonstrated benign acute inflammation and the brushings of the CBD mass were positive for CCA on cytological analysis. While the stricture seen at ERCP was subtle, the CBD mass was very apparent on EUS (Figure 2) and led to a rigorous work up.

DISCUSSION

The case highlights that EUS is a safe and valuable tool in establishing the diagnosis and staging of CCA in patients with cirrhosis. EUS-FNA has been successfully used for the staging of CCA before consideration of liver transplantation[4-8]. The technique has been extensively used to biopsy the bile duct, gallbladder[6,7], hepatic hilum[8], regional lymph nodes[9] pancreatic lesions[10] and hepatic lesions[11] as well as for aspiration of malignant ascites[12]. CT guided FNA has been utilized to biopsy peritoneal and omental masses[13].

This case also delineates the difficulties encountered while managing patients with cholangiocarcinoma and cirrhosis[14,15]. Moreover, the association of autoimmune hepatitis with cholangiocarcinoma is interesting. Only one other case of autoimmune hepatitis has been described in association with CCA and the authors of the report suggested that autoimmune hepatitis is a potential risk factor for the development of CCA[16]. In that particular case, the patient had a diagnosis of autoimmune hepatitis for 30 years and was treated with azathioprine and prednisone and was found to have a small hepatic lesion. That patient underwent a liver transplantation with the presumed diagnosis of hepatocellular carcinoma and developed recurrence of cholangiocarcinoma in distant lymph nodes within a few months of liver transplantation and expired[16].

Our patient underwent EUS that showed a 15-mm hypoechoic CBD mass. EUS guided FNA was not done on this particular patient because of the risk of potential tumor seeding. Instead, the patient underwent a second ERCP with brushing and cytological analysis which documented the correct diagnosis of cholangiocarcinoma, sparing her exploratory laporotomy, general anesthesia, insufflation of the abdomen and tissue biopsy.

This case describes a rare association of CCA with autoimmune hepatitis. The patient developed hepatitis while taking an herbal medication CholestOff which consists of plant sterols/stanols, tribasic calcium phosphate, croscarmellose sodium, calcium carbonate, hydroxypropyl methyl-cellulose, silicon dioxide, magnesium stearate, taranium dioxide, polyethyelene glycol, triethyl citrate, polysorbate 80 and sodium citrate. Only one other case of autoimmune hepatitis has been described in association with CCA and it has been suggested that autoimmune hepatitis is a potential risk factor for the development of CCA[16]. It is possible that the herbal medicine may have caused bile duct toxicity, autoimmune hepatitis and resulted in transformation to malignant cells. However, it appears more plausible that the herbal remedy simply resulted in drug-induced hepatitis with histological findings that mimic autoimmune hepatitis[17]. The case also reinforces the suspicion that the association of autoimmune hepatitis with CCA may be more than mere coincidence.

REFERENCES

1 **Lim JH**. Cholangiocarcinoma: morphologic classification according to growth pattern and imaging findings. *AJR* 2003; **181**: 819-827

2 **Mosconi S**, Beretta GD, Labianca R, Zampino MG, Gatta G, Heinemann V. Cholangiocarcinoma. *Crit Rev Oncol Hematol* 2009; **69**: 259-270

3 **Nguyen K**, Sing JT Jr. Review of endoscopic techniques in the diagnosis and management of cholangiocarcinoma. *World J Gastroenterol* 2008; **14**: 2995-2999

4 **Harewood GC**. Endoscopic tissue diagnosis of cholangiocarcinoma. *Curr Opin Gastroenterol* 2008; **24**: 627-630

5 **Rauws EA**, Kloek JJ, Gouma DJ, Van Gulik TM. Staging of cholangiocarcinoma: the role of endoscopy. *HPB (Oxford)* 2008; **10**: 110-112

6 **Meara RS**, Jhala D, Eloubeidi MA, Eltoum I, Chhieng DC, Crowe DR, Varadarajulu S, Jhala N. Endoscopic ultrasound-guided FNA biopsy of bile duct and gallbladder: analysis of 53 cases. *Cytopathology* 2006; **17**: 42-49

7 **Eloubeidi MA**, Chen VK, Jhala NC, Eltoum IE, Jhala D, Chhieng DC, Syed SA, Vickers SM, Mel Wilcox C. Endoscopic ultrasound-guided fine needle aspiration biopsy of suspected cholangiocarcinoma. *Clin Gastroenterol Hepatol* 2004; **2**: 209-213

8 **Fritscher-Ravens A**, Broering DC, Sriram PV, Topalidis T, Jaeckle S, Thonke F, Soehendra N. EUS-guided fine-needle aspiration cytodiagnosis of hilar cholangiocarcinoma: a case series. *Gastrointest Endosc* 2000; **52**: 534-540

9 **Gleeson FC**, Rajan E, Levy MJ, Clain JE, Topazian MD, Harewood GC, Papachristou GI, Takahashi N, Rosen CB, Gores GJ. EUS-guided FNA of regional lymph nodes in patients with unresectable hilar cholangiocarcinoma. *Gastrointest Endosc* 2008; **67**: 438-443

10 **Hahn M**, Faigel DO. Frequency of mediastinal lymph node metastases in patients undergoing EUS evaluation of pancreaticobiliary masses. *Gastrointest Endosc* 2001; **54**: 331-335

11 **Singh P**, Erickson RA, Mukhopadhyay P, Gopal S, Kiss A, Khan A, Ulf Westblom T. EUS for detection of the hepatocellular carcinoma: results of a prospective study. *Gastrointest Endosc* 2007; **66**: 265-273

12 **Kaushik N**, Khalid A, Brody D, McGrath K. EUS-guided paracentesis for the diagnosis of malignant ascites. *Gastrointest Endosc* 2006; **64**: 908-913

13 **Souza FF**, Mortelé KJ, Cibas ES, Erturk SM, Silverman SG. Predictive value of percutaneous imaging-guided biopsy of peritoneal and omental masses: results in 111 patients. *AJR* 2009; **192**: 131-136

14 **Maggs J**, Cullen S. Management of autoimmune liver disease. *Minerva Gastroenterol Dietol* 2009; **55**: 173-206

15 **Saich R**, Chapman R. Primary sclerosing cholangitis, autoimmune hepatitis and overlap syndromes in inflammatory bowel disease. *World J Gastroenterol* 2008; **14**: 331-337
16 **Elfaki DH**, Gossard AA, Lindor KD. Cholangiocarcinoma: expanding the spectrum of risk factors. *J Gastrointest Cancer* 2008; **39**: 114-117
17 **Krawitt EL**. Clinical features and management of autoimmune hepatitis. *World J Gastroenterol* 2008; **14**: 3301-3305

S- Editor Zhang HN **L- Editor** Roemmele A **E- Editor** Liu N

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
doi:10.4253/wjge.v2.i12.408

World J Gastrointest Endosc 2010 December 16; 2(12): 408-412
ISSN 1948-5190 (online)

CASE REPORT

Successful type-oriented endoscopic resection for gastric carcinoid tumors: A case report

Shouji Shimoyama, Mitsuhiro Fujishiro, Yutaka Takazawa

Shouji Shimoyama, Gastrointestinal Unit, Settlement Clinic, Tokyo 120-0003, Japan
Mitsuhiro Fujishiro, Department of Internal Medicine, Tokyo University, Tokyo 113-8655, Japan
Yutaka Takazawa, Department of Pathology, The University of Tokyo Hospital, Tokyo 113-8655, Japan
Author contributions: Shimoyama S managed the patient and prepared the manuscript; Fujishiro M treated the patient; and Takazawa Y contributed with the pathology.
Correspondence to: Shouji Shimoyama, MD, Gastrointestinal Unit, Settlement Clinic., 4-20-7, Towa, Adachi-ku, Tokyo 120-0003, Japan. shimoyama@apost.plala.or.jp
Telephone: +81-3-36057747 Fax: +81-3-36050244
Received: August 14, 2010 Revised: October 28, 2010
Accepted: November 4, 2010
Published online: December 16, 2010

Abstract

The standard treatment in Japan for gastric carcinoid has been gastrectomy with lymphadenectomy. This report describes the possibility of endoscopic treatment as an appropriate option for gastric carcinoid fulfilling certain conditions. A 46 year old woman underwent endoscopic mucosal resection for two 3 mm gastric carcinoids. The patient had hypergastrinemia with pernicious anemia and type A chronic atrophic gastritis, suggesting that the tumors were type Ⅰ in Rindi's classification. Both tumors were located in the mucosal layer with no cellular polymorphism and were chromogranin A positive. Neither tumor recurrence in the stomach nor distant metastases have been documented during the 5 years of follow-up. Although many type Ⅰ gastric carcinoids may be clinically indolent, reports on successful endoscopic treatment for this carcinoid have been scanty in the literature in Japan, presumably because of the hitherto surgical treatment stance for the disease. This report discusses how the size, number, depth and histological grading of the type Ⅰ gastric carcinoid could allow the correct identification of a benign or malignant propensity of an individual tumor and how endoscopic resection could be a treatment of choice when these factors render it feasible. This stance could also obviate unnecessary surgical resection for more benign tumors.

Key words:: Endoscopic resection; Gastric carcinoid; Hypergastrinemia; Pernicious anemia; Type A chronic atrophic gastritis.

Peer reviewers: Kinichi Hotta, MD, Department of Gastroenterology, Saku Central Hospital, 197 Usuda, Saku, Nagano 384-0301, Japan; Ichiro Oda, MD, Endoscopy Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

Shimoyama S, Fujishiro M, Takazawa Y. Successful typeoriented endoscopic resection for gastric carcinoid tumors: A case report. *World J Gastrointest Endosc* 2010; 2(12): 408-412 Available from: URL: http://www.wjgnet.com/1948-5190/full/v2/i12/408.htm DOI: http://dx.doi.org/10.4253/wjge.v2.i12.408

INTRODUCTION

Gastric carcinoids (GCDs) were previously thought to be extremely rare in the West, constituting only 2.6% of all gastrointestinal carcinoids in the 1950s[1]. Their incidence, however, has chronologically increased to 8.7% in the 1990s[2]. Interestingly, GCDs, the second most common (21%-27%) gastrointestinal carcinoids in Japan[3], have also seen an increase in cases over the past 5 decades[4]. These trends may be due to an actual increase but the more likely reason is improvements in diagnostic technology and increased awareness. Despite the steady rise in the incidence of GCDs in the gastrointestinal tract in both regions, GCDs have been considered to be a curiosity accounting for less than 1%[5] of all gastric tumors and such rarity has made it difficult to understand precisely

the biological nature of them and to establish the optimal treatment options for the disease.

GCDs are an enigmatic malignancy that, while slow in growth compared with adenocarcinoma, can sometimes behave aggressively. This has led to a debate concerning the optimal treatment for GCDs. In Japan, radical gastrectomy has been recommended as a general treatment for them due to the concern over the substantial metastatic rates (4.6%-30%) even among small and/or submucosal GCDs[3,4,6,7]. On the other hand, Western researchers have recently proposed a spectrum of treatment options for GCDs[8] ranging from less invasive endoscopic polypectomy to more aggressive surgery on the basis of the background gastric pathological characteristics with or without hypergastrinemia as a pathogenetic trait[9-11]. Here we report a case of GCDs with hypergastrinemia successfully treated by endoscopic mucosal resection (EMR) followed by no evidence of recurrence for 5 years. Because of the hitherto aggressive treatment stance in Japan, cases of successful endoscopic treatment for GCDs have been scarce in the literature. This report raises the possibility that pathobiological analyses of individual GCDs could select patients to benefit from less invasive treatment, so realizing type-oriented patient management.

CASE REPORT

A 46 year old woman underwent upper gastrointestinal endoscopy in 2003 due to upper abdominal discomfort. Endoscopic examination revealed two tiny elevated lesions 3 mm in diameter located on the anterior and posterior walls of the upper third of the stomach (Figure 1). Atrophy was more marked in the body-fundus than in the antrum. Biopsy specimens from both lesions showed microlobular-trabecular cell clusters with no cellular polymorphism. No extragastric hormonal syndromes such as flushes or diarrhea were identified. Patient interview revealed a previous diagnosis of pernicious anemia at the age of 30 and investigation showed combined iron (56 mg/dL) and vitamin B_{12} (230 pg/mL) deficiency anemia with low levels of hemoglobin (10.4 g/dL) and mean corpuscular volume (89.6 fL). The positivity of both anti-parietal cell and anti-intrinsic factor antibodies, as well as corpus predominant atrophic gastritis and elevated serum gastrin level (3827 pg/mL), suggested that the elevated lesions were type I [9-11] carcinoid tumor associated with pernicious anemia and type A chronic atrophic gastritis (CAG/A)[12]. Endoscopic ultrasonography failed to evaluate the tumor depth definitively. There was no evidence of lymph node or liver metastases. She had been diagnosed with epilepsy 30 years prior to this visit and sodium valproate had been prescribed since then. Continuous prescription of proton pump inhibitors was not confirmed. After fully informed consent, she underwent cap-assisted EMR, an "inject, suck and cut" technique, for both lesions in July 2004. The postoperative course was uneventful.

Both resected specimens showed a histological architecture of microlobular-trabecular cell clusters in the mucosal layer with marked fundic gland atrophy (Figure 2). Endocrine cell micronests were observed in the mucosal layer and in the lamina propria mucosa. Neither cellular polymorphism nor mitoses were observed. Neither lymphatic nor vascular invasion were documented. Both tumors as well as endocrine cell micronests were chromogranin A positive (Figure 2, inset). All resection margins were negative for carcinoid cells.

Under the postoperative annual endoscopies, any lesions of concern for the endoscopist were biopsied and there has been no evidence of tumor recurrence in

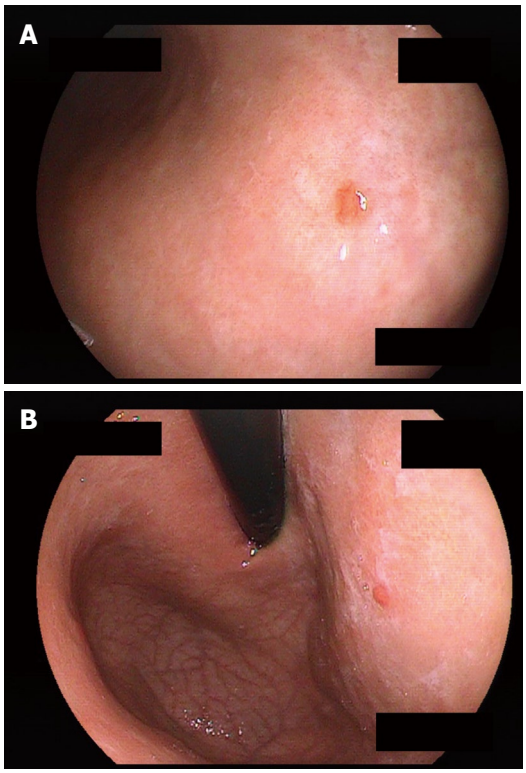


Figure 1 Tiny elevated lesions, 3 mm in diameter detected on the posterior (A) and the anterior (B) walls of the upper third of the stomach.

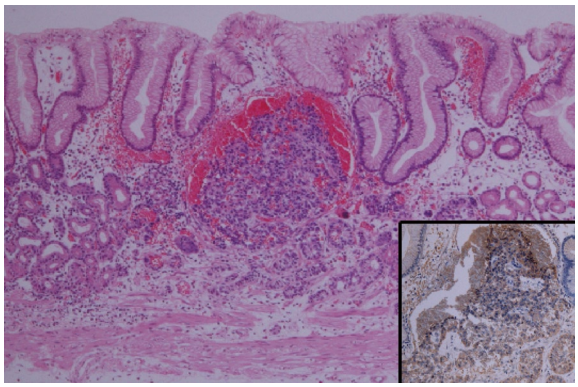


Figure 2 Histological findings of the tumor located on the posterior wall of the stomach (Hematoxylin-eosin stain, × 40). The tumor exhibits microlobular-trabecular growth patterns with chromogranin A positive (inset, × 100). No cellular polymorphism is observed. The other tumor showed the same findings.

Table 1 Histological tumor grading proposed by Rindi *et al*[14]

Grade 1a	Tumors characterized by small and microlobular-trabecular aggregates formed by regularly distributed, often aligned cells with regular monomorphic nuclei, usually inapparent nucleoli, rather abundant fairly eosinophilic cytoplasm and almost absent mitoses.
Grade 1b	Tumors characterized by significant areas with solid structure, absence of cell alignment, round to spindle cell shape, irregular and moderately polymorphic nuclei of larger size, often with evident nucleoli and rather few, morphologically typical mitoses.
Grade 2	Tumors showed prevalence of solid cellular aggregates and large trabeculae, crowding and irregular distribution of round to spindle and polyhedric tumor cells, fairly large vesicular nuclei with prominent eosinophilic nucleoli or smaller, hyperchromatic nuclei with irregular chromatin clumps and small nucleoli, considerable mitotic activity, sometimes with atypical mitotic figures and scant necrosis.
Grade 3	Tumors showed severe histological atypia with solid to diffuse structure and frequent central necrosis. They were composed of tightly packed, small to mid-sized tumor cells showing large, irregular, polymorphic and hyperchromatic nuclei, scant cytoplasm and frequent, often atypical, mitosis.

the stomach. Neither liver nor lymph node metastases were detected by the most recent abdominal computed tomography and abdominal ultrasonography. The serum gastrin level remained high (2500 pg/mL) at 4 years after resection.

DISCUSSION

The optimal treatment options for GCDs have not been precisely defined. Earlier Japanese literature reviews or case collections elucidated that the risk of metastasis depended on the tumor size and depth. Only minute (< 0.5 cm in diameter) GCDs showed no metastases but then began to spread outside the stomach in correlation with tumor size[7], the incidences being 6.7% for < 1 cm, 27.7% for < 2 cm and 45.8% for < 3 cm in diameter[3]. In addition, metastatic rates of GCDs situated in mucosal, submucosal and proper muscle layers were 7.5%, 13.2%-15.5% and 44.8% respectively[4,6]. Even small submucosal GCDs (< 1.0 cm) were found to metastasize at a substantial rate (7.9%)[6] equal to or even higher than those of submucosal gastric cancer[13], suggesting that GCDs often metastasize even when they are small (< 1 cm) or confined to the submucosal layer. Therefore, in Japan, total or subtotal gastrectomy with lymphadenectomy has been recommended and indeed performed for GCDs, irrespective of size, depth or number.

On the other hand, an Italian research group[9-11] has proposed a new classification for GCDs by dividing them into three types: type Ⅰ is those arising in CAG/A with hypergastrinemia; type Ⅱ occurs in patients with hypergastrinemia due to the Zollinger-Ellison syndrome in association with multiple endocrine neoplasia type Ⅰ; and type Ⅲ is sporadic GCDs not associated with any specific pathogenetic background. This classification is of great worth because of its ability to predict the biological aggressiveness of GCDs. Types Ⅰ and Ⅱ GCDs were low grade tumor diseases with excellent prognosis although a relatively higher degree of aggressiveness was observed for type Ⅱ whereas those independent of gastrin promotion (type Ⅲ) were life-threatening neoplasms[9-11]. Metastatic rates were 0%-7.8% in type Ⅰ, 18.1%-30.0% in type Ⅱ and 16.7%-75.0% in type Ⅲ tumors[9-11,14-16]. Type Ⅰ GCDs were mainly restricted to the mucosa or submucosal layer and were usually smaller in size at presentation[9-11,16] whereas increasing type numbers (from type Ⅰ to Ⅲ) correlated with deeper tumor infiltration and larger tumor size. Even a conservative approach for type Ⅰ GCDs was proposed by observations of spontaneous regression[17] or the absence of clinical problems[18] for varying periods of follow-up. These observations suggest that type Ⅰ GCDs will not become clinically overt and that endoscopic treatment is considered safe.

Against this background, Gilligan *et al*[8] advocated a treatment algorithm for GCDs, including parameters of the above-mentioned subtypes as well as sizes and numbers of the tumors. In types Ⅰ and Ⅱ GCDs, initial treatment is an endoscopic polypectomy for less numerous (< 3-5 lesions) and smaller (< 1 cm) tumors and antrectomy or local resection for more numerous (> 3-5 lesions) and larger (> 1 cm) ones. Both treatments should be followed by endoscopic surveillance biannually and any recurrence should be treated by local excision, antrectomy or wider gastrectomy. On the other hand, *en bloc* surgical resection with lymphadenectomy is recommended for type Ⅲ tumors. Subsequently, the rationale for this type-oriented treatment has been confirmed by prospective[16] and retrospective[19] studies. In addition, guidelines for gastrointestinal endocrine tumors from the United Kingdom have stated that surveillance only is considered appropriate for many type Ⅰ GCDs[20].

The Japanese aggressive treatment stance thus far has been based on cases of small but node-positive GCDs. Taking the tripartite classification into account, however, these tumors presumably comprise of pathobiologically heterogeneous types of neoplasms because they were not stratified by subtype in some reports[21] or were at least non-type Ⅰ in others[22,23]. Nevertheless, it is also a fact that type Ⅰ GCDs may occasionally countermand the anticipated biological behavior[14,16,24]. In this regard, histological grading (Table 1) and tumor depth[14,16,24] have been demonstrated to be characteristics by which individual tumor aggressiveness is predictable with a higher accuracy than would be by simple tripartite classification. Therefore, integration of these factors into the Gilligan's decision tree could allow more correct identification of benign or malignant propensities in individual tumors and endoscopic treatments such as EMR and endoscopic submucosal dissection (ESD) could be a treatment of choice when size, number, depth and histological grading of a tumor render them feasible. These stances

Table 2 Clinicopathological characteristics of gastric carcinoid cases with hypergastrinemia successfully resected endoscopically or were followed-up only, published in Japan after the year (1995) of Gilligan's proposal

Authors	Age	Male/Female	Gastrin (pg/mL)	Anti-PCA/ anti-IFA	Number of tumor	Size (mm)	Treatment	Tumor depth	Follow-up length (mo)
Kawaguchi[26]	33-69[1]	10/3	74-2100	NA/NA	1 or multiple	NA	EMR	NA	NA
Hosokawa[29]	46-69[1]	3/5	442-3800	(+) in 7/NA	multiple	1-15	follow-up only	NA	18-130
Higashino[30]	34-78[1]	3/3	195-1800	NA/NA	1 or 2	0.73[2]	EMR	m, sm	4-78
Ichikawa[31]	35-66[1]	3/1	319-1122	(+) in 3/(+) in 1	1	3-8	EMR	m, sm	6-56
Shimazu[32]	65	0/1	3400	(+)/NA	9	5	EMR or hot biopsy	m	48
Yoshikane[33]	43	1/0	600	(+)/(-)	1	9	EMR	sm	9
Hori[34]	51	1/0	> 800	(+)/NA	1	7	EMR	m	144
Anjiki[35]	40	0/1	5197	(+)/(-)	3	7	EMR	sm	22
Yamamoto[36]	40's	1/0	6250	(+)/(+)	1	7	EMR	sm	12

[1]Thirteen[26], eight[29], six[30] and four[31] collected cases. One case in reference [31] is omitted because of the subsequent surgery; [2]Mean value; PCA: parietal cell antibody; IFA: intrinsic factor antibody; EMR: endoscopic mucosal resection; ESD: endoscopic submucosal dissection; NA: not available; m: mucosal layer; sm: submucosal layer.

are in accordance with those published very recently[25] and can help avoid any unnecessary gastrectomy for type I GCDs with the more benign phenotype[26], something which undoubtedly impairs personal well-being without any advantage.

The selection of endoscopic treatment modalities depends on the size and degree of the submucosal involvement of the target lesion. In general, EMR is applied for smaller (e.g. < 1 cm) lesions without submucosal invasion or fibrosis[27] whereas ESD, an "inject, incise the mucosa and dissect the submucosa" technique, is applied for lesions larger in size and/or with some submucosal involvement[28]. The goal of both techniques is an *en bloc* resection realizing a precise histological diagnosis. ESD, by the nature of its technique, could achieve more increased *en bloc* and histologically complete resection rates compared with EMR but is associated with longer average operation times and a higher incidence of intraoperative bleeding and perforation[28]. In this case, we consider that intramucosal and small (3 mm each) lesions render EMR feasible.

Even after Gilligan's proposal and in the era of technically advanced endoscopic resection, reports in Japan on GCDs associated with hypergastrinemia with a successful resultant of endoscopic treatment or follow-up only have remained rare in the literature, probably due to the less common consideration of the GCD classification (Table 2)[26,29-36]. In the present case, the Gilligan's recommendation and the intramucosal localization with a his tologically less aggressive grade of tumor justify the endoscopic resection and repeated follow up endoscopies as a treatment strategy. Despite conditions of persistent hypergastrinemia, a relatively longer tumor free period of 5 years as compared with those (between 9 mo and 12 years) in the reported cases in the literature confirms the rationale of our strategy.

Pernicious anemia or CAG/A predispose the development of both gastric cancer and GCDs[37,38] as separated[25] or mixed[39,40] tumors, underscoring the importance of continuous repeated endoscopic monitoring for type I GCDs even after successful endoscopic resection. One of the presumed underlying mechanisms is a trophic effect and tumorigenic potential of inappropriately sustained hypergastrinemia. Awareness of these facts is important at each step of the sequence of patient management, i.e. at the time of diagnosis, treatment and each follow-up examination.

REFERENCES

1 **Godwin JD 2nd**. Carcinoid tumors. An analysis of 2,837 cases. *Cancer* 1975; **36**: 560-569
2 **Modlin IM**, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer* 2003; **97**: 934-959
3 **Soga J**. Carcinoid tumors: A statistical anaysis of a Japanese series of 3126 reported and 1180 autopsy cases. *Acta Medica et Biologica* 1994; **42**: 87-102
4 **Soga J**. Gastric carcinoids: a statistical evaluation of 1,094 cases collected from the literature. *Surg Today* 1997; **27**: 892-901
5 **Modlin IM**, Lye KD, Kidd M. Carcinoid tumors of the stomach. *Surg Oncol* 2003; **12**: 153-172
6 **Soga J**. Early-stage carcinoids of the gastrointestinal tract: an analysis of 1914 reported cases. *Cancer* 2005; **103**: 1587-1895
7 **Morise K**, Kusugami K, Hayakawa M, Nakata S, Inagaki T, Hayashi N, Kato Y. Minute carcinoid tumor of the stomach: report of two cases and review of the Japanese literature. *Gastroenterol Jpn* 1985; **20**: 596-603
8 **Gilligan CJ**, Lawton GP, Tang LH, West AB, Modlin IM. Gastric carcinoid tumors: the biology and therapy of an enigmatic and controversial lesion. *Am J Gastroenterol* 1995; **90**: 338-352
9 **Rindi G**, Luinetti O, Cornaggia M, Capella C, Solcia E. Three subtypes of gastric argyrophil carcinoid and the gastric neuroendocrine carcinoma: a clinicopathologic study. *Gastroenterology* 1993; **104**: 994-1006
10 **Rindi G**. Clinicopathologic aspects of gastric neuroendocrine tumors. *Am J Surg Pathol* 1995; **19** Suppl 1: S20-S29
11 **Rindi G**, Bordi C, Rappel S, La Rosa S, Stolte M, Solcia E. Gastric carcinoids and neuroendocrine carcinomas: pathogenesis, pathology, and behavior. *World J Surg* 1996; **20**: 168-172
12 **Strickland RG**, Mackay IR. A reappraisal of the nature and significance of chronic atrophic gastritis. *Am J Dig Dis* 1973; **18**: 426-440
13 **Shimoyama S**, Yasuda H, Mafune K, Kaminishi M. Indications of a minimized scope of lymphadenectomy for submucosal gastric cancer. *Ann Surg Oncol* 2002; **9**: 625-631
14 **Rindi G**, Azzoni C, La Rosa S, Klersy C, Paolotti D, Rappel

S, Stolte M, Capella C, Bordi C, Solcia E. ECL cell tumor and poorly differentiated endocrine carcinoma of the stomach: prognostic evaluation by pathological analysis. *Gastroenterology* 1999; **116**: 532-542
15 **Rappel S**, Altendorf-Hofmann A, Stolte M. Prognosis of gastric carcinoid tumours. *Digestion* 1995; **56**: 455-462
16 **Borch K**, Ahrén B, Ahlman H, Falkmer S, Granérus G, Grimelius L. Gastric carcinoids: biologic behavior and prognosis after differentiated treatment in relation to type. *Ann Surg* 2005; **242**: 64-73
17 **Harvey RF**, Bradshaw MJ, Davidson CM, Wilkinson SP, Davies PS. Multifocal gastric carcinoid tumours, achlorhydria, and hypergastrinaemia. *Lancet* 1985; **1**: 951-954
18 **Ravizza D**, Fiori G, Trovato C, Fazio N, Bonomo G, Luca F, Bodei L, Pelosi G, Tamayo D, Crosta C. Long-term endoscopic and clinical follow-up of untreated type 1 gastric neuroendocrine tumours. *Dig Liver Dis* 2007; **39**: 537-543
19 **Dakin GF**, Warner RR, Pomp A, Salky B, Inabnet WB. Presentation, treatment, and outcome of type 1 gastric carcinoid tumors. *J Surg Oncol* 2006; **93**: 368-372
20 **Ramage JK**, Davies AH, Ardill J, Bax N, Caplin M, Grossman A, Hawkins R, McNicol AM, Reed N, Sutton R, Thakker R, Aylwin S, Breen D, Britton K, Buchanan K, Corrie P, Gillams A, Lewington V, McCance D, Meeran K, Watkinson A. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours. *Gut* 2005; **54** Suppl 4: iv1-iv16
21 **Ura K**, Kira M, Matsuo S, Kuroda Y, Mizumachi N, Tsunoda T, Yoshino R, Harada N, Tsuchiya R. Three cases of gastric carcinoid (in Japanese with English abstract). *Nihon Rinsho Gekagakkai Zasshi* 1986; **47**: 1600-1604
22 **Shinohara T**, Ohyama S, Nagano H, Amaoka N, Ohta K, Matsubara T, Yamaguchi T, Yanagisawa A, Kato Y, Muto T. Minute gastric carcinoid tumor with regional lymph node metastasis. *Gastric Cancer* 2003; **6**: 262-266
23 **Suganuma K**, Otani Y, Furukawa T, Saikawa Y, Yoshida M, Kubota T, Kumai K, Kameyama K, Mukai M, Kitajima M. Gastric carcinoid tumors with aggressive lymphovascular invasion and lymph node metastasis. *Gastric Cancer* 2003; **6**: 255-261
24 **Iwashita A**, Takayaka S, Oishi K, Iwai K, Yao T, Shimoda T, Haraoka S, Kurihara K, Hashimoto N, Toyoshima S, Ooshiro Y, Hashimoto H, Hattanda Y, Takeshita S, Yamamoto I, Fukuda T. A clinicopathological study on gastric carcinoid tumors – With special referenceoto differenceof nodal metastasis between tumors with type A gastritis and those with non-type A gastritis (in Japanese with English abstract). *I to Cho (Stomach and Intestine)* 2000; **35**: 1365-1368
25 **Gladdy RA**, Strong VE, Coit D, Allen PJ, Gerdes H, Shia J, Klimstra DS, Brennan MF, Tang LH. Defining surgical indications for type I gastric carcinoid tumor. *Ann Surg Oncol* 2009; **16**: 3154-3160
26 **Kawaguchi M**, Takagi Y, Tokita H, Suzuki K, Koyanagi Y, Miharu T, Oono H, Misaka R, Moriyasu F, Saito T. Treatment of gastric carcinoid (in Japanese with English abstract). *I to Cho (Stomach and Intestine)* 2000; **35**: 1405-1415
27 **Watanabe K**, Ogata S, Kawazoe S, Watanabe K, Koyama T, Kajiwara T, Shimoda Y, Takase Y, Irie K, Mizuguchi M, Tsunada S, Iwakiri R, Fujimoto K. Clinical outcomes of EMR for gastric tumors: historical pilot evaluation between endoscopic submucosal dissection and conventional mucosal resection. *Gastrointest Endosc* 2006; **63**: 776-782
28 **Fujishiro M**. Perspective on the practical indications of endoscopic submucosal dissection of gastrointestinal neoplasms. *World J Gastroenterol* 2008; **14**: 4289-4295
29 **Hosokawa O**, Kaizaki Y, Hattori M, Douden K, Hayashi H, Morishita M, Ohta K. Long-term follow up of patients with multiple gastric carcinoids associated with type A gastritis. *Gastric Cancer* 2005; **8**: 42-46
30 **Higashino K**, Iishi H, Narahara H, Uedo N, Yano H, Ishiguro S, Tatsuta M. Endoscopic resection with a two-channel videoendoscope for gastric carcinoid tumors. *Hepatogastroenterology* 2004; **51**: 269-272
31 **Ichikawa J**, Tanabe S, Koizumi W, Kida Y, Imaizumi H, Kida M, Saigenji K, Mitomi H. Endoscopic mucosal resection in the management of gastric carcinoid tumors. *Endoscopy* 2003; **35**: 203-206
32 **Shimazu T**, Yao K, Matsui T, Sato S, Matsumura M, Furukawa K, Yao T, Ooshige K, Iwashita A. Multiple gastric carcinoid tumors associated with type A gastritis, report of a case treated by endoscopic resection (in Japanese with English abstract). *I to Cho (Stomach and Intestine)* 2000; **35**: 1435-1441
33 **Yoshikane H**, Hidano H, Sakakibara A, Ayakawa T, Taki N, Mizuno K, Uchida H, Arakawa D, Takio Y. A case of gastric carcinoid tumor associated wit type A atrophic gastritis treated with endoscopic aspiration submucosectomy (in Japanese with English abstract). *Gastroenterol Endosc* 2000; **42**: 2256-2262
34 **Hori K**, Fukui H, Imura J, Kojima T, Fujita M, Kawamata H, Chiba T, Fujimori T. Benign gastric carcinoid tumor with hypergastrinemia followed up for 12 years. *Gastric Cancer* 2000; **3**: 161-164
35 **Anjiki H**, Ishii T, Osaki Y, Abe K, Tsutsumi H, Kawakami T, Saito M, Yamamoto T, Sanaka M, Kuyama Y, Takikawa H, Imamura T. A case of gastric carcinoid tumor with type A gastritis resected by endoscopy (in Japanese with English abstract). *Gastroenterol Endosc* 2006; **48**: 2277-2282
36 **Yamamoto S**, Uedo N, Ishii H, Yamamoto S, Takeuchi Y, Higashino K, Ishihara R, Ishiguro S, Tatsuta M. A case of gastric carcinoid with type A gastritis (in Japanese with English abstract). *Nippon Shokakibyo Gakkai Zasshi (JJSG)*. 2008; **105**: 529-534
37 **Borch K**, Renvall H, Liedberg G. Gastric endocrine cell hyperplasia and carcinoid tumors in pernicious anemia. *Gastroenterology* 1985; **88**: 638-648
38 **Lahner E**, Caruana P, D'Ambra G, Ferraro G, Di Giulio E, Delle Fave G, Bordi C, Annibale B. First endoscopic-histologic follow-up in patients with body-predominant atrophic gastritis: when should it be done? *Gastrointest Endosc* 2001; **53**: 443-448
39 **Seki K**, Obata H, Amakata Y, Iwamoto S. A case report of gastric carcinoid concurrent with gastric early cancer in the same lesion (in Japanese with English abstract). *Gastroenterol Endosc* 2009; **51**: 2877-2885
40 **Adhikari D**, Conte C, Eskreis D, Urmacher C, Ellen K. Combined adenocarcinoma and carcinoid tumor in atrophic gastritis. *Ann Clin Lab Sci* 2002; **32**: 422-427

S- Editor Zhang HN **L- Editor** Roemmele A **E- Editor** Liu N

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
doi:10.4253/wjge.v2.i12.413

World J Gastrointest Endosc 2010 December 16; 2(12): 413-416
ISSN 1948-5190 (online)

Idiopathic non-hypertrophic pyloric stenosis in an infant successfully treated *via* endoscopic approach

Wikrom Karnsakul, Mary L Cannon, Stacey Gillespie, Richard Vaughan

Wikrom Karnsakul, Division of Pediatric Gastroenterology and Nutrition, Johns Hopkins University School of Medicine, Baltimore, MD 21287, United State
Wikrom Karnsakul, Mary L Cannon, Stacey Gillespie, Richard Vaughan, Department of Pediatrics, West Virginia University School of Medicine Morgantown, WV 26506, United States
Author contributions: Karnsakul W, Cannon ML, Gillespie S and Vaughan R are clinical providers who contributed to the care of this child during hospitalization, proofread and approved this manuscript.
Correspondence to: Wikrom Karnsakul, MD, Assistant Professor, Division of Pediatric Gastroenterology and Nutrition, Johns Hopkins University School of Medicine, Brady 320, 600 North Wolfe Street, Baltimore, MD 21287, United States. wkarnsa1@jhmi.edu
Telephone: +1-410-9558769 Fax: +1-410-9551464
Received: July 14, 2010 Revised: September 27, 2010
Accepted: October 4, 2010
Published online: December 16, 2010

Abstract

Non-peptic, non-hypertrophic pyloric stenosis has rarely been reported in pediatric literature. Endoscopic pyloric balloon dilation has been shown to be a safe procedure in treating gastric outlet obstruction in older children and adults. Partial gastric outlet obstruction (GOO) was diagnosed in an infant by history and confirmed by an upper gastrointestinal series (UGI). Abdominal ultrasonography and computed tomography scan excluded idiopathic hypertrophic pyloric stenosis, abdominal tumors, gastrointestinal and hepato-biliary-pancreatic anomalies. Endoscopic findings showed a pinhole-sized pylorus and did not indicate peptic ulcer disease, Helicobacter pylori infection, antral web, or evidence of allergic and inflammatory bowel diseases. Three sessions of a step-wise endoscopic pyloric balloon dilation were conducted under general anesthesia and a fluoroscopy at two week intervals using catheter balloons (Boston Scientific Microvasive®, MA, USA) of increasing diameters. Repeat UGI after the first session revealed normal gastrointestinal transit and no intestinal obstruction. The patient tolerated solid food without any gastrointestinal symptoms since the first session. The endoscope was able to be passed through the pylorus after the last session. Although the etiology of GOO in this infant is unclear (proposed mechanisms are herein discussed), endoscopic pyloric balloon dilation was a safe procedure for treating this young infant with non-peptic, non-hypertrophic pyloric stenosis and should be considered as an initial approach before pyloroplasty in such presentations.

Key words: Non-hypertrophic pyloric stenosis; Endoscopic pyloric balloon dilation; Gastric outlet obstruction

Peer reviewers: Kenneth Kak Yuen Wong, MD, PhD, Assistant Professor, Department of Surgery, The University of Hong Kong, Queen Mary Hospital, Pokfulam Road, Hong Kong, China; Takayuki Yamamoto, MD, PhD, Inflammatory Bowel Disease Center, Yokkaichi Social Insurance Hospital, 10-8, Hazuyamacho, Yokkaichi 510-0016, Japan

Karnsakul W, Cannon ML, Gillespie S, Vaughan R. Idiopathic non-hypertrophic pyloric stenosis in an infant successfully treated *via* endoscopic approach. *World J Gastrointest Endosc* 2010; 2(12): 413-416 Available from: URL: http://www.wjgnet.com/1948-5190/full/v2/i12/413.htm DOI: http://dx.doi.org/10.4253/wjge.v2.i12.413

TO THE EDITOR

We recently read a very good review on Endoscopic balloon dilation for benign gastric outlet obstruction in adults by Kochhar R *et al*[1]. We would like to share our pediatric perspective how endoscopic balloon dilation was safely used to treat an infant with gastric outlet obstruction (GOO) of unknown cause, using guidelines similar to those suggested in that article.

Idiopathic hypertrophic pyloric stenosis (IHPS) is

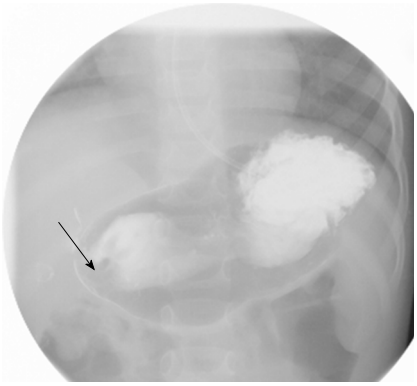


Figure 1 Filling defect of swollen pylorus (arrow).

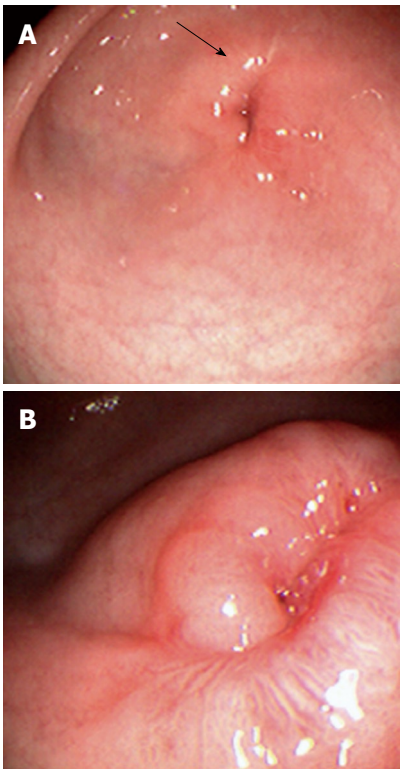


Figure 2 Upper gastrointestinal endoscopic image. A: Narrow pyloric opening with edema around pyloric canal (arrow); B: Close-up view of pin-hole pyloric stenosis.

probably the most common cause of GOO in children which presents after birth, generally in the first 3 mo of life. Endoscopic pyloric balloon dilation (EPBD) has been shown to be a safe and effective procedure in treating gastric outlet obstruction in older children and adults[2-5]. An eighteen month old Caucasian boy had fever at the beginning of his illness, followed by persistent vomiting for a total of 3 wk. His physical examination revealed a weight of 9.21 kilograms (below 3rd percentile), height of 83.5 cms (on 75th percentile), normal vital signs, pallor, no acute distress, no palpable mass, no hepatosplenomegaly, and a non-tender, non-distended abdomen. A review of past medical history demonstrated a previously healthy infant with a viral-like episode following illness in all family members a few weeks prior to admission. The patient breast fed until the age of 12 mo when solid food was introduced and subsequently advanced. There was no history of food or drug allergy, gastrointestinal (GI) bleeding, other gastrointestinal symptoms, consumption of raw meat and fish or any history of foreign body or caustic ingestion. Intravenous fluid was given to correct a mild degree of dehydration.

On admission his laboratory analyses showed mild hypochloremic metabolic alkalosis and moderate iron deficiency anemia without eosinophilia. Stool occult blood had been negative on several occasions. Gastric distension was noted on plain abdominal series. A pyloric ultrasound revealed redundancy of the antral walls and duodenum. Pyloric channel length was 14 mm. But its width was unmeasurable due to an inability to identify the pylorus in the transverse plane. GOO was observed on an upper GI series (Figure 1). Computed tomography (CT) images of the abdomen following the administration of intravenous and oral contrast media showed no evidence of an abnormal mass in the stomach or duodenum or any external mass compressing the pylorus. An upper endoscopy (EGD) demonstrated mild erythema of the distal esophagus, markedly enlarged, thickened, and asymmetric folds with a pin-hole opening that did not allow the passage of a Pentax-EG-1840 endoscope. A normal granulocytic oxidative burst was reported from dihydrorhodamine (DHR) flow cytometry assays which was inconsistent with the diagnosis of CGD. The patient received total parenteral nutrition, 15 mg daily of oral Prevacid®, iron therapy, and a 5 d course of 2 grams per kg per day of methylprednisolone (to reduce pyloric edema). After 3 wk of Prevacid® a repeat EGD showed findings of thickened pylorus with pin-hole opening similar to the initial results (Figure 2). The pathologic report showed 1-2 eosinophils per high power field and no evidence of *Helicobacter pylori*, lymphoid follicles in the gastric mucosa, or granulomatous formation. Three sessions of EPBD with fluoroscopic guidance were conducted under general anesthesia over a period of 6 wk at two weeks intervals (Figure 3). Catheter balloons (Boston Scientific Microvasive®, MA, USA) of increasing diameters (first session at 6 mm and 8 mm, second session at 10 mm and 12.5 mm, and third session at 15 mm) were used to insert through the biopsy channel of a Pentax-EG-2731 endoscope and inflated with the use of a pressure gauge system for 60-120 s. The Pentax-EG-1840 endoscope was able to be passed through the pylorus after the first session. Pyloric and duodenal mucosa appeared normal. Repeat UGI series and gastric emptying scan after the third session were normal. The patient had eaten a regular diet and gained weight appropriately without vomiting and abdominal distention after a two year follow-up.

Although the child's endoscopic findings are consistent with IHPS, the sonographic findings are inconsistent with this diagnosis. A group in Galveston described this as a condition of "burned-out IHPS" in children with less severe symptoms than those seen in classical IHPS. Left undiagnosed and untreated, the hypertrophied pylorus in these cases was thought to regress and cause fibrosis leading to pyloric stenosis. These children failed to thrive and often vomited prior to the diagnosis[6].

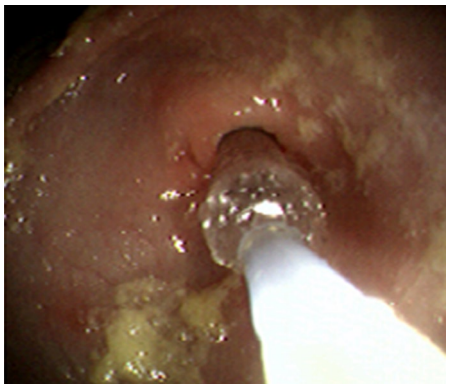


Figure 3 Pneumatic dilation across the pyloric channel.

Other causes of GOO include antral web, gastric duplication, gastric volvulus, pyloric atresia, epidermolysis bullosa, congenital granulomatous disease (CGD), ectopic pancreas, caustic ingestion, bezoars, migration of gastrostomy tube balloons, infection (such as *Helicobacter pylori*, *Anisakis simplex* or anisakiasis), peptic ulcer disease (PUD), extramural compression, eosinophilic gastritis, Crohn disease, hematoma, gastroparesis, and solitary intestinal fibromatosis[2-5].

Achalasia of the pylorus is a possible diagnosis due to the quick response to EPBD in this child. Achalasia is primarily a motor disorder of the esophagus which presents as a functional obstruction at the lower esophageal sphincter (LES). The etiology is thought to be related to reduced function or numbers of postganglionic inhibitory ganglion cells following an inflammatory episode. Achalasia of the pylorus is rarely reported in the medical literature[7]. An inflammatory process in this condition is thought to predispose to persistent pylorospasm which leads to muscular hypertrophy. This is also proposed to be a mechanism that causes obstruction in IHPS. Castro *et al* reported a 12-year-old boy diagnosed with achalasia and IHPS attributed to nitric oxide (NO) absence. NO has been identified as the main inhibitory neurotransmitter in both the LES and the pyloric sphincter. Moreover, the absence of NO synthase in the LES and the pylorus has been implicated in the pathogenesis of IHPS and achalasia[8]. Williams reported three adult patients with acquired GOO and proposed achalasia of the pylorus as an etiology[7]. All were treated with partial gastrectomy and no obvious pathology could explain the cause of pyloric obstruction in these cases. Nine children (age 3 mo to 17 years) presented with a history of late-onset primary GOO of unknown etiology[9]. Eight of them underwent Heineke-Mikulicz pyloroplasty as a result of gastric dilatation with no intrinsic or extrinsic mechanical obstruction at the pylorus. Pneumatic dilation was used in two sessions to successfully dilate a pyloric obstruction in a four year old boy[9]. Pyloric achalasia was proposed as the etiology of the late-onset functional GOO in these cases[9]. Markowitz *et al*[10] suggested a pyloric channel ulcer as a cause of development of pyloric stenosis. Although pyloric ulcer was not observed in our patient during a thorough examination of the pyloric channel after Prevacid® therapy for 3 wk, the presence of antroduodenal inflammation and ulcer deformity or pyloric mucosal scarring was reported in most patients with peptic pyloric stenosis[3].

CGD is a hereditary disorder of granulocyte function which causes progressive multisystemic inflammation and pyloric obstruction. A previously healthy child with acute onset of GOO described by Varma *et al*[11] had normal pyloric histology on endoscopic biopsy, but a full thickness biopsy during laparotomy and the DHR study confirmed the diagnosis of CGD.

EPBD has been used to treat IHPS and other causes of GOO including a pyloric stricture secondary to caustic ingestion, peptic ulcer disease, and delayed gastric emptying[2-5]. Balloon dilatation was a successful alternative procedure to surgery in two infants with IHPS who had inadequate pyloromyotomy and in an 11-year-old boy with surgical damage to the vagus nerve. EPBD was used as a treatment after failed pyloromyotomy in children with hypertrophic pyloric stenosis[5]. The success of EPBD in treating pyloric stenosis or GOO is explained by a complete and longitudinal disruption of the seromuscular ring without any damage to mucosal integrity (tearing)[6].

Idiopathic pyloric stenosis is a rare condition. A "burned out" IHPS, achalasia of the pylorus, and peptic pyloric stenosis are strongly suggested, based on clinical history. We believe the late presentation of acquired pyloric stenosis may depend upon the timing of advancing feeds, food consistency, gastric accommodation, and prior acute illness predisposing to dysmotility. While pyloromyotomy is a recommended operation for IHPS and pyloroplasty in other surgical GOO, we propose that some children who do not fit into the ultrasonographic criteria for IHPS may be good candidates for EPBD.

REFERENCES

1 **Kochhar R**, Kochhar S. Endoscopic balloon dilation for benign gastric outlet obstruction in adults. *World J Gastrointest Endosc* 2010; **2**: 29-35

2 **Treem WR**, Long WR, Friedman D, Watkins JB. Successful management of an acquired gastric outlet obstruction with endoscopy guided balloon dilatation. *J Pediatr Gastroenterol Nutr* 1987; **6**: 992-996

3 **Chan KL**, Saing H. Balloon catheter dilatation of peptic pyloric stenosis in children. *J Pediatr Gastroenterol Nutr* 1994; **18**: 465-468

4 **Israel DM**, Mahdi G, Hassall E. Pyloric balloon dilation for delayed gastric emptying in children. *Can J Gastroenterol* 2001; **15**: 723-727

5 **Heymans HS**, Bartelsman JW, Herweijer TJ. Endoscopic balloon dilatation as treatment of gastric outlet obstruction in infancy and childhood. *J Pediatr Surg* 1988; **23**: 139-140

6 **Mulvihill SJ**, Fonkalsrud EW. Pyloroplasty in infancy and childhood. *J Pediatr Surg* 1983; **18**: 930-936

7 **William AF**. Achalasia of the pylorus in adults. *Lancet* 1950; **1**: 991-993

8 **Castro A**, Mearin F, Gil-Vernet JM, Malagelada JR. Infantile hypertrophic pyloric stenosis and achalasia: NO-related or non-related conditions? *Digestion* 1997; **58**: 596-598

9 **Lin JY**, Lee ZF, Yen YC, Chang YT. Pneumatic dilation in treatment of late-onset primary gastric outlet obstruction in childhood. *J Pediatr Surg* 2007; **42**: e1-e4

10 **Markowitz RI**, Wolfson BJ, Huff DS, Capitanio MA. Infantile hypertrophic pyloric stenosis--congenital or acquired? *J Clin Gastroenterol* 1982; **4**: 39-44

11 **Varma VA**, Sessions JT, Kahn LB, Lipper S. Chronic granulomatous disease of childhood presenting as gastric outlet obstruction. *Am J Surg Pathol* 1982; **6**: 673-676

S- Editor Zhang HN **L- Editor** Hughes D **E- Editor** Liu N

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
www.wjgnet.com

World J Gastrointest Endosc 2010 December 16; 2(12): I
ISSN 1948-5190 (online)

Acknowledgments to reviewers of *World Journal of Gastrointestinal Endoscopy*

Many reviewers have contributed their expertise and time to the peer review, a critical process to ensure the quality of *World Journal of Gastrointestinal Endoscopy*. The editors and authors of the articles submitted to the journal are grateful to the following reviewers for evaluating the articles (including those published in this issue and those rejected for this issue) during the last editing time period.

Mohammad Al-Haddad, MD, Assistant Professor of Clinical Medicine, Director, Endoscopic Ultrasound Fellowship Program, Indiana University School of Medicine, 550 N. University Blvd, Suite 4100, Indianapolis, IN 46202, United States

Majid Abdulrahman Almadi, MD, FRCPC, Department of Gastroenterology Division, McGill University Health Center, Montreal, H3A 1A1, Canada

Wai-Keung Chow, Visiting Staff, Division of Gastroenterology, Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan, China

David J Desilets, MD, PhD, Chief, Division of Gastroenterology, Springfield Bldg, Rm S2606, Department of Medicine; Assistant Professor of Clinical Medicine, Tufts University School of Medicine, Springfield Campus, Baystate Medical Center, Springfield, MA 01199, United States

J Enrique Dominguez-Munoz, MD, Director of the Department of Gastroenterology, University Hospital of Santiago de Compostela, Spain

Carlo M Girelli, MD, 1st Department of Internal Medicine, Service of Gastroenterology and Digestive Endoscopy, Hospital of Busto Arsizio, Via Arnaldo da Brescia, Busto Arsizio, VA 121052, Italy

Lesur Gilles, MD, Hopital Ambroise Paré, 9 avenue Charles de Gaulle, Boulogne 92100, France

Kinichi Hotta, MD, Department of Gastroenterology, Saku Central Hospital, 197 Usuda, Saku, Nagano 384-0301, Japan

Dimitrios Kapetanos, MD, Gastroenterology Department, George Papanikolaou Hospital, Exohi, Thessaloniki 57010, Greece

Shinji Nishiwaki, MD, PhD, Director, Department of Internal Medicine, Nishimino Kosei Hospital, Yoro-cho, Yoro-gun, Gifu 503-1394, Japan

Ichiro Oda, MD, Endoscopy Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

Vasileios Panteris, MD, FEBG, Department of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands

Perminder Phull, MD, FRCP, FRCPE, Gastrointestinal and Liver Service, Room 2.58, Ashgrove House, Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB25 2ZN, United Kingdom

Kaushal Kishor Prasad, MD, PDCC, Associate Professor, Chief, Division of GE Histopathology, Department of Superspeciality for Gastroenterology, Postgraduate Institute of Medical Education and Research, Sector-12, Chandigarh, UT 160012, India

Kenneth Kak Yuen Wong, MD, PhD, Assistant Professor, Department of Surgery, The University of Hong Kong, Queen Mary Hospital, Pokfulam Road, Hong Kong, China

Takayuki Yamamoto, MD, PhD, Inflammatory Bowel Disease Center, Yokkaichi Social Insurance Hospital, 10-8, Hazuyamacho, Yokkaichi 510-0016, Japan

Jiang-Fan Zhu, MD, Professor of Surgery, Department of General Surgery, East Hospital of Tongji University, Pudong 200120, Shanghai, China

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
www.wjgnet.com

World J Gastrointest Endosc 2010 December 16; 2(12): I
ISSN 1948-5190 (online)

Meetings

Events Calendar 2010

January 25-26
Tamilnadu, India
International Conference on Medical Negligence and Litigation in Medical Practice

January 25-29
Waikoloa, HI, United States
Selected Topics in Internal Medicine

January 26-27
Dubai, United Arab Emirates
2nd Middle East Gastroenterology Conference

February 11-13
Fort Lauderdale, FL, United States
21th Annual International Colorectal Disease Symposium

February 26-28
Carolina, United States
First Symposium of GI Oncology at The Caribbean

March 05-07
Peshawar, Pakistan
26th Pakistan Society of Gastroenterology & Endoscopy Meeting

March 12-14
Bhubaneswar, India
18th Annual Meeting of Indian National Association for Study of the Liver

March 25-28
Beijing, China
The 20th Conference of the Asian Pacific Association for the Study of the Liver

March 27-28
San Diego, California, United States
25th Annual New Treatments in Chronic Liver Disease

April 07-09
Dubai, United Arab Emirates
The 6th Emirates Gastroenterology and Hepatology Conference, EGHC 2010

April 14-17
Landover, Maryland, United States
12th World Congress of Endoscopic Surgery

April 14-18
Vienna, Austria
The International Liver Congress™ 2010

April 28-May 01
Dubrovnik, Croatia
3rd Central European Congress of surgery and the 5th Croatian Congress of Surgery

May 01-05
New Orleans, LA, United States
Digestive Disease Week Annual Meeting

May 15-19
Minneapolis, MN, United States
American Society of Colon and Rectal Surgeons Annual Meeting

June 04-06
Chicago, IL, United States
American Society of Clinical Oncologists Annual Meeting

June 16-19
Hong Kong, China
ILTS: International Liver Transplantation Society ILTS Annual International Congress

June 20-23
Mannheim, Germany
16th World Congress for Bronchoesophagology-WCBE

August 28-31
Boston, Massachusetts, United States
10th OESO World Congress on Diseases of the Oesophagus 2010

September 10-12
Montreal, Canada
International Liver Association's Fourth Annual Conference

September 11-12
La Jolla, CA, United States
New Advances in Inflammatory Bowel Disease

September 16-18
Prague, Czech Republic
Prague Hepatology Meeting 2010

September 23-26
Prague, Czech Republic
The 1st World Congress on Controversies in Gastroenterology & Liver Diseases

October 07-09
Belgrade, Serbia
The 7th Biannual International Symposium of Society of Coloproctology

October 15-20
San Antonio, TX, United States
ACG 2010: American College of Gastroenterology Annual Scienitfic Meeting

October 23-27
Barcelona, Spain
18th United European Gastroenterology Week

October 29-November 02
Boston, Massachusetts, United States
The Liver Meeting® 2010--AASLD's 61st Annual Meeting

November 13-14
San Francisco, CA, United States
Case-Based Approach to the Management of Inflammatory Bowel Disease

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
www.wjgnet.com

World J Gastrointest Endosc 2010 December 16; 2(12): I-V
ISSN 1948-5190 (online)

Instructions to authors

GENERAL INFORMATION

World Journal of Gastrointestinal Endoscopy (*World J Gastrointest Endosc*, *WJGE*, online ISSN 1948-5190, DOI: 10.4253), is a monthly, open-access (OA), peer-reviewed online journal supported by an editorial board of 400 experts in gastrointestinal endoscopy from 45 countries.

The biggest advantage of the OA model is that it provides free, full-text articles in PDF and other formats for experts and the public without registration, which eliminates the obstacle that traditional journals possess and usually delays the speed of the propagation and communication of scientific research results.

Maximization of personal benefits

The role of academic journals is to exhibit the scientific levels of a country, a university, a center, a department, and even a scientist, and build an important bridge for communication between scientists and the public. As we all know, the significance of the publication of scientific articles lies not only in disseminating and communicating innovative scientific achievements and academic views, as well as promoting the application of scientific achievements, but also in formally recognizing the "priority" and "copyright" of innovative achievements published, as well as evaluating research performance and academic levels. So, to realize these desired attributes of *WJGE* and create a well-recognized journal, the following four types of personal benefits should be maximized. The maximization of personal benefits refers to the pursuit of the maximum personal benefits in a well-considered optimal manner without violation of the laws, ethical rules and the benefits of others. (1) Maximization of the benefits of editorial board members: The primary task of editorial board members is to give a peer review of an unpublished scientific article via online office system to evaluate its innovativeness, scientific and practical values and determine whether it should be published or not. During peer review, editorial board members can also obtain cutting-edge information in that field at first hand. As leaders in their field, they have priority to be invited to write articles and publish commentary articles. We will put peer reviewers' names and affiliations along with the article they reviewed in the journal to acknowledge their contribution; (2) Maximization of the benefits of authors: Since *WJGE* is an open-access journal, readers around the world can immediately download and read, free of charge, high-quality, peer-reviewed articles from *WJGE* official website, thereby realizing the goals and significance of the communication between authors and peers as well as public reading; (3) Maximization of the benefits of readers: Readers can read or use, free of charge, high-quality peer-reviewed articles without any limits, and cite the arguments, viewpoints, concepts, theories, methods, results, conclusion or facts and data of pertinent literature so as to validate the innovativeness, scientific and practical values of their own research achievements, thus ensuring that their articles have novel arguments or viewpoints, solid evidence and correct conclusion; and (4) Maximization of the benefits of employees: It is an iron law that a first-class journal is unable to exist without first-class editors, and only first-class editors can create a first-class academic journal. We insist on strengthening our team cultivation and construction so that every employee, in an open, fair and transparent environment, could contribute their wisdom to edit and publish high-quality articles, thereby realizing the maximization of the personal benefits of editorial board members, authors and readers, and yielding the greatest social and economic benefits.

Aims and scope

The major task of *WJGE* is to report rapidly the most recent results in basic and clinical research on gastrointestinal endoscopy including: gastroscopy, intestinal endoscopy, colonoscopy, capsule endoscopy, laparoscopy, interventional diagnosis and therapy, as well as advances in technology. Emphasis is placed on the clinical practice of treating gastrointestinal diseases with or under endoscopy. Papers on advances and application of endoscopy-associated techniques, such as endoscopic ultrasonography, endoscopic retrograde cholangiopancreatography, endoscopic submucosal dissection and endoscopic balloon dilation are also welcome.

Columns

The columns in the issues of *WJGE* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Article: To report innovative and original findings in gastrointestinal endoscopy; (9) Brief Article: To briefly report the novel and innovative findings in gastrointestinal endoscopy; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJGE*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of gastrointestinal endoscopy; and (13) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on basic research and clinical practice in gastrointestinal endoscopy.

Name of journal

World Journal of Gastrointestinal Endoscopy

CSSN

ISSN 1948-5190 (online)

Indexed and Abstracted in

PubMed Central

Published by

Baishideng Publishing Group Co., Limited

SPECIAL STATEMENT

All articles published in this journal represent the viewpoints of the authors except where indicated otherwise.

Biostatistical editing

Statisital review is performed after peer review. We invite an expert in Biomedical Statistics from to evaluate the statistical method used in the paper, including *t*-test (group or paired comparisons), chi-

squared test, Ridit, probit, logit, regression (linear, curvilinear, or stepwise), correlation, analysis of variance, analysis of covariance, *etc*. The reviewing points include: (1) Statistical methods should be described when they are used to verify the results; (2) Whether the statistical techniques are suitable or correct; (3) Only homogeneous data can be averaged. Standard deviations are preferred to standard errors. Give the number of observations and subjects (*n*). Losses in observations, such as drop-outs from the study should be reported; (4) Values such as ED50, LD50, IC50 should have their 95% confidence limits calculated and compared by weighted probit analysis (Bliss and Finney); and (5) The word 'significantly' should be replaced by its synonyms (if it indicates extent) or the *P* value (if it indicates statistical significance).

Conflict-of-interest statement

In the interests of transparency and to help reviewers assess any potential bias, *WJGE* requires authors of all papers to declare any competing commercial, personal, political, intellectual, or religious interests in relation to the submitted work. Referees are also asked to indicate any potential conflict they might have reviewing a particular paper. Before submitting, authors are suggested to read "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Ethical Considerations in the Conduct and Reporting of Research: Conflicts of Interest" from International Committee of Medical Journal Editors (ICMJE), which is available at: http://www.icmje.org/ethical_4conflicts.html.

Sample wording: [Name of individual] has received fees for serving as a speaker, a consultant and an advisory board member for [names of organizations], and has received research funding from [names of organization]. [Name of individual] is an employee of [name of organization]. [Name of individual] owns stocks and shares in [name of organization]. [Name of individual] owns patent [patent identification and brief description].

Statement of informed consent

Manuscripts should contain a statement to the effect that all human studies have been reviewed by the appropriate ethics committee or it should be stated clearly in the text that all persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study should be omitted. Authors should also draw attention to the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964, as revised in 2004).

Statement of human and animal rights

When reporting the results from experiments, authors should follow the highest standards and the trial should comform to Good Clinical Practice (for example, US Food and Drug Administration Good Clinical Practice in FDA-Regulated Clinical Trials; UK Medicines Research Council Guidelines for Good Clinical Practice in Clinical Trials) and/or the World Medical Association Declaration of Helsinki. Generally, we suggest authors follow the lead investigator's national standard. If doubt exists whether the research was conducted in accordance with the above standards, the authors must explain the rationale for their approach and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study.

Before submitting, authors should make their study approved by the relevant research ethics committee or institutional review board. If human participants were involved, manuscripts must be accompanied by a statement that the experiments were undertaken with the understanding and appropriate informed consent of each. Any personal item or information will not be published without explicit consents from the involved patients. If experimental animals were used, the materials and methods (experimental procedures) section must clearly indicate that appropriate measures were taken to minimize pain or discomfort, and details of animal care should be provided.

SUBMISSION OF MANUSCRIPTS

Manuscripts should be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Number all pages consecutively, and start each of the following sections on a new page: Title Page, Ab stract, Introduction, Materials and Methods, Results, Discussion, Acknowledgements, References, Tables, Figures, and Figure Legends. Neither the editors nor the publisher are responsible for the opinions expressed by contributors. Manuscripts formally accepted for publication become the permanent property of Baishideng Publishing Group Co., Limited, and may not be reproduced by any means, in whole or in part, without the written permission of both the authors and the publisher. We reserve the right to copy-edit and put onto our website accepted manuscripts. Authors should follow the relevant guidelines for the care and use of laboratory animals of their institution or national animal welfare committee. For the sake of transparency in regard to the performance and reporting of clinical trials, we endorse the policy of the International Committee of Medical Journal Editors to refuse to publish papers on clinical trial results if the trial was not recorded in a publicly-acces sible registry at its outset. The only register now available, to our knowledge, is http://www. clinicaltrials.gov sponsored by the Uni ted States National Library of Medicine and we encourage all potential contributors to register with it. However, in the case that other registers become available you will be duly notified. A letter of recommendation from each author's organization should be provided with the contributed article to ensure the privacy and secrecy of research is protected.

Authors should retain one copy of the text, tables, photographs and illustrations because rejected manuscripts will not be returned to the author(s) and the editors will not be responsible for loss or damage to photographs and illustrations sustained during mailing.

Online submissions

Manuscripts should be submitted through the Online Submission System at: wjge@wjgnet.com. Authors are highly recommended to consult the ONLINE INSTRUCTIONS TO AUTHORS (http://www.wjgnet.com/1948-5190/g_info_20100316080002.htm) before attempting to submit online. For assistance, authors encountering problems with the Online Submission System may send an email describing the problem to http://www.wjgnet.com/1948-5190office/, or by telephone: +86-10-59080038. If you submit your manuscript online, do not make a postal contribution. Repeated online submission for the same manuscript is strictly prohibited.

MANUSCRIPT PREPARATION

All contributions should be written in English. All articles must be submitted using word-processing software. All submissions must be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Style should conform to our house format. Required information for each of the manuscript sections is as follows:

Title page

Title: Title should be less than 12 words.

Running title: A short running title of less than 6 words should be provided.

Authorship: Authorship credit should be in accordance with the standard proposed by International Committee of Medical Journal Editors, based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

Institution: Author names should be given first, then the complete name of institution, city, province and postcode. For example, Xu-Chen Zhang, Li-Xin Mei, Department of Pathology, Chengde Medical College, Chengde 067000, Hebei Province, China. One author may be represented from two institutions, for example, George Sgourakis, Department of General, Visceral, and

Transplantation Surgery, Essen 45122, Germany; George Sgourakis, 2nd Surgical Department, Korgialenio-Benakio Red Cross Hospital, Athens 15451, Greece

Author contributions: The format of this section should be: Author contributions: Wang CL and Liang L contributed equally to this work; Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research; Wang CL, Zou CC, Hong F and Wu XM performed the research; Xue JZ and Lu JR contributed new reagents/analytic tools; Wang CL, Liang L and Fu JF analyzed the data; and Wang CL, Liang L and Fu JF wrote the paper.

Supportive foundations: The complete name and number of supportive foundations should be provided, e.g., Supported by National Natural Science Foundation of China, No. 30224801

Correspondence to: Only one corresponding address should be provided. Author names should be given first, then author title, affiliation, the complete name of institution, city, postcode, province, country, and email. All the letters in the email should be in lower case. A space interval should be inserted between country name and email address. For example, Montgomery Bissell, MD, Professor of Medicine, Chief, Liver Center, Gastroenterology Division, University of California, Box 0538, San Francisco, CA 94143, United States. montgomery.bissell@ucsf.edu

Telephone and fax: Telephone and fax should consist of +, country number, district number and telephone or fax number, e.g., Telephone: +86-10-59080039 Fax: +86-10-85381893

Peer reviewers: All articles received are subject to peer review. Normally, three experts are invited for each article. Decision for acceptance is made only when at least two experts recommend an article for publication. Reviewers for accepted manuscripts are acknowledged in each manuscript, and reviewers of articles which were not accepted will be acknowledged at the end of each issue. To ensure the quality of the articles published in *WJGE*, reviewers of accepted manuscripts will be announced by publishing the name, title/position and institution of the reviewer in the footnote accompanying the printed article. For example, reviewers: Professor Jing-Yuan Fang, Shanghai Institute of Digestive Disease, Shanghai, Affiliated Renji Hospital, Medical Faculty, Shanghai Jiaotong University, Shanghai, China; Professor Xin-Wei Han, Department of Radiology, The First Affiliated Hospital, Zhengzhou University, Zhengzhou, Henan Province, China; and Professor Anren Kuang, Department of Nuclear Medicine, Huaxi Hospital, Sichuan University, Chengdu, Sichuan Province, China.

Abstract

There are unstructured abstracts (no more than 256 words) and structured abstracts (no more than 480). The specific requirements for structured abstracts are as follows:

An informative, structured abstracts of no more than 480 words should accompany each manuscript. Abstracts for original contributions should be structured into the following sections. AIM (no more than 20 words): Only the purpose should be included. Please write the aim as the form of "To investigate/study/…; MATERIALS AND METHODS (no more than 140 words); RESULTS (no more than 294 words): You should present *P* values where appropriate and must provide relevant data to illustrate how they were obtained, e.g. 6.92 ± 3.86 *vs* 3.61 ± 1.67, $P < 0.001$; CONCLUSION (no more than 26 words).

Key words

Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

Text

For articles of these sections, original articles, rapid communication and case reports, the main text should be structured into the following sections: INTRODUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both. The main text format of these sections, editorial, topic highlight, case report, letters to the editors, can be found at: http://www.wjgnet.com/1948-5190/g_info_20100316080002.htm.

Illustrations

Figures should be numbered as 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are applicable. Figures should be either Photoshop or Illustrator files (in tiff, eps, jpeg formats) at high-resolution. Examples can be found at: http://www.wjgnet.com/1007-9327/13/4520.pdf; http://www.wjgnet.com/1007-9327/13/4554.pdf; http://www.wjgnet.com/1007-9327/13/4891.pdf; http://www.wjgnet.com/1007-9327/13/4986.pdf; http://www.wjgnet.com/1007-9327/13/4498.pdf. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Pathological changes in atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: …*etc.* It is our principle to publish high resolution-figures for the printed and E-versions.

Tables

Three-line tables should be numbered 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each table. Detailed legends should not be included under tables, but rather added into the text where applicable. The information should complement, but not duplicate the text. Use one horizontal line under the title, a second under column heads, and a third below the Table, above any footnotes. Vertical and italic lines should be omitted.

Notes in tables and illustrations

Data that are not statistically significant should not be noted. $^{a}P < 0.05$, $^{b}P < 0.01$ should be noted ($P > 0.05$ should not be noted). If there are other series of *P* values, $^{c}P < 0.05$ and $^{d}P < 0.01$ are used. A third series of *P* values can be expressed as $^{e}P < 0.05$ and $^{f}P < 0.01$. Other notes in tables or under illustrations should be expressed as ^{1}F, ^{2}F, ^{3}F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multi-curve illustration, each curve should be labeled with ●, ○, ■, □, ▲, △, *etc.*, in a certain sequence.

Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

REFERENCES

Coding system

The author should number the references in Arabic numerals according to the citation order in the text. Put reference numbers in square brackets in superscript at the end of citation content or after the cited author's name. For citation content which is part of the narration, the coding number and square brackets should be typeset normally. For example, "Crohn's disease (CD) is associated with increased intestinal permeability[1,2]". If references are cited directly in the text, they should be put together within the text, for example, "From references[19,22-24], we know that..."

When the authors write the references, please ensure that the order in text is the same as in the references section, and also

ensure the spelling accuracy of the first author's name. Do not list the same citation twice.

PMID and DOI

Pleased provide PubMed citation numbers to the reference list, e.g. PMID and DOI, which can be found at http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed and http://www.crossref.org/SimpleTextQuery/, respectively. The numbers will be used in E-version of this journal.

Style for journal references

Authors: the name of the first author should be typed in bold-faced letters. The family name of all authors should be typed with the initial letter capitalized, followed by their abbreviated first and middle initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR). The title of the cited article and italicized journal title (journal title should be in its abbreviated form as shown in PubMed), publication date, volume number (in black), start page, and end page [PMID: 11819634 DOI: 10.3748/wjg.13.5396].

Style for book references

Authors: the name of the first author should be typed in bold-faced letters. The surname of all authors should be typed with the initial letter capitalized, followed by their abbreviated middle and first initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR) Book title. Publication number. Publication place: Publication press, Year: start page and end page.

Format

Journals

English journal article (list all authors and include the PMID where applicable)

1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

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

Organization as author

4 **Diabetes Prevention Program Research Group**. Hyperten sion, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

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

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

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

Patent (list all authors)

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

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/wjg/help/15.doc.

Abbreviations

Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and

Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

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.*

Examples for paper writing

Editorial: http://www.wjgnet.com/1948-5190/g_info_20100316080004.htm

Frontier: http://www.wjgnet.com/1948-5190/g_info_20100313155344.htm

Topic highlight: http://www.wjgnet.com/1948-5190/g_info_20100316080006.htm

Observation: http://www.wjgnet.com/1948-5190/g_info_20100107124105.htm

Guidelines for basic research: http://www.wjgnet.com/1948-5190/g_info_20100313155908.htm

Guidelines for clinical practice: http://www.wjgnet.com/1948-5190/g_info_20100313160015.htm

Review: http://www.wjgnet.com/1948-5190/g_info_20100107124313.htm

Original articles: http://www.wjgnet.com/1948-5190/g_info_20100107133454.htm

Brief articles: http://www.wjgnet.com/1948-5190/g_info_20100313160645.htm

Case report: http://www.wjgnet.com/1948-5190/g_info_20100107133659.htm

Letters to the editor: http://www.wjgnet.com/1948-5190/g_info_20100107133856.htm

Book reviews: http://www.wjgnet.com/1948-5190/g_info_20100313161146.htm

Guidelines: http://www.wjgnet.com/1948-5190/g_info_20100313161315.htm

SUBMISSION OF THE REVISED MANUSCRIPTS AFTER ACCEPTED

Please revise your article according to the revision policies of *WJGE*. The revised version including manuscript and high-resolution image figures (if any) should be copied on a floppy or compact disk. The author should send the revised manuscript, along with printed high-resolution color or black and white photos, copyright transfer letter, and responses to the reviewers by courier (such as EMS/DHL).

Editorial Office

World Journal of Gastrointestinal Endoscopy
Editorial Department: Room 903, Building D,
Ocean International Center,
No. 62 Dongsihuan Zhonglu,
Chaoyang District, Beijing 100025, China
E-mail: wjge@wjgnet.com
http://www.wjgnet.com
Telephone: +86-10-59080038
Fax: +86-10-85381893

Language evaluation

The language of a manuscript will be graded before it is sent for revision. (1) Grade A: priority publishing; (2) Grade B: minor language polishing; (3) Grade C: a great deal of language polishing needed; and (4) Grade D: rejected. Revised articles should reach Grade A or B.

Copyright assignment form

Please download a Copyright assignment form from http://www.wjgnet.com/1948-5190/g_info_20100107134847.htm.

Responses to reviewers

Please revise your article according to the comments/suggestions provided by the reviewers. The format for responses to the reviewers' comments can be found at: http://www.wjgnet.com/1948-5190/g_info_20100107134601.htm.

Proof of financial support

For paper supported by a foundation, authors should provide a copy of the document and serial number of the foundation.

Links to documents related to the manuscript

WJGE will be initiating a platform to promote dynamic interactions between the editors, peer reviewers, readers and authors. After a manuscript is published online, links to the PDF version of the submitted manuscript, the peer-reviewers' report and the revised manuscript will be put on-line. Readers can make comments on the peer reviewer's report, authors' responses to peer reviewers, and the revised manuscript. We hope that authors will benefit from this feedback and be able to revise the manuscript accordingly in a timely manner.

Science news releases

Authors of accepted manuscripts are suggested to write a science news item to promote their articles. The news will be released rapidly at EurekAlert/AAAS (http://www.eurekalert.org). The title for news items should be less than 90 characters; the summary should be less than 75 words; and main body less than 500 words. Science news items should be lawful, ethical, and strictly based on your original content with an attractive title and interesting pictures.

Publication fee

Authors of accepted articles must pay a publication fee.
EDITORIAL, TOPIC HIGHLIGHTS, BOOK REVIEWS and LETTERS TO THE EDITOR are published free of charge.