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Reviews

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Review

Approach to gastroenterological diseases in primary care

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Summary. Gastroenterological diseases are a source of morbidity, mortality and costs, and have a high frequency in general practice; for this reason, we have evaluated the current literature regarding the knowledge and management of these disorders by general practitioners, finding little knowledge and adherence to guidelines, highlighting the need for continuous updating in this regard, and greater collaboration between specialists and general practitioners. (www.actabiomedica.it)

Key words: primary care, general practitioners, general practice, gastroenterological, gastrointestinal, disorders, diseases, review

Background and aim of the work

Gastroenterological diseases are common in general practice, approximately 10% of consultations in general practice in the UK are for gastrointestinal symptoms or problems (1). These disorders are also a source of morbidity, mortality, and cost. In 2015, in the United States the annual health care expenditures for gastrointestinal (GI) diseases totaled $ 135.9 billion, with 11.0 million colonoscopies and 6.1 million upper endoscopies performed in the same year; the mortality is also huge with 144.300 GI cancer deaths and 97.700 deaths from non-malignant diseases (2). In Italy the situation is specular: GI diseases are the 5th cause of death in men and the 7th in women, and with 1 million hospitalizations a year they–represent the first or second cause of hospitalization in the last 10 years (3). The aim of this narrative review is to evaluate the current literature on the existing role of general practitioners (GPs) in the diagnosis and management of some of the principal GI disorders in order to point out the importance of early diagnosis and correct managements in reduce morbidity, mortality and costs.

Methods

Articles reviewed were found through literature searches on PubMed and Google Scholar from keywords related with primary care and specific GI diseases.

Upper gastrointestinal disorders

Gastroesophageal reflux disease (GERD)

GERD is a highly prevalent condition defined as symptoms or complications resulting from the reflux of gastric contents into the esophagus, or beyond into the oral cavity or lung. Epidemiological evidence indicates that the prevalence of GERD in the Western world is 10%–20%, with a lower prevalence in Asia (4). The disease represents also the fourth most common chronic condition seen in primary care practice (5) (Fig. 1). Because of its prevalence in general population GPs play a crucial role in its management, but the diagnosis is not as easy as it seems, typical symptoms of GERD are heartburn and regurgitation, however, these symptoms are not as sensitive as most believe

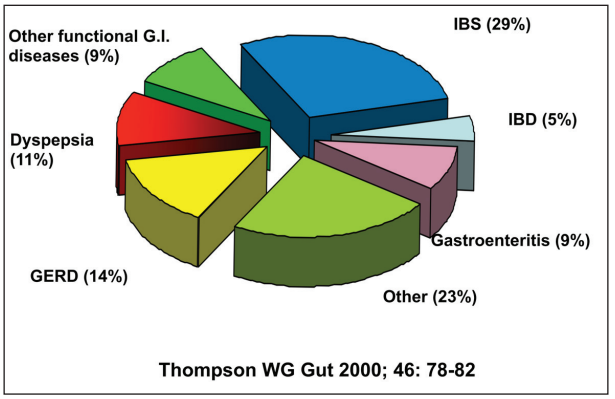

Figure 1.

and patients with GERD may present with a broad range of symptoms as dyspepsia or extraesophageal manifestations (such as chronic cough and asthma). Caution is needed for patients with chest pain: a cardiac cause should be excluded before starting a GI evaluation. Moreover, many patients (70%) with typical GERD symptoms do not have endoscopic erosive disease (non-erosive reflux disease NERD), suggesting that endoscopy is of limited value in guiding disease management (6). This pan-European study showed that across countries, 28-47% of patients reported a significant GERD symptom load at initial consultation with a GP, thereafter, 30-100% of patients were prescribed a proton pump inhibitor (PPI), but a significant GERD symptom load was still experienced by 15-30% at follow-up. In most of patients (65-88%), no diagnostic procedures were performed between initial consultation and follow-up. Those findings indicate that current management of primary care patients with GERD is far from optimal, and accounts for a marked burden on patients and healthcare systems (7). Several studies have demonstrated that there is often poor agreement between patients and physicians in their assessment of GERD symptom severity, and physicians tend to underestimate symptom severity and the impact on health-related quality of life, which is an essential component of providing proper medical care, improvement in clinician-patient communication is suggested in order to bridge this gap (8, 9).

Esophageal cancer

The incidence of esophageal cancer (EC) is increasing: the reason for this major epidemiological shift is an increase in GERD and its principal complication, Barrett's esophagus, the only known precursor lesion for EC (10). The role of H. pylori eradication in this increase is yet uncertain. While the incidence of squamous cell carcinoma of the esophagus has recently been stable or declined in Western societies, the incidence of esophageal adenocarcinoma has risen more rapidly than that of any other cancer in many countries since the 1970s. Esophageal adenocarcinoma is associated with gastro-esophageal reflux and obesity, whereas squamous cell carcinoma is associated with use of tobacco and alcohol. Overall, the prognosis for patients diagnosed with esophageal cancer is poor, but those whose tumors are detected at an early stage have a good chance of survival (11). Hence the importance of effective prevention and early diagnosis but evidence shows that diagnosis of EC is often delayed, and the interval between symptom onset and diagnosis ranges from 1.2–11.7 months (12). Implications for primary care include advising patients that persistent heartburn is not a trivial complaint, especially if unresponsive to lifestyle changes and over-the-counter medication, and encouraging consultation. GPs will need to consider referring for endoscopy early, rather than the current practice of treating blindly with acid suppression (13).

Helicobacter pylori, dyspepsia, and "the gastric precancerous cascade"

H. pylori is a common bacterium, that colonizes human stomach, discovered in 1983 by Warren and

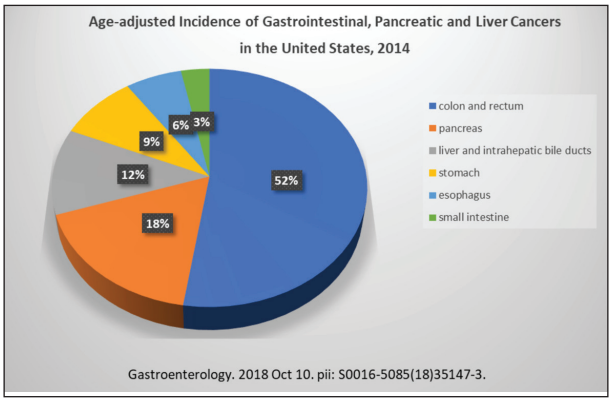

Figure 2.

Marshall (14). This global systematic review shows that in 2015, approximately 4.4 billion individuals worldwide were estimated to be positive for H. pylori with a wide variation in the prevalence of H. pylori between regions and countries (15). H. pylori has been established as a major cause of chronic gastritis, duodenal ulcer, peptic ulcer, dyspepsia and gastric cancer. IARC classified H. pylori as a group 1 carcinogen in 1994, and hence the most recent guidelines suggest a test-and-threat strategy in patients with dyspeptic symptoms in order to reduce the incidence of gastric cancer (16-18). Correa et al demonstrated the role of H. pylori as initiator of the "gastric precancerous cascade" consisting of the following steps: normal gastric mucosa → non-atrophic gastritis (NAG) → multifocal atrophic gastritis (MAG) without intestinal metaplasia → intestinal metaplasia of the small intestine type → intestinal metaplasia of the colonic type → low-grade non-invasive neoplasia → high-grade non-invasive neoplasia → invasive adenocarcinoma (19). GPs are at the forefront of H. pylori management but overall adherence to guidelines seems low, for example in this Israeli study only 43.6% of GPs routinely confirm eradication with a noninvasive test, in accordance with guidelines. Of the total, 41.1% respondents treat all patients found to harbor H. pylori infection and 58.1% only treat symptomatic patients. The etiological link between H. pylori and gastric cancer was believed to be "definite" by 45.0% of GPs; only 30.9% respondents "consistently" or "usually" screen first-degree relatives of gastric cancer patients and only 14.1% respondents "consistently" or "usually" screen before initiating long-term therapy with NSAIDs (20). Things aren't much different in other part of the word (21-25). A 2009 study by Spiegel et al found that there was a significant difference in guideline adherence regarding dyspepsia between gastroenterologists and GPs (74% versus 57%, respectively) (26).

Gastric cancer

Gastric cancer (GC) is the fifth most common malignancy in the world, and the third leading cause of cancer death in both sexes worldwide (27). Early diagnosis is the only way to reduce the mortality but at present time there isn't a consensus on GC screening program; although most recent guidelines suggest that validated serological tests for H pylori and markers of atrophy (i.e. pepsinogens and gastin-17) are the best available non-invasive tests to identify subjects at high risk of gastric cancer (28). H. pylori serology combined with serum pepsinogen I/II ratio may constitute a non-invasive method to detect premalignant conditions (29, 30). A significant proportion of patients with early GC experience only nonspecific dyspeptic symptoms; because dyspepsia is very common in the general population, the difficulty for GPs is in deciding which patients should be referred early for investigation. In a study from Italy authors concluded that a panel composed of PGI, PGII, G-17 and IgG-Hp could be used as a first approach in the 'test and scope' and/or 'test and treat' strategy in the primary care management of dyspeptic patients (31). Even an alarm symptom such as the onset of iron deficiency anemia in post-menopausal women and men seem managed sub optimally by GPs: in this study, in UK, it was noticed that only 47% of 431 patients presenting to their general practitioner with an iron-deficient anemia were adequately managed and 39% of patients who were otherwise fit for investigation had no tests at all. It is worth noticing that only 29 of the 41 GI cancers (22 lower, seven upper) were found as a result of satisfactory GI investigations (32). A similar study from Netherlands showed that only 31% of male and postmenopausal female patients with iron deficiency anemia received some form of endoscopic evaluation (33).

Lower gastrointestinal disorders

Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a global healthcare problem with a sustained increasing incidence. It includes two major forms, Crohn's disease (CD) and ulcerative colitis (UC); CD can cause transmural inflammation and affect any part of the gastrointestinal tract (most commonly, the terminal ileum or the perianal region) in a non-continuous type and is frequently associated with complications such as abscesses, fistulas and strictures. In contrast, UC is typi-

fied by mucosal inflammation and limited to the colon. Although the etiology of IBD remains largely unknown, recent research indicated that the individual's genetic susceptibility, external environment, intestinal microbial flora and immune responses are all involved and functionally integrated in the pathogenesis of IBD (34). IBD affects primarily young adults for the rest of their life, resulting in a huge impact on health services. These patients, indeed, require life-lasting medical care as well as clinical and laboratory investigation (35). A significant part of these services refers to primary care, in which the GP plays a key role, especially regarding early diagnosis and monitoring the compliance of patient to treatment, in this challenge they are helped by fecal calprotectin (FC)with the emerging evidence that it is a useful non-invasive marker of mucosal healing and short-term clinical outcome in patients with IBD (36). Unfortunately, the literature on the role of GPs in IBD management suggests a poor knowledge of the disease: in Australia 37% of the GPs reported being generally "uncomfortable" with IBD management. Specifically, they were only somewhat comfortable in providing/using maintenance therapy, steroid therapy or unspecified therapy for an acute flare, but they were uncomfortable with the use of immunomodulators and biologicals (71 and 91%, respectively) (37). However, not all the fault seems to be of GPs as shown by Bezzio et al: in this study respondents indeed, declare numerous unmet needs in managing IBD patients as increasing bureaucracy, lack of extra-gastroenterological IBD expertise, lack of diagnostic techniques and budget limitations. About professional updating they indicated that helpful topics are practical medicine, managing difficult patients, and guidelines. The most desired modality for updating is residential courses on clinical practice (38).

Irritable bowel syndrome

Irritable bowel syndrome (IBS) is a disorder of gut-brain interaction that affects around 11.2% of the population globally with higher prevalence in young women (39). Guidelines emphasize that IBS is not a diagnosis of exclusion, and encourage clinicians to make a positive diagnosis using the Rome criteria alone, however most community providers believe IBS is a diagnosis of exclusion. Spiegel et al showed that experts were less likely than GPs to endorse IBS as a diagnosis of exclusion (8% vs. 72%, respectively). Experts were more likely to make a positive diagnosis of IBS (67% vs. 38%), to perform fewer tests (2.0 vs. 4.1), and to expend less money on testing (US$297 vs. $658). Providers who believed IBS is a diagnosis of exclusion ordered 1.6 more tests and consumed $364 more than others (40). Available data show that IBS criteria are largely unknown and are poorly validated in general practice where most patients are treated (41, 42).

Diverticulosis and diverticular disease

Diverticulosis of the colon is the most frequent anatomical colonic alteration, frequently detected during colonoscopy. It is a structural alteration of the colonic wall characterized by the presence of herniation of the colonic mucosa and sub-mucosa though muscle layer, called "diverticula". The real prevalence of diverticulosis is unknown. In Europe, it is largely age-dependent and is uncommon (prevalence of 5%) in those under the age of 40 years, increasing up to 65% in those aged 65 years or more. Diverticulosis is the presence of colonic diverticula; diverticular disease (DD) instead is defined as clinically significant and symptomatic diverticulosis, that could be uncomplicated (symptomatic uncomplicated diverticular disease (SUDD)) or complicated (diverticulitis) (43). According to Ubaldi et al DD is becoming a leading chronic condition in terms of costs and burden for the health service. The management of DD greatly relies on GPs who must approach patients also in terms of diet, lifestyle and prevention of complications (44). In Italy the economic burden of patients suffering from acute episodes of diverticulitis is estimated at €63.5 million a year (45). The current literature data and current guidelines are quite concordant in advising CT colonography when the colon must be investigated by radiology (46), and fecal calprotectin (FC) as a useful tool in the differential diagnosis between SUDD and IBS, as well in assessing response to therapy in DD (47) and diverticulitis recurrence (48). There is no evidence that pharmacological treatment is useful in asymptomatic diverticulosis and there is no rationale

to avoid in the diet the consumption of nut, corn and popcorn to prevent diverticular complications. Fiber supplementation alone provides controversial results in terms of symptoms relief and there is insufficient evidence that probiotics are effective in reducing symptoms (49). Despite these indications De Bastiani et al found that a high-fiber diet was widely prescribed in diverticulosis (44%) by GPs together with advice to avoid seeds (30%). Rifaximin (26%) and probiotics (25%) were the most frequent prescribed drugs in this population. 19% of them use double-contrast barium enema to pose diagnosis of SUDD instead of colonoscopy. Finally, only 14% of GPs prescribe fecal calprotectin in the follow-up of the patients with SUDD or acute diverticulitis (AD). Authors concluded that the current management of diverticulosis and DD in primary care still conflicts with the literature and more recent guidelines (50).

Colorectal cancer

Colorectal cancer (CRC) is a major cause of morbidity and mortality throughout the world. It accounts for over 9% of all cancer incidence. It is the third most common cancer worldwide and the fourth most common cause of death. Worldwide mortality attributable to CRC is approximately half that of the incidence. Western diet, obesity, sedentary life, cigarette smoking, heavy alcohol consumption, IBD, and family history of CRC are all risk factors for the development of this neoplasm (51). The detection and subsequent removal of precursor lesions detected during screening and the detection of CRC at an earlier, more favorable stage have been shown to significantly reduce incidence and mortality. For these reasons, most recent guidelines recommend starting screening for CRC at age 45 years and continuing it up to age 75 years (52). GPs are at the hearth of CRC screening program but unfortunately, it remains underused: only 77.5% of physicians report use of the US national screening guidelines and only 51.7% use recommendations consistent with the guidelines (53). GPs reported insufficient training, and some doubted the relevance of screening. They expressed concerns in terms of the time available for the test during the consultation and they, also, reported practical and administrative obstacles. Other barriers to CRC screening evidenced by the GPs included the difficulties in convincing patients, especially those not experiencing signs and symptoms (54). In this study Stroud et al demonstrate that a protocol adopted by primary care staff based on simple tools such as chart stickers, to draw attention to patients requiring screening, generation of referral forms that were numbered for follow-up and faxed to the gastroenterologists, and patient educational material on colorectal cancer screening, is very effective in increase adherence to the screening program (from the baseline of 47% in year 2001 to 86% in year 2002) (55).

Conclusions

The role of GPs is crucial in the diagnosis and management of gastroenterological diseases and can positively influence the economic burden of them. However, the literature review shows a lack of knowledge and a poor adherence to guidelines, for these reasons continuing educational courses are mandatory for primary care. Authors also hope for greater collaboration between specialists and GPs, and to use more time to establish a stronger doctor-patient relationship in order to increase adherence to screening programs and cares. The communication time should be considered as a cure time.

References

1. Jones, R. "Primary care research and clinical practice: gastroenterology." Postgraduate medical journal 84.995 (2008): 454-458.
2. Peery, Anne F., et al. "Burden and Cost of Gastrointestinal, Liver, and Pancreatic Diseases in the United States: Update 2018." Gastroenterology (2018)
3. https://www.webaigo.it/download/AIGO_2012_scheda_malattie_gastro.pdf
4. Dent, J., et al. "Epidemiology of gastro-oesophageal reflux disease: a systematic review." Gut 54.5 (2005): 710-717.
5. Ornstein, Steven M., et al. "The prevalence of chronic diseases and multimorbidity in primary care practice: a PPRNet report." The Journal of the American Board of Family Medicine 26.5 (2013): 518-524.
6. Savarino, Edoardo, Patrizia Zentilin, and Vincenzo Savarino. "NERD: an umbrella term including heterogeneous subpopulations." Nature reviews Gastroenterology & hepatology 10.6 (2013): 371.

7. Gisbert, Javier P., et al. "Management of gastro-oesophageal reflux disease in primary care: a European observational study." Current medical research and opinion 25.11 (2009): 2777-2784.
8. Fallone, C. A., et al. "Do physicians correctly assess patient symptom severity in gastro-oesophageal reflux disease?." Alimentary pharmacology & therapeutics 20.10 (2004): 1161-1169.
9. McColl, Elaine, et al. "Assessing symptoms in gastroesophageal reflux disease: how well do clinicians' assessments agree with those of their patients?." The American journal of gastroenterology 100.1 (2005): 11.
10. van Soest, Eva M., et al. "Increasing incidence of Barrett's oesophagus in the general population." Gut 54.8 (2005): 1062-1066.
11. Lagergren, Jesper, and Pernilla Lagergren. "Oesophageal cancer." Bmj 341 (2010): c6280.
12. Witzig, R., et al. "Delays in diagnosis and therapy of gastric cancer and esophageal adenocarcinoma." Endoscopy 38.11 (2006): 1122-1126.
13. Watson, Anthony, and John Galloway. "Heartburn, Barrett's oesophagus and cancer: implications for primary care." (2014): 120-121.
14. Warren, J. Robin, and Barry Marshall. "Unidentified curved bacilli on gastric epithelium in active chronic gastritis." The lancet 321.8336 (1983): 1273-1275.
15. Hooi, James KY, et al. "Global prevalence of Helicobacter pylori infection: systematic review and meta-analysis." Gastroenterology 153.2 (2017): 420-429.
16. Malfertheiner, P., et al. "Management of Helicobacter pylori infection—the Maastricht V/Florence consensus report." Gut 66.1 (2017): 6-30.
17. Sugano, Kentaro, et al. "Kyoto global consensus report on Helicobacter pylori gastritis." Gut 64.9 (2015): 1353-1367.
18. Zagari, Rocco Maurizio, et al. "Guidelines for the management of Helicobacter pylori infection in Italy: the III Working Group Consensus Report 2015." Digestive and Liver Disease 47.11 (2015): 903-912.
19. Correa, Pelayo, and M. Blanca Piazuelo. "The gastric precancerous cascade." Journal of digestive diseases 13.1 (2012): 2-9.
20. Boltin, Doron, et al. "Attitudes and practice related to Helicobacter pylori infection among primary care physicians." European journal of gastroenterology & hepatology 28.9 (2016): 1035-1040.
21. Thomas Breuer MD, M. S., et al. "How do clinicians practicing in the US manage Helicobacter pylori-related gastrointestinal diseases?: a comparison of primary care and specialist physicians." The American journal of gastroenterology 93.4 (1998): 553-561.
22. Bennett, K., et al. "Impact of Helicobacter pylori on the management of dyspepsia in primary care." Alimentary pharmacology & therapeutics 24.4 (2006): 637-641.
23. Kim, Byeong Gwan, et al. "Discrepancies between primary physician practice and treatment guidelines for Helicobacter pylori infection in Korea." World Journal of Gastroenterology: WJG 12.1 (2006): 66.
24. Ahmed, Shahid, et al. "Helicobacter pylori infection: approach of primary care physicians in a developing country." BMC gastroenterology 9.1 (2009): 23.
25. Seifert, Bohumil, et al. "The management of common gastrointestinal disorders in general practice: a survey by the European Society for Primary Care Gastroenterology (ESPCG) in six European countries." Digestive and Liver Disease 40.8 (2008): 659-666.
26. Spiegel, B. M. R., et al. "Adherence to best practice guidelines in dyspepsia: a survey comparing dyspepsia experts, community gastroenterologists and primary-care providers." Alimentary pharmacology & therapeutics 29.8 (2009): 871-881.
27. Ferlay, Jacques, et al. "Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012." International journal of cancer 136.5 (2015): E359-E386.
28. Asaka, Masahiro, Mototsugu Kato, and David Y. Graham. "Strategy for eliminating gastric cancer in Japan." Helicobacter 15.6 (2010): 486-490.
29. Agréus, Lars, et al. "Rationale in diagnosis and screening of atrophic gastritis with stomach-specific plasma biomarkers." Scandinavian journal of gastroenterology 47.2 (2012): 136-147.
30. Di Mario, F., et al. "'Serological biopsy'in first-degree relatives of patients with gastric cancer affected by Helicobacter pylori infection." Scandinavian journal of gastroenterology 38.12 (2003): 1223-1227.
31. Germaná, B., et al. "Clinical usefulness of serum pepsinogens I and II, gastrin-17 and anti-Helicobacter pylori antibodies in the management of dyspeptic patients in primary care." Digestive and liver disease 37.7 (2005): 501-508.
32. Logan, E. C. M., et al. "Investigation and management of iron deficiency anaemia in general practice: a cluster randomised controlled trial of a simple management prompt." Postgraduate medical journal 78.923 (2002): 533-537.
33. Droogendijk, Jolanda, et al. "Screening for gastrointestinal malignancy in patients with iron deficiency anemia by general practitioners: an observational study." Scandinavian journal of gastroenterology 46.9 (2011): 1105-1110.
34. Zhang, Yi-Zhen, and Yong-Yu Li. "Inflammatory bowel disease: pathogenesis." World journal of gastroenterology: WJG 20.1 (2014): 91.
35. Sprangers, M. A., and J. F. Bartelsman. "Predictors of health care utilization in patients with inflammatory bowel disease: a longitudinal study." European journal of gastroenterology & hepatology 10.9 (1998): 783-789.
36. Kostas, Athanasios, et al. "Fecal calprotectin measurement is a marker of short-term clinical outcome and presence of mucosal healing in patients with inflammatory bowel disease." World journal of gastroenterology 23.41 (2017): 7387.
37. Tan, M., et al. "General practitioners' knowledge of and attitudes to inflammatory bowel disease." Internal medicine journal 42.7 (2012): 801-807.
38. Bezzio, Cristina, et al. "Unmet needs of Italian physicians

managing patients with inflammatory bowel disease." Digestive and Liver Disease (2018).
39. Lovell, Rebecca M., and Alexander C. Ford. "Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis." Clinical gastroenterology and hepatology 10.7 (2012): 712-721.
40. Spiegel, Brennan MR, et al. "Is irritable bowel syndrome a diagnosis of exclusion?: a survey of primary care providers, gastroenterologists, and IBS experts." The American journal of gastroenterology 105.4 (2010): 848.
41. Gladman, L. M., and D. A. Gorard. "General practitioner and hospital specialist attitudes to functional gastrointestinal disorders." Alimentary pharmacology & therapeutics 17.5 (2003): 651-654.
42. Olafsdottir, Linda Bjork, et al. "Irritable bowel syndrome: physicians' awareness and patients' experience." World journal of gastroenterology: WJG 18.28 (2012): 3715.
43. Tursi, A., A. Papa, and Silvio Danese. "the pathophysiology and medical management of diverticulosis and diverticular disease of the colon." Alimentary pharmacology & therapeutics 42.6 (2015): 664-684.
44. Ubaldi, Enzo, et al. "Overview on the management of diverticular disease by Italian General Practitioners." Digestive and Liver Disease (2018).
45. Mennini, F. S., et al. "Economic burden of diverticular disease: An observational analysis based on real world data from an Italian region." Digestive and Liver Disease 49.9 (2017): 1003-1008.
46. Spada, Cristiano, et al. "Clinical indications for computed tomographic colonography: European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Gastrointestinal and Abdominal Radiology (ESGAR) guideline." European radiology 25.2 (2015): 331-345.
47. Tursi, Antonio, et al. "Faecal calprotectin in colonic diverticular disease: a case–control study." International journal of colorectal disease 24.1 (2009): 49-55.
48. Tursi, Antonio, et al. "Increased faecal calprotectin predicts recurrence of colonic diverticulitis." International journal of colorectal disease 29.8 (2014): 931-935.
49. Cuomo, Rosario, et al. "Italian consensus conference for colonic diverticulosis and diverticular disease." United European gastroenterology journal 2.5 (2014): 413-442.
50. De Bastiani, Rudi, et al. "The management of patients with diverticulosis and diverticular disease in primary care: an online survey among Italian general pratictioners." Journal of clinical gastroenterology 50 (2016): S89-S92.
51. Haggar, Fatima A., and Robin P. Boushey. "Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors." Clinics in colon and rectal surgery 22.4 (2009): 191.
52. Wolf, Andrew MD, et al. "Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society." CA: a cancer journal for clinicians (2018).
53. Meissner, Helen I., et al. "Patterns of colorectal cancer screening uptake among men and women in the United States." Cancer Epidemiology and Prevention Biomarkers 15.2 (2006): 389-394.
54. Lionis, Christos, and Elena Petelos. "Early detection of colorectal cancer: barriers to screening in the primary care setting." (2011): 589-591.
55. Stroud, Joyce, Chris Felton, and Barbara Spreadbury. "Collaborative colorectal cancer screening: a successful quality improvement initiative." Baylor University Medical Center Proceedings. Vol. 16. No. 3. Taylor & Francis, 2003.

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Review

Clinical approach to the patient with acute gastrointestinal bleeding

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Summary. Gastrointestinal bleeding (GIB) is a very common condition at all ages, with high rates of morbidity and mortality, especially in case of acute presentation. The optimal management of acute GIB requires a timely overview of vital signs and clinical presentation to stabilize the patient if necessary and set up the most adequate diagnostic and therapeutic approach, based on the suspected etiology. Endoscopy plays a major role both in diagnosis and treatment of acute GIB, as allows the application of several hemostasis techniques during the diagnostic session, which should preferably be performed within 24 hours from the acute event. The hemostasis technique should be chosen based on type, etiology of the bleeding and the operator preference and expertise. Nevertheless, several challenging cases need the cooperation of radiology especially in the diagnostic phase, and even in the therapeutic phase for those bleedings in which medical and endoscopic techniques have failed. Imaging diagnostic techniques include mainly CT angiography, scintigraphy with labeled erythrocytes and arteriography. This last technique plays also a therapeutic role in case arterial embolization is needed. Only those patients in which the previous techniques have failed, both in diagnosis and treatment, are candidates for emergency surgery. (www.actabiomedica.it)

Key words: gastrointestinal bleeding, hemostasis, endoscopy, videocapsule endoscopy, device-assisted enteroscopy

Background

Gastrointestinal bleeding (GIB) is a very common condition in clinical practice, with an incidence of about 50-150 cases per 100.000 population (1) with high mortality rates up to 5-10% (2, 3). Therefore, it represents a relevant problem for public health, being morbidity and mortality rates still high, despite continue ameliorations in medical and endoscopic treatment (4). Even though prevalent in adults, gastrointestinal bleeding may present at any age, with an incidence around 6% (5) and highest mortality rates associated with GI bleeding especially in cases with intestinal perforation (8.7%) and esophageal perforation (8.4%) in pediatric age (6).

Overall, gastrointestinal bleeding may have a wide variety of clinical presentations, with different signs, symptoms and severity, therefore a timely and precise diagnostic and therapeutic approach is mandatory to optimize the patient's management minimizing the risk of complications.

Gastrointestinal bleedings can be divided in upper GIB (UGIB) and lower GIB (LGIB) based on the location, which can be proximal or distal to the liga-

ment of Treitz. Among LGIBs, those located in the small intestine have shown to be separated entities from colonic bleeding, in terms of etiology, and accessibility and can be defined middle GIB (MGIB) (7).

Moreover, GIB can be defined acute if as being of recent duration (arbitrarily less than 3 days) and might cause instability of vital signs, anemia and/or the need for blood transfusion, or chronic in case the blood loss lasts for several days with an intermittent and slow evolution (7). Besides, GIB is defined obscure in case the bleeding of unknown origin that persists or recurs after negative findings on initial evaluation using bidirectional endoscopy (5).

The aim of the present review is to focus on acute GIB with a practical clinical approach.

Initial evaluation

Acute GIB may present as a clinical emergency, therefore priority is represented by vital signs evaluations, respiratory and circulatory function with hemodynamic resuscitation if necessary (8). Firstly, ventilation must be guaranteed either with non-invasive (aspiration of secretions, blood or vomit) or invasive methods (oro-tracheal intubation, cricothyrotomy or tracheotomy) to protect the patient against aspiration pneumonia. In parallel, the eventual status of hemorrhagic shock must be checked, with the evaluation of blood pressure, temperature, cardiac and respiratory frequency. Furthermore a venous access must be prepared to adequately provide for fluids and/or blood transfusion to reach a hemoglobin concentration of approximately 7 to 8 g/dL, administer eventual medications and to take blood samples (7, 8). Early intensive hemodynamic resuscitation of patients with acute GIB has been shown to significantly decrease mortality (9). Nevertheless, aggressive resuscitation with blood products and crystalloid should be avoided as it theoretically can increase portal pressures, leading to increased risk of rebleeding and mortality (8).

Hypovolemia and the grade of severity of anemia present with recognizable signs. In case of mild hypovolemia (loss <15% of the total blood volume) the patient presents with tachycardia, tachypnea, pallor, low temperature and augmented capillary refill time. In case of moderate and severe hypovolemia the patient presents with orthostatic hypotension (orthostatic blood pressure drop >10 mmHg), central hypoperfusion signs including lethargy and coma, oliguria and hyperlactacidemia (9).

History and clinical examination

Once the patient is stabilized, an accurate history must be made with the aim to identify specific signs of gastrointestinal bleeding and other conditions predisposing to hemorrhage. Among the most typical signs of GIB we recognize hematemesis, melena and hematochezia.

Hematemesis consists in the emission of blood in concomitance with vomit; blood can be either bright red or brown, based on the length of permanence in contact with chloridric acid in the stomach. Melena consists in the passage of dark tarry stools with characteristic smell due to the transformation of hemoglobin into hematin by intestinal microbiome and digestive enzymes; melena may present in case of upper, lower GIB or middle GIB, even though it is a manifestation of distal lower GIB only if the transit is very prolonged (paralytic ileus) (7). Hematochezia consists in the emission of bright red during evacuation, while proctorrhage is the passage of bright red independently from evacuations. Hematochezia and proctorrhage are more typical of LGIBs from left colon, rectum of anus, although rarely the may present in case of UGIB due to accelerated transit and/or severe bleeding (7, 10). Clinical evaluation should be also focused on conditions predisposing to hemorrhage. Firstly, localization of bleeding other than the gastrointestinal tract should be excluded, such as nasal, pharyngeal, laryngeal and bleeding from the respiratory tract, which can mimic GIB due to the emission of swallowed blood from these areas. Hepatic disease as a possible cause of portal hypertension and coagulopathy should be investigated. Moreover, accurate medication history should be carried out, with attention to the assumption of anticoagulants, antiplatelets, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) or corticosteroids (4). Coagulopathy (defined as an international normalized ratio of prothrombin time >1.5) underlying GIB is a

frequent and adverse prognostic factor and can be associated to thrombocytopenia (<50,000 platelets/μl). They should be treated with fresh frozen plasma and platelet transfusion respectively (8). Anyway, the treatment of coagulopathy is not yet precisely established, both with regards to the INR threshold which should be reached (1.5-1.8), and to the optimal transfusion which should be administered (fresh frozen plasma, vitamin K to reverse AVK drugs, prothrombin complex) (7, 8). Also volume replacement presents several therapeutic options, remaining the preference of crystalloids over colloids a matter of debate (7). An accurate clinical examination should be also directed to research for signs pathognomonic of underlying diseases e.g. anal lesions could suggest the presence of Crohn disease, or the typical peroral pigmentation could be suggestive for Peutz-Jeghers syndrome. Moreover, clinical examination could highlight eventual painful regions to better direct the consequent diagnostic approach, which should be always directed based on the suspected underlying cause.

Upper acute GI bleeding

Upper GIB can be divided into variceal and non-variceal bleeding. The first category is consequent to portal hypertension and formation of esophageal and gastric varices, while the second one is comprehensive of all other possible causes of bleeding. Details are shown in Table 1.

In accordance to US registries, peptic ulcer is the most frequent cause of UGIB, representing up to 27-40% of cases in adult population (11). Peptic ulcer is frequently associated to Helicobacter pylori infection, whose prevalence is still high among western countries populations up to 22-48% and eradication rates not yet satisfactorily (12, 13). Duodenal ulcers are usually more frequent than gastric ulcers, even though the bleeding risk is comparable and consequent to an arteriolar erosion at the base of the ulcer (11). Risk factors for bleeding peptic ulcer due to Helicobacter pylori infection include NSAIDs use, alcohol intake and renal failure (14). NSAIDs may cause gastric and duodenal

Table 1. Main etiologies of acute upper gastrointestinal bleeding

Upper gastrointestinal bleeding: Main etiologies		
Variceal	Non-variceal	
	Primary	Secondary
- Rupture or bleeding of esophageal varices	- Mallory-Weiss Syndrome	- Gastric or duodenal ulcer (e.g. Helicobacter pylori ulcer)
- Rupture or bleeding of gastric varices	- Boerhaave Syndrome	
- Hypertensive gastropathy (GAVE)	- Peptic esophagitis	- Gastritis due to drugs (e.g. NSAIDs)
	- Esophageal benign or e malignant tumors	- Gastritis due to caustic ingestion
	- Gastric or duodenal idiopathic ulcer	- Post-mucosectomy/submucosectomy bleeding
	- Gastric benign or e malignant tumors	- Hemobilia post ERCP
	- Angiodysplasias	- Anastomotic bleeding
	- Rendu-Osler-Weber Syndrome	
	- Aorto-enteric fistulas	
	- Dieulafoy lesion	

ulcers independently from other predisposing factors, by inhibiting COX-mediated prostaglandins synthesis, which are well known protective factors for the gastrointestinal mucosa. It is esteemed that daily use of NSAIDs can increase the risk of developing duodenal ulcer up to 40 times (5). Among bleeding lesions associated to episodes of vomit, Mallory-Weiss Syndrome and Boerhaave Syndrome are described. The first one consists in a linear lesion of the gastro-esophageal junction mucosa and represents around 15% of cases of UGIB, while the second one consists in a transmural lesion and is quite rare. Dieulafoy lesion is a vascular anomaly, characterized by the presence of a tortuous artery with augmented diameter, located in the submucosal layer of the gastrointestinal tract. This clinical condition is rare, with an incidence of 5% for all causes of GIB.

More rare causes of UGIB include aorto-enteric fistula, due to the erosion of the aortic wall which flows into the gastrointestinal lumen; the most frequently interested area is the II-III duodenal tract. Angiodysplasia of the upper GI tract represent 2-4% of cases of UGIB and are consequent to vascular abnormalities and enlargement of mucosal and submucosal vessels (15). Among iatrogenic UGIB are of note post-mucosectomy or post-submucosectomy bleedings. This complication can occur in up to 3.7% of cases and should be always considered particularly after asportation of large lesions >2cm of diameter, and in patients under antiplatelet or anticoagulant treatment (16).

Anastomotic bleeding after major surgery of the gastrointestinal tract is a rare but potentially life-threatening complication, occurring in up to 2% of cases (17).

Lower and middle acute GI bleeding

Although a patient presenting with hematochezia is strongly suspected for having a LGIB, often it is difficult to predict and understand location, etiology and severity of the bleeding at the moment of clinical presentation. A variable proportion from 10% to 20% of patients with suspected LGIB, result having an upper or middle source of bleeding and in 10% of cases the source remains unidentified. Lower GI bleeding represents around 20-30% of all GIB. Annual incidence in USA is esteemed to be around 20-27 cases per 100.000 populations, while in Europe it is esteemed to be of about 9 cases per 100.000 populations (18). Main etiologies are shown in Table 2.

As for UGIB, the causes of LGIB are numerous and can vary greatly in terms of severity, mortality and population more frequently interested. Recent prevalence data show that the most frequent cause of acute LGIB is diverticular bleeding (30-65% of cases), followed by bleeding angiodysplasias (4-15% of cases), hemorroidal bleeding (4-12%), ischemic colitis (4-11%), inflammatory colitis including Inflammatory Bowel Diseases (IBD) (3-15%), polyps and umoral bleeding (2-11%), post mucosectomy/submucosectomy (2-7%), rectal ulcer (0-8%) (19).

Furthermore, an infectious colitis should always be excluded in case of acute diarrhea mixed with blood. The most common etiologic agents are Salmonella, Shigella, Campylobacter, Yersinia enterocolitica, Clostridium difficile, Escherichia Coli (0157: H7), Entamoeba Histolitica and should be searched on stool cultures. Also for LGIBs and middle GIBs, NSAIDs play a major role in causing hemorrhage, as their mechanism of action can provoke ulcers throughout the whole gastrointestinal tract, in particular, NSAIDs assumption is related to bleeding colonic diverticula (19, 20). Ischemic colitis is the etiology in 9–24% of all patients hospitalized for acute lower gastrointestinal bleeding (21). It is rare in children with CI are only rarely reported, but CI occurs in adults of all ages

Table 2. Main etiologies of acute lower and middle gastrointestinal bleeding

Lower and middle gastrointestinal bleedings: Main etiologies
- Complicated diverticulosis
- Angiodysplasias
- Ischemic colitis
- Inflammatory Bowel Diseases
- Benign and malignant tumors
- Post mucosectomy and submucosectomy bleeding
- Solitary Rectal ulcer
- Dieulafoy lesion
- Hemorrhagic Enterocolitis (e.g. infectious, NSAIDs induced)
- Vasculitis (e.g. Schonlein-Henoch purpura)
- Meckel diverticulum

and increases with age, especially after the age of 49 years. Ischemic colitis is consequent to alterations in the systemic or mesenteric circulation, even though it is believed that local hypoperfusion and reperfusion is the main cause of the injury (21).

Of all the sources of GI bleeding, only a small percentage (5%) is attributed to small-bowel sources. Among the main etiologies of middle GIB Angiodysplasias of the small bowel account for 20% to 30% of small-bowel bleeding and are more frequent in older patients. Small-bowel tumors (eg, GI stromal tumors, carcinoid tumors, lymphomas, and adenocarcinomas) should also be considered, as they can present with small-bowel bleeding in both younger and older patients (22).

Diagnosis of acute GIB

Diagnostic endoscopy

The diagnostic gold standard of GIB is represented by endoscopy, which should be performed within 12-24 hours from the event, to optimize the management of the patient, not only providing a diagnosis, but also permitting hemostasis at the same time (8). The correct timing of endoscopy is of paramount importance to improve patient's outcomes, including hospital stay and the assessment of the risk of rebleeding (8). Based on signs, the diagnostic approach is started either by esophagogastroduodenoscopy (EGDS) or colonoscopy. All endoscopic procedures should be performed only once the patient is stabilized, and with a continuous monitoring of ECG and vital parameters. In case of UGIB an EGDS should be promptly performed, to allow direct visualization of gastrointestinal mucosa until distal duodenum. With regards to the assessment of rebleeding risk, in case a non-variceal etiology is individuated, it is recommended to apply the Forrest classification, which aims to identify patients at risk of persistent ulcer bleeding, rebleeding and mortality. Forrest classification is defined as follows: FIa spurting hemorrhage, FIb oozing hemorrhage, FIIa nonbleeding visible vessel, FIIb an adherent clot, FIIc flat pigmented spot, and FIII clean base ulcer (23). In case a variceal bleeding is identified, endoscopy allows a morphologic evaluation and localization of varices, which is necessary to set up a therapeutic decision and/or a follow up (24).

Most importantly, EGDS not only allows a prompt and precise identification of the bleeding source proximal to the ligament of Treitz, but also allows timely hemostasis (see paragraph "endoscopic therapy"). Patients presenting with hematochezia and concurrent hemodynamic instability should be firstly evaluated by EGDS to exclude an upper gastrointestinal bleeding source. Otherwise, ileo-colonoscopy is recommended as the first step in the evaluation of acute LGIB, being the diagnostic yield high up to 89–97% (7). The optimal timing of ileo-colonoscopy after initial presentation ranges from 12 h to 48 hours. As well as EGDS, colonoscopy can determine the source and type of bleeding, and helps identifying patients with ongoing bleeding or those who are at high risk of rebleeding, moreover, allows endoscopic hemostasis if necessary. Unlikely EGDS, ileo-colonoscopy requires thorough cleansing of the colon even in acute LGIBs, to improve sensitivity and safety of the procedure by decreasing the risk of perforation. Although in urgent procedures it is not always possible, an optimal purge of the colon consists in the assumption of 3–6 litres of a polyethylene glycol-based solution, anyway patients generally tolerate consumption of 1-2 l per hour (7). In case of negative upper and lower endoscopy and presence of GIB, the small bowel should be investigated. Usually, the exploration of the small intestine is elective and performed by using firstly Video Capsule Endoscopy (VCE), then by performing device-assisted enteroscopy (DAE) in case an operative endoscopic intervention is needed (22). This last technique, which encompasses Balloon-assisted enteroscopy (BAE) and Push-enteroscopy, is certainly more complex than VCE, has lower availability among Endoscopic Centers and should be performed in trained tertiary-care centers. In multiple large studies of patients with small-bowel bleeding who underwent BAE, the diagnostic yield ranged from 43% to 81%, and rates of treatment success ranged between 43% and 84% (22).

Imaging

Because of the multitude of pathologic processes that provoke GI bleeding, and its often intermittent na-

ture, imaging can be applied in case of negative upper and lower endoscopy and/or in case of contraindications for endoscopy (25). Computed Tomography (CT) is a readily available imaging method in the emergency departments of most hospitals. CT should always be applied with intravenous contrast, especially in case of GI bleeding, when contrast material extravasation can be revealed with rates of less than 0.4 mL/min. However, contrast-enhanced CT has limited utility in cases of intermittent hemorrhage and involves intravenous contrast material and a relatively high radiation dose, therefore this technique should always be used in case of active hemorrhage: studies demonstrate that the CT sensitivity reaches rates of 91%-92% in case of active hemorrhage, while shows lower values in case of obscure GIB, down to 45%-47% (25). Visceral arteriography is also used to typically identify active bleeding, when the rate is at least 0.5-1 ml/min. The specificity of this procedure is 100%, but sensitivity varies from 47% with acute LGIB to 30% with recurrent bleeding. Arteriography should be reserved for patients who have massive bleeding that precludes colonoscopy, or for whom endoscopies were negative. visceral angiography has a complication rate of 9.3% (7). Angiography may be also applied to achieve hemostasis by intra-arterial infusion of vasopressin or arterial embolization via the angiographic catheter. Compared to intra-arterial infusion of vasopressin, transcatheter embolization is a more definitive means of controlling hemorrhage. Nevertheless transcatheter embolization presents rate of bowel infarction ranging from 13 to 33%, therefore its use should really follow precise indications and be chosen after failure of other techniques (2). Nuclear scintigraphy is a sensitive method for detecting gastrointestinal bleeding at a rate of 0.1 ml/min. Compared to angiography, the method is more sensitive, but less specific. The technique mainly applies either technetium sulphur colloid or [99Tcm] pertechnetate labeled red blood cells and localizes bleeding only to an area of the abdomen, until the intra luminal blood is moved away by intestinal motility. When scans are positive within 2 h after injection of the labeled erythrocytes, localization is correct in 95–100% of cases, although accuracy decreases to 57–67%. For longer times. Overall, scintigraphy might be useful, especially for recurrent bleeding, when other methods have failed (2, 7).

Endoscopic therapy

Endoscopic hemostasis is a promptly available technique which can be very often applied directly during the diagnostic exploration. Treatment modalities include injection therapy, the use of mechanical devices such as metallic clips and band ligation, application of hemospray and electrocautery therapy.

The choice depends on the site and the features of the bleeding lesion, the clinician's personal experience with the devices, and access to the bleeding site (7). Injection therapy is based on the use of a needle to inject locally a chemical agent. Injection therapy agents include epinephrine and sclerosant agents. Epinephrine, prepared in 1:10.0000 to 1:20.0000 dilutions, is the most commonly employed agent. Side effects due to first-pass metabolism through the liver are usually low (transient tachycardia and hypertension). Epinephrine can be injected into the submucosa and/or directly into the ulcer base. Typically, "4 quadrant injection" in 0.5 to 2 ml aliquots of 1:10.000 epinephrine is performed within 3 mm of the bleeding vessel (1). Sclerosants agents (sodium monrrhuate, sodium tetradecyl sulphate and ethanol) induce localized thrombosis of the bleeding vessel with consequent hemostasis. Sclerosants are mostly used to treat varices and should be used with caution for colonic lesions given the unpredictable depth of penetration through the thin colonic wall. Risks related to injection therapy include increased bleeding, rebleeding, bowel ischemia and perforation. Mechanical therapy is based on the use of devices like clips and band ligation (the last one is mostly used for variceal bleeding), alone or combined with other techniques. Endoscopic clips directly tampon the bleeding without causing tissue damage. Their efficacy has been excellent in non- variceal bleeding. The available clips differ in several features (open and close, clip rotation, disposable or not) with a common minimum channel size (2.8 mm). Their jaw length varies from 9 to 11 mm, making them ideal for lesions between 10 and 15 mm wide. Indications for positioning clips are: bleeding vessel in ulcer base, intractable bleeding after mucosal biopsy or bleeding at the site of polypectomy. If the ulcer base is fibrotic, tissue apposition with clips can be much more difficult. Typically, more than one clip is applied to the bleeding site.

A particular type of clips is represented by the over the scope clips (OTSC) system, (Ovesco, Tübingen, Germany). This device is composed of an application cap, which is mounted onto the distal tip of the endoscope and a connected releasing mechanism, installed on the handle of the scope. Unlike common endoscopic clips, the OTSC is able to compress larger quantities of tissue. The efficacy of this system has been proved for the same indications as standard hemoclips, even though at present its availability is still lower than common clips (26). Band ligation is mostly used in the treatment of esophageal varices, but its use has also been described in the management of Dieulafoy lesions, blue rubber bleb nevus syndrome, Mallory-Weiss, gastric ectasia, duodenal ulcers and treatment of haemorrhoids. In the colon caution must be taken when suctioning the lesion into the friction fit adapter to prevent full thickness entrapment, subsequent necrosis and perforation (5). Hemospray (TC-325) (Cook Medical, USA), a novel proprietary inorganic powder which achieves hemostasis by adhering to the bleeding site, provoking a mechanical tamponade and, by concentrating and activating platelets and coagulation factors, promotes thrombus formation. Hemospray can quickly cover large areas and does not require frontal view or direct contact with the bleeding lesion, although its application alone has not been proven to sufficient to manage profuse hemorrhages. The high rates of both acute hemostasis and recurrent bleeding suggest that Hemospray is probably best used as a temporary bridge toward more definitive therapy (27). Cautery therapy is based on the application of thermal energy to achieve coagulation of the tissue. It acts by denaturing or coagulating proteins and then through the evaporation of tissue water causing atrophy (28). Argon plasma coagulation (APC) is preferred for the treatment of angiodysplastic lesions as artero-venous malformations, bleeding ulcer and ablation of adenomatous tissue. It needs a non-contact device that uses argon gas. Coagulation is a few millimetres deep and a larger area of tissue can be treated at one time compared to bipolar electrocautery (1). Noncontact and contact coagulation have comparable efficacy for hemostasis, rebleeding, transfusion requirement and need for surgery, moreover are superior to pharmacotherapy alone; a systematic review performed on 49 adults showed that coagulation was superior to injection therapy or pharmacotherapy alone (28).

Surgery

In case GIB cannot clearly be identified and conservative therapies, either endoscopic or therapeutic imaging, have failed, surgery should be considered. Whenever possible, intraoperative endoscopy should be carried out to help clarify and localize the bleeding source. Directed segmental resection is the treatment of choice because of its low morbidity, mortality (about 4%) and rebleeding rate (about 6%) (7, 29).

Conclusions

Gastrointestinal bleeding may be a life-threatening condition. A well structures emergency treatment and timely diagnostic approach based on suspected cause of bleeding can significantly reduce mortality rates in these patients. Endoscopy plays a major role both in diagnosis and management of bleeding throughout the entire gastrointestinal tract. Nevertheless, cooperation with radiologists and surgeons is essential to cope with challenging clinical cases with the aim of a general optimization of acute gastrointestinal bleeding.

References

1. Biecker E. Diagnosis and therapy of non-variceal upper gastrointestinal bleeding. World J Gastrointest Pharmacol Ther 2015; 6(4): 172-82.
2. Farrell JJ, Friedman LS. Gastrointestinal bleeding in the elderly. Gastroenterol Clin North Am 2001; 30(2): 377-407, viii.
3. Lanas A, Garcia-Rodriguez LA, Polo-Tomas M, Ponce M, Alonso-Abreu I, Perez-Aisa MA, et al. Time trends and impact of upper and lower gastrointestinal bleeding and perforation in clinical practice. Am J Gastroenterol 2009; 104(7): 1633-41.
4. Kim BS, Li BT, Engel A, Samra JS, Clarke S, Norton ID, et al. Diagnosis of gastrointestinal bleeding: A practical guide for clinicians. World J Gastrointest Pathophysiol 2014; 5(4): 467-78.
5. Romano C, Oliva S, Martellossi S, Miele E, Arrigo S, Graziani MG, et al. Pediatric gastrointestinal bleeding: Perspectives from the Italian Society of Pediatric Gastroenterology. World J Gastroenterol 2017; 23(8): 1328-37.

6. Pant C, Sankararaman S, Deshpande A, Olyaee M, Anderson MP, Sferra TJ. Gastrointestinal bleeding in hospitalized children in the United States. Curr Med Res Opin 2014; 30(6): 1065-9.
7. Barnert J, Messmann H. Diagnosis and management of lower gastrointestinal bleeding. Nat Rev Gastroenterol Hepatol 2009; 6(11): 637-46.
8. Gralnek IM, Dumonceau JM, Kuipers EJ, Lanas A, Sanders DS, Kurien M, et al. Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2015; 47(10): a1-46.
9. Baradarian R, Ramdhaney S, Chapalamadugu R, Skoczylas L, Wang K, Rivilis S, et al. Early intensive resuscitation of patients with upper gastrointestinal bleeding decreases mortality. Am J Gastroenterol 2004; 99(4): 619-22.
10. Singhi S, Jain P, Jayashree M, Lal S. Approach to a child with upper gastrointestinal bleeding. Indian J Pediatr 2013; 80(4): 326-33.
11. Stabile BE, Stamos MJ. Surgical management of gastrointestinal bleeding. Gastroenterol Clin North Am 2000; 29(1): 189-222.
12. Hu Y, Zhu Y, Lu NH. Novel and Effective Therapeutic Regimens for Helicobacter pylori in an Era of Increasing Antibiotic Resistance. Front Cell Infect Microbiol 2017; 7: 168.
13. Manfredi M, Bizzarri B, Sacchero RI, Maccari S, Calabrese L, Fabbian F, et al. Helicobacter pylori infection in clinical practice: probiotics and a combination of probiotics + lactoferrin improve compliance, but not eradication, in sequential therapy. Helicobacter 2012; 17(4): 254-63.
14. Cheung FK, Lau JY. Management of massive peptic ulcer bleeding. Gastroenterol Clin North Am 2009; 38(2): 231-43.
15. Boonpongmanee S, Fleischer DE, Pezzullo JC, Collier K, Mayoral W, Al-Kawas F, et al. The frequency of peptic ulcer as a cause of upper-GI bleeding is exaggerated. Gastrointest Endosc 2004; 59(7): 788-94.
16. Albeniz E, Fraile M, Ibanez B, Alonso-Aguirre P, Martinez-Ares D, Soto S, et al. A Scoring System to Determine Risk of Delayed Bleeding After Endoscopic Mucosal Resection of Large Colorectal Lesions. Clin Gastroenterol Hepatol 2016; 14(8): 1140-7.
17. Kim KH, Kim MC, Jung GJ, Jang JS, Choi SR. Endoscopic treatment and risk factors of postoperative anastomotic bleeding after gastrectomy for gastric cancer. Int J Surg 2012; 10(10): 593-7.
18. Committee ASoP, Pasha SF, Shergill A, Acosta RD, Chandrasekhara V, Chathadi KV, et al. The role of endoscopy in the patient with lower GI bleeding. Gastrointest Endosc 2014; 79(6): 875-85.
19. Strate LL, Naumann CR. The role of colonoscopy and radiological procedures in the management of acute lower intestinal bleeding. Clin Gastroenterol Hepatol 2010; 8(4): 333-43; quiz e44.
20. de Martino M, Chiarugi A, Boner A, Montini G, De' Angelis GL. Working Towards an Appropriate Use of Ibuprofen in Children: An Evidence-Based Appraisal. Drugs 2017; 77(12): 1295-311.
21. Brandt LJ, Feuerstadt P, Longstreth GF, Boley SJ, American College of G. ACG clinical guideline: epidemiology, risk factors, patterns of presentation, diagnosis, and management of colon ischemia (CI). Am J Gastroenterol 2015; 110(1): 18-44; quiz 5.
22. Committee ASoP, Gurudu SR, Bruining DH, Acosta RD, Eloubeidi MA, Faulx AL, et al. The role of endoscopy in the management of suspected small-bowel bleeding. Gastrointest Endosc 2017; 85(1): 22-31.
23. Gralnek IM, Barkun AN, Bardou M. Management of acute bleeding from a peptic ulcer. N Engl J Med 2008; 359(9): 928-37.
24. Hwang JH, Shergill AK, Acosta RD, Chandrasekhara V, Chathadi KV, Decker GA, et al. The role of endoscopy in the management of variceal hemorrhage. Gastrointest Endosc 2014; 80(2): 221-7.
25. Geffroy Y, Rodallec MH, Boulay-Coletta I, Julles MC, Ridereau-Zins C, Zins M. Multidetector CT angiography in acute gastrointestinal bleeding: why, when, and how. Radiographics 2011; 31(3): E35-46.
26. Monkemuller K, Peter S, Toshniwal J, Popa D, Zabielski M, Stahl RD, et al. Multipurpose use of the 'bear claw' (over-the-scope-clip system) to treat endoluminal gastrointestinal disorders. Dig Endosc 2014; 26(3): 350-7.
27. Yau AH, Ou G, Galorport C, Amar J, Bressler B, Donnellan F, et al. Safety and efficacy of Hemospray(R) in upper gastrointestinal bleeding. Can J Gastroenterol Hepatol 2014; 28(2): 72-6.
28. Rey JW, Fischbach A, Teubner D, Dieroff M, Heuberger D, Nguyen-Tat M, et al. Acute gastrointestinal bleeding - a new approach to clinical and endoscopic management. Eur J Gastroenterol Hepatol 2015; 27(5): 483-91.
29. Quak SH, Prabhakaran K. Colonoscopy in children with bleeding per rectum. Singapore Med J 1990; 31(5): 454-6.

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Review

Eosinophilic esophagitis in pediatric age, state of the art and review of the literature

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Summary. Eosinophilic esophagitis (EoE) is a chronic immune-mediated relapsing disease caused by eosinophilic infiltration of the esophageal mucosa which is normally lacking these cells. EoE belongs to the group of the so called Eosinophilic Gastrointestinal Disorders (EGIDs). From a rare and unusual disease, EoE has become an emerging entity and in recent years its incidence and prevalence have increased all over the world, also in children. The pathogenesis is very complex and still not completely clear. Esophageal disfunction symptoms (e.g. dysphagia and food impaction) represent the typical manifestation of EoE and this condition could be difficult to recognize, more in pediatric age than in adults. Moreover, symptoms can often overlap with those of gastro-esophageal reflux disease (GERD), leading to a delayed diagnosis. EoE is often related to atopy and an allergological evaluation is recommended. Untreated EoE could provoke complications such as strictures, esophageal rings, narrowing of the esophagus. Diagnosis is confirmed by the demonstration in biopsy specimens obtained through upper endoscopy of eosinophilic inflammation (>15 for high powered field) of the esophageal mucosa and other histological features. Other tests could be useful not specifically for the diagnosis, but for the characterization of the subtype of EoE. Since EoE incidence and knowledge about physiopathology and natural history have increased, the goal of the review is to provide some helpful tools for the correct management in pediatric age together with an overview about epidemiology, pathogenesis, clinical, diagnosis and treatment of the disease. (www.actabiomedica.it)

Key words: eosinophilic esophagitis, food impaction, pediatric endoscopy, esophageal biopsy, eosinophils

Introduction

Eosinophilic esophagitis (EoE) is a chronic, antigen-immune inflammatory mediated disease (1) caused by infiltration of eosinophils in the esophageal mucosa (>15 eosinophils/high powered field) in absence of other causes of eosinophilia. It is characterized by esophageal dysfunction symptoms such as dysphagia, food impaction or refusal, even if gastro-esophageal reflux symptoms could be the only one referred (2). EoE is also defined as an atopic inflammatory disease and is sometimes named "asthma of the esophagus" because of shared clinical and pathophysiologic characteristics with asthma (3, 4). The first EoE cases appeared in the 1970s but it was defined as a distinct clinic-pathologic syndrome in the early 1990s. Currently, it is the most prevalent cause of esophagitis after gastro-esophageal reflux disease (GERD). Until two decades ago, it was considered a rare disorder, but its diagnosis surprisingly has increased in the last years, also in children, becoming an epidemiologically relevant disease. The exact incidence and prevalence are difficult to establish, with differences among various geographic regions. Some data show a prevalence rate of 30-90 cases per 100.000 in USA and other countries and an incidence of about 1:2000; actually,

both incidence and prevalence tend to gradually increase all over the world (2, 5). EoE seems to affect predominantly the male gender even if clear reasons of this predominance have not been understood yet; a single nucleotide polymorphism within TSLP gene (thymic stromal lymphopoietin receptor) is considered a probable etiologic mechanism, but further studies are needed. However, males are 3-4 times more commonly affected than females and caucasians are more likely affected than other races. Several studies suggest an important genetic predisposition to EoE although environmental risk factors (gut barrier function, nature and timing of oral antigen or aeroallergen exposure, impaired microbioma after physiologic events such birth) play a crucial role. In addition, the majority of patients with EoE is often affected from one or more atopic disease: asthma, eczema, allergic rhinitis and food allergies (4, 6). Children could have difficulty to report symptoms associated to esophageal dysfunction: at this age, a clinical recognition of signs is important and crucial to guide further investigations, namely and upper endoscopy, which is determinant for a certain diagnosis (7).

Pathogenesis

EoE pathogenesis is complex and not completely clear. The presence of an eosinophilic infiltration into the esophageal mucosa is crucial for diagnosis: this subtype of cells are normally absent in this gastrointestinal district (4, 8). Multiple factors as genetic, immune, environmental as well as damage mucosa and fibrosis mechanisms are involved in the onset of disease. Evidences suggest that EoE is associated with T helper cell-2 (Th2) type immune responses, which are typical of other atopic conditions. In particular, high levels of the Th2 cytokines, interleukin IL-4, IL-5, and IL-13, as well as mast cells, have been found in the esophageal biopsies of EoE patients (8, 9). These cytokines play an important role for the recruitment of eosinophils to the specific site; eosinophils are crucial cells for the remodeling of esophageal tissues. Eosinophilic granule cationic proteins, particularly the major basic protein (MBP) and the elaboration of fibrogenic growth factors are other mechanisms involved in fibrosis (8). The importance of genetic inheritance is shown by several studies: the rate of monozygotic twin concordance of inheritance of the disease is significantly increased in approximately 40% of cases and the risk of EoE is increased in people with first-degree relatives with EoE. Other single candidate genes are supposed to be involved in the pathogenesis (eotaxin-3, filaggrin, TSLP, calpain14) but their specific role remains still unclear. Indeed, several monogenic disorders with incomplete penetrance (e.g. Loeys-Dietz syndrome, Marfan syndrome, Netherton syndrome, etc) have been associated with an increased risk of EoE (4). As stated previously, there is a strong connection between EoE and atopy. Food allergens seem to be the most common triggers of mucosal inflammation in EoE and many studies have examined the benefit of dietary elimination of food allergens for the treatment of EoE (10). The link with environmental allergens is also important. Therefore, identification of EoE patient's aeroallergen sensitivities and appropriate management of allergic rhinitis can be an important step towards the prevention of flares of EoE (5, 11). EoE is substantially defined as a mixed IgE and non-IgE-mediated allergic response both to food and environmental allergens, although current literature describes that a non-IgE mediated mechanism predominate on others (12). Skin prick test (SPT) and atopy patch test (APT) to foods and/or aeroallergens result positive in many patients with EoE (4).

Clinical aspects and diagnosis

The typical onset of EoE in pediatric age occurs in childhood. Nevertheless, it could present at any age, with the type of symptoms depending on the age of presentation (13, 14). Specifically, clinical manifestations of EoE in children can vary depending on their ability to report symptoms (6). Actually, in infants and toddler or younger children, symptoms can be vague and/or ambiguous and includes feeding difficulties which could lead to prolonged mealtime, food refusal, gagging or GERD-like symptoms such as heartburn, regurgitation or vomiting (15, 16) and less commonly, failure to thrive (4). Prevalent symptoms in school aged children and adolescents include dysphagia, food

impaction, and choking/gagging with meals, particularly while eating foods with coarse texture. A careful medical history in children and adolescents with EoE reveals that they have learned to compensate for these symptoms by eating slowly, chewing excessively or taking small bites, drinking excessively with meals, lubricating meals inordinately with sauces, and avoiding specific food consistencies such as meat (or other foods with coarse texture) (17, 18). Adolescents and adults present with dysphagia (which may or not respond to medical treatment) and less frequently with food impaction. Continued dysphagia could be also caused by the formation of esophageal rings and strictures; EoE strictures could in some cases require an endoscopic dilation. However, all possible symptoms related to EoE are not relieved by anti-acid treatment with proton pump inhibitor (PPI) (5), even if sometimes patients with EoE could be asymptomatic and the diagnosis may be incidental during upper endoscopy performed for other indications, since many symptoms overlap with GERD (4). About one third of the patients with endoscopic and clinic features of EoE respond to treatment with PPI in monotherapy and this entity is referred as PPI-responsive esophageal eosinophilia (PPI-REE). It is debated if PPI-REE represents a subtype of EoE or GERD, but latest updates tend to consider it a pattern of EoE (13, 19). Recent advances in the comprehension of this heterogeneous expression of EoE lead to hypothesize a classification in phenotypes of EoE with final implications in care and response to treatment. For instance, some patients may be more prone to develop esophageal strictures whereas others do not. Additionally, some patients may respond to dietary treatment, whereas others continue to have symptoms and inflammation despite limiting specific foods. The clinical characterization of these groups may help understanding pathophysiological mechanisms and guide the therapeutic approach (20, 21). Although IgE serum level is not considered a prominent marker in EoE, a stratification risk on the basis of IgG4 serum level (an immunoglobulin that is thought to be a primary mediator of allergen tolerance but described in other non-atopic diseases) have been recently associated with active EoE. Patients with major serum levels of IgG4 have a stronger association with fibrotic clinical phenotype (22). Diagnostic evaluation for EoE requires several tools, but histological evaluation is essential. Symptoms may lead to suspect the disease, but the diagnosis is confirmed by upper endoscopy with biopsies and evidence of esophageal eosinophilia after other causes of eosinophilia and GERD have been ruled out. Other tests could be helpful depending on cases (6). Radiologic evaluation could be considered to identify focal esophageal strictures, narrowing or ring-like indentations because of its sensitivity and non-invasive approach (23-25) and to rule out the presence of a markedly narrow esophagus in severely symptomatic patients prior to endoscopy. However, barium swallow exposes to ionizing radiations and it does not allow a certain diagnosis compared to endoscopy. Several endoscopic findings are associated to EoE including esophageal edema and rings ("trachealization"), white exudate, longitudinal furrows, esophageal strictures, narrow caliber esophagus and crêpe paper esophagus. Endoscopic findings alone do not reliably establish a diagnosis of EoE. Their value to assess disease activity needs further evaluation but endoscopic reference score (EREFS) is a score system that grades the presence and severity of endoscopic features proved also in children (2, 26, 27). Biopsy specimens from both mid and distal esophagus should be obtained (26) and at least four biopsies are required to obtain adequate sensitivity for detection of EoE (also if 5-6 biopsies are still recommended) (1). The current gold standard for diagnosis of EoE is represented from an eosinophil predominant inflammation of the esophageal epithelium (cut off value of >15 eosinophils/high power field) (15). Additional histologic evaluations include basal cell hyperplasia, dilated intercellular spaces, retepeg elongation, and lamina propria fibrosis; sometimes eosinophilic microabscesses and eosinophil layering of the surface epithelium can be observed (28, 29). Allergy assessment (including patient and family medical history for atopy) is important in pediatric age, even more than in adult patients affected by EoE and is founded on Skin Prick Test (SPT) or blood testing for allergen-specific IgE, especially for patients with IgE-mediated food allergy (30). Allergy tests are discouraged if the patient does not present an history of immediate reactions. APT can be performed to study a non-IgE mediated food allergy, even if the positive predictive value remains poor (31, 32).

Treatment

Untreated EoE is usually associated with persistent symptoms and inflammation, leading to esophageal remodeling resulting in stricture formation and functional abnormalities (2) that sometimes require emergency interventions. Therapy is necessary to resolve symptoms, to induce remission and to prevent potential complications (fibrosis and esophageal strictures) (5). Strategies for treatment include: avoidance of triggered foods through dietary elimination, pharmacological therapy and mechanical dilations of the esophagus, if needed (33).

Dietary elimination

Dietary elimination (DE) can be used to induce clinical and histological remission in EoE. There are several forms of DE in EoE: elemental diet (ED), empiric dietary restrictions (EDR) and targeted dietary restrictions (TDR) based on allergy testing. ED consists in the removal of all sources of potentially allergenic protein from the patient's diet through the use of an amino acid-based formula for nutritional support (4, 5). ED achieves a high rate of clinical and histological improvement in children with EoE (>90%) but symptoms often recur after normalization of the patient's diet (31, 34). Because of the low compliance due to unpalatable taste of amino-acidic formulas, ED should be employed after considering target and empiric dietary restrictions. TDR is based on the elimination of foods resulted positive at SPT and APT and has a success rate of about 70% (although lower in adults) (35). Instead, EDR consists in the elimination of the most common allergenic foods when both SPT and APT results are negative. The first trial performed by many allergologists is cow's milk elimination, but other available strategies are the six-food elimination (dairy, eggs, wheat, soy, peanuts/tree nuts, and fish/shellfish) or four-food elimination diet (dairy, eggs, wheat, and legumes, as studies suggest tree nuts, fish, and shellfish are less commonly implicated in EoE) (36, 37, 38). EDR presents a success rate of approximately 70% (40). Open questions on DE regard the duration of the avoidance of specific foods and the correct timing for the reintroduction. Moreover, clearer indications on the management of follow-up (how often to perform endoscopy with biopsy) during the diet and the identification of potential risks of nutritional lacks are awaited.

Pharmacological treatment

Since the characterization of PPI-REE as a new entity, PPI administration is considered the first therapeutic approach for patients with EoE and it seems to induce clinical and histological remission in over 50% of cases (40, 41). In vitro, PPI seem to have an anti-inflammatory effect independently from their ability to inhibit acid production (42, 43). Treatment with corticosteroids is also an effective therapeutic option. Despite its effectiveness, systemic (oral) corticosteroids administration is associated to important side effects related to a prolonged use (44), while topical corticosteroids are confirmed to be safe and effective. Both swallowed fluticasone propionate (500-1000 μ/die) and oral viscous budesonide (1000-2000 μ/die) have been shown to be effective in EoE (19, 26). A recent meta-analysis confirmed its effectiveness in the treatment of EoE, with minimal adverse effects and no evidence of adrenal suppression (45). Patients using topical corticosteroids for EoE should be advised not to eat, drink, or rinse their mouth for 30 min after using the medication. After 6-8 weeks of topical therapy, patients should repeat endoscopy to ensure the histologic response to therapy. If a therapeutic response is confirmed, treatment should be reduced to the lowest effective dose with appropriate follow up. It is important to note that symptoms and pathological changes often recur after discontinuation of topical corticosteroids. Therefore, many patients with EoE require long-term treatment. Other tested treatments are montelukast (the leukotriene receptor antagonist) and immunosuppressive agents (azathioprine and 6-mercaptopurine) with low success rate (46, 47, 48). Biologics drugs based on use monoclonal antibodies against specific targets of the disease (IL-4, IL-5, IL-13 and IgE) have been found to be a promising option for EoE patients. While anti-IL-5 and anti-IgE monoclonal antibodies have presented controversial results in term of effec-

tiveness (49, 50, 51), others like anti-IL-13 and specifically anti-IL-4 monoclonal antibodies (dupilumab) appear the most promising novel therapeutic options for the disease, but further studied are needed to drive final conclusions (52, 53). Endoscopic dilations of EoE are required just in severely symptomatic cases or when medical treatment is not sufficient to quickly resolve symptoms (2). Dilation techniques may vary depending on age, severity of strictures and other features.

Conclusions

EoE is an emerging disease with a complex and not completely understood pathogenesis. Treatment options will continuously increase as soon as new pharmacological targets will be available. All physicians including pediatricians should be familiar with this clinical entity and manage it in cooperation with other specialists such as gastroenterologists and allergologists.

References

1. Papadopoulou A, Koletzko S, Heuschkel R, et al. Management Guidelines of Eosinophilic Esophagitis in Childhood. JPGN 2014; 58: 107-118.
2. Lucendo AJ, Molina-Infante J, Arias A. Guidelines on eosinophilic esophagitis:evidence-based statements and recommendations for diagnosis and management in children and adults. United European Gastroenterology Journal 2017; 5(3): 335-358.
3. Arora AS, Yamazaki K. Eosinophilic esophagitis: asthma of the esophagus? Clin Gastroenterol Hepatol 2004; 29(7): 523-30.
4. Carr S, Chan ES, Watson W. Eosinophilic esophagitis. Allergy Asthma Clin Immunol 2018; 14(Suppl 2): 58.
5. Ruffner MA, Spergel JM. Eosinophilic Esophagitis in Children. Curr Allergy Asthma Rep 2017; 17: 54.
6. Lee K, Furuta Glenn T, Nguyen N. Eosinophilic Esophagitis Is an Underlying Cause for Gastrointestinal Concerns in Children. Frontiers in Pediatrics 2018; 6: 1-7.
7. Straumann A, Aceves SS, Blanchard C. Pediatric and adult eosinophilic esophagitis: similarities and differences. Allergy 2012; 67: 477-490.
8. D'Alessandro A, Esposito D, Pesce M, Cuomo R, De Palma GD, Sarnelli G. Eosinophilic esophagitis: from pathophysiology to treatment. World J Gastrointest Pathophysiol 2015; 6(4): 150-8.
9. Furuta GT, Katzka DA. Eosinophilic esophagitis. N Engl J Med 2015; 373(17): 1640-8.
10. Kagalwalla AF, Shah A, Li BUK, Sentongo TA, Ritz S, Manuel-Rubio M, et al. Identification of specific foods responsible for inflammation in children with eosinophilic esophagitis successfully treated with empiric elimination diet. J Pediatr Gastroenterol Nutr 2011; 53: 145-9.
11. Ram G, Lee J, Ott M, Brown-Whitehorn TF, Cianferoni A, Shuker M, et al. Seasonal exacerbation of esophageal eosinophilia in children with eosinophilic esophagitis and allergic rhinitis. Ann AllergyAsthma Immunol 2015; 115: 224-228.e
12. Simon D, Cianferoni A, Spergel JM, Aceves S, Holbreich M, Venter C, Rothenberg ME, Terreehorst I, Muraro A, Lucendo AJ, Schoepfer A, Straumann A, Simon HU. Eosinophilic esophagitis is characterized by a non-IgE-mediated food hypersensitivity. Allergy 2016; 71(5): 611-20.
13. Franciosi JP, Liacouras CA. Eosinophilic esophagitis. Immunol Allergy Clin North Am 2009; 29(1): 19-27.
14. Miehlke S. Clinical features of eosinophilic esophagitis in children and adults. Best Pract Res Clin Gastroenterol 2015; 29(5): 739-48.
15. Furuta GT, Liacouras CA, Collins MH, Gupta SK, Justinich C, Putnam PE, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment.Gastroenterology 2007; 133: 1342-63.
16. Liacouras CA, Spergel J, Gober LM. Eosinophilic esophagitis: clinical presentation in children. Gastroenterol Clin North Am 2014; 43: 219-29.
17. Putman PE. Evaluation of the child who has eosinophilic esophagitis.Immunol Allergy Clin North Am 2009; 29(1): 1-10.
18. Putman PE. Eosinophilic esophagitis in children: clinical manifestations.Gastrointest Endosc Clin North Am 2008; 18(1): 11-23.
19. Chen JW, Kao JY. Eosinophilic esophagitis: update on management and controversies. BMJ 2017; 359: j4482.
20. Dellon ES, Kim HP, Sperry SL, Rybnicek DA, Woosley JT, Shaheen NJ. A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. Gastrointest Endosc 2014; 79: 577-85.e4.
21. Singla MB, Chehade M, Brizuela D, Maydonovitch CL, Chen YJ, Riffle ME, et al. Early Comparison of inflammatory vs. fibrostenotic phenotype in eosinophilic esophagitis in a multicenter longitudinal study. Clin Transl Gastroenterol 2015; 6: e132.
22. Ferguson AE, and Fulkerson PC. Eosinophilic esophagitis: Time to classify into endotypes? J Allergy Clin Immunol 2018; 142: 71-2.
23. Feczko PJ, Halpert RD, Zonca M. Radiographic abnormalities in eosinophilic esophagitis. Gastrointest Radiol 1985; 10: 321-4.
24. White SB, Levine MS, Rubesin SE, Spencer GS, Katzka DA, Laufer I. The small-caliber esophagus: radiographic sign of idiopathic eosinophilic esophagitis. Radiology 2010; 256: 127-34.
25. Menard-Katcher C, Swerdlow MP, Mehta P, Furuta GT,

Fenton LZ. Contribution of esophagram to the evaluation of complicated pediatric eosinophilic esophagitis. J Pediatr Gastroenterol Nutr 2015; 61: 541-6.
26. Dellon ES, Gonsalves N, Hirano I, Furuta GT, Liacouras CA, Katzka DA, et al. ACG clinical guideline: evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). Am J Gastroenterol 2013; 108: 679-92.
27. Wechsler JB, Bolton S, Amsden K, Wershil BK, Hirano I, Kagalwalla AF. Eosinophilic esophagitis reference score accurately identifies disease activity and treatment effects in children. Clin Gastroenterol Hepatol 2017.
28. Collins MH. Histopathologic features of eosinophilic esophagitis and eosinophilic gastrointestinal diseases. Gastroenterol Clin. North Am 2014; 43: 257-68.
29. CollinsMH,Martin LJ, Alexander ES, Boyd JT, Sheridan R, He H, et al. Newly developed and validated eosinophilic esophagitis histology scoring systemand evidence that it outperforms peak eosinophil count for disease diagnosis and monitoring. Dis Esophagus 2016; 30: 1-8.
30. Spergel JM. An allergist's perspective to the evaluation of eosinophilic esophagitis. Best Pract Res Clin Gastroenterol 2015; 29(5): 771-81.
31. Spergel JM, Andrews T, Brown-Whitehorn TF, Beausoleil JL, Liacouras CA. Treatment of eosinophilic esophagitis with specific food elimination diet directed by a combination of skin prick and patch tests. Ann Allergy Asthma Immunol 2005; 95(4): 336-43.
32. Ballmer-Weber BK. Value of allergy tests for the diagnosis of food allergy. Dig Dis 2014; 32(1-2): 84-8.
33. Singla MB, Moawad FJ. An overview of the diagnosis and management of eosinophilic esophagitis. Clin Transl Gastroenterol 2016; 7(3): e155.
34. Markowitz JE, Spergel JM, Ruchelli E, Liacouras CA. Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents. Am J Gastroenterol 2003; 98(4): 777-82.
35. Warners MJ, Vlieg-Boerstra BJ, Bredenoord AJ. Elimination and elemental diet therapy in eosinophilic oesophagitis. Best Pract Res Clin Gastroenterol 2015; 29(5): 793-803.
36. Kagalwalla AF, Amsden K, Shah A, Ritz S, Manuel-Rubio M, Dunne K, Nelson SP, Wershil BK, Melin-Aldana H. Cow's milk elimination: a novel dietary approach to treat eosinophilic esophagitis. J Pediatr Gastroenterol Nutr 2012; 55(6): 711-6.
37. Kruszewski PG, Russo JM, Franciosi JP, Varni JW, Platts-Mills TA, Erwin EA. Prospective, comparative effectiveness trial of cow's milk elimination and swallowed fluticasone for pediatric eosinophilic esophagitis. Dis Esophagus 2016; 29(4): 377-84.
3. Kagalwalla AF, Sentongo TA, Ritz S, Hess T, Nelson SP, Emerick KM, Melin-Aldana H, Li BU. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. Clin Gastroenterol Hepatol 2006; 4(9): 1097-102.
39. Molina-Infante J, Arias A, Barrio J, Rodríguez-Sánchez J, Sanchez-Cazalilla M, Lucendo AJ. Four-food group elimination diet for adult eosinophilic esophagitis: a prospective multicenter study. J Allergy Clin Immunol 2014; 134(5): 1093-9.
40. Liacouras CA, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol 2011; 128: 3-20.e6. quiz: 1-2.
41. Lucendo AJ, Arias A, Molina-Infante J. Efficacy of proton pump inhibitor drugs for inducing clinical and histologic remission in patients with symptomatic esophageal eosinophilia: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2016; 14: 13-22.e1.
42. Zhang X, Cheng E, Huo X, Yu C, Zhang Q, Pham TH, et al. Omeprazole blocks STAT6 binding to the eotaxin-3 promoter in eosinophilic esophagitis cells. PLoS ONE 2012; 7: e50037.
43. Park JY, Zhang X, Nguyen N, Souza RF, Spechler SJ, Cheng E. Proton pump inhibitors decrease eotaxin-3 expression in the proximal esophagus of children with esophageal eosinophilia. PLoS ONE 2014; 9: e101391.
44. Liacouras CA, Wenner WJ, Brown K, Ruchelli E. Primary eosinophilic esophagitis in children: successful treatment with oral corticosteroids. J Pediatr Gastroenterol Nutr 1998; 26(4): 380-5.
45. Murali AR, Gupta A, Attar BM, Ravi V, Koduru P. Topical steroids in eosinophilic esophagitis: systematic review and meta-analysis of placebo-controlled randomized clinical trials. J Gastroenterol Hepatol 2016;31(6):1111-9.
46. Attwood SE, Lewis CJ, Bronder CS, Morris CD, Armstrong GR, Whittam J. Eosinophilic oesophagitis: a novel treatment using montelukast. Gut 2003; 52(2): 181-5.
47. Lucendo AJ, De Rezende LC, Jimenez-Contreras S, Yague-Compadre JL, Gonzalez-Cervera J, Mota-Huertas T, Guagnozzi D, Angueira T, González-Castillo S, Arias A. Montelukast was inefficient in maintaining steroid-induced remission in adult eosinophilic esophagitis. Dig Dis Sci 2011; 56(12): 3551-8.
48. Netzer P, Gschossmann JM, Straumann A, Sendensky A, Weimann R, Schoepfer AM. Corticosteroid-dependent eosinophilic oesophagitis: azathioprine and 6-mercaptopurine can induce and maintain long-term remission. Eur J Gastroentol Hepatol 2007; 19(10): 865-9.
49. Straumann A, Conus S, Grzonka P, Kita H, Kephart G, Bussmann C, Beglinger C, Smith DA, Patel J, Byrne M, Simon HU. Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial. Gut 2010; 59(1): 21-30.
50. Spergel JM, Rothenberg ME, Collins MH, Furuta GT, Markowitz JE, Fuchs G 3rd, O'Gorman MA, Abonia JP, Young J, Henkel T, Wilkins HJ, Liacouras CA. Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. J Allergy Clin Immunol 2012; 129(2): 456-63.
51. Holgate S, Casale T, Wenzel S, Bousquet J, Deniz Y, Reis-

ner C. The anti-inflammatory effects of omalizumab confirm the central role of IgE in allergic inflammation. J Allergy Clin Immunol 2005; 115(3): 459-65.
52. Straumann A. Medical therapy in eosinophilic oesophagitis. Best Pract Res Clin Gastroenterol 2015; 29(5): 805-14.
53. Rothenberg ME, Wen T, Greenberg A, Alpan O, Enav B, Hirano I, Nadeau K, Kaiser S, Peters T, Gunawardena KA. Intravenous anti-IL-13 mAb QAX576 for the treatment of eosinophilic esophagitis. J Allergy Clin Immunol 2015; 135(2): 500-7.

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Review

Endoscopic dilation in pediatric esophageal strictures: a literature review

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Summary. *Background:* Esophageal strictures in pediatric age are a quite common condition due to different etiologies. Esophageal strictures can be divided in congenital, acquired and functional. Clinical manifestations are similar and when symptoms arise, endoscopic dilation is the treatment of choice. Our aim was to consider the efficacy of this technique in pediatric population, through a wide review of the literature. *Method:* A search on PubMed/Medline was performed using "esophageal strictures", "endoscopic dilations" and "children" as key words. Medline, Scopus, PubMed publisher and Google Scholar were searched as well. As inclusion criteria, we selected clinical studies describing dilations applied to all type of esophageal strictures in children. Papers referred to single etiology strictures dilations or to adult population only were excluded, as well as literature-review articles. *Results:* We found 17 studies from 1989 to 2018. Overall, 738 patients in pediatric age underwent dilation for esophageal strictures with fixed diameter push-type dilators (bougie dilators) and/or radial expanding balloon dilators. Severe complications were observed in 33/738 patients (4,5%) and perforation was the most frequent (29/33). Conversion to surgery occurred only in 16 patients (2,2%). *Conclusions:* Endoscopic dilation is the first-choice treatment of esophageal strictures, it can be considered a safe procedure in pediatric age. Both, fixed diameter push-type dilators and radial expanding balloon dilators, showed positive outcomes in term of clinical results and cases converted to surgery. However, it's essential to perform these procedure in specialized Centers by an experienced team, in order to reduce complications. (www.actabiomedica.it)

Key words: endoscopic dilation, pediatric endoscopy, Savary-Gilliard dilator, balloon dilator

Introduction

Esophageal strictures in pediatric age are a quite common condition, that may have different etiologies (1). In adults, esophageal tumors are the most common cause of strictures, while in children the etiological spectrum is broader (2). It is possible to distinguish among congenital forms, acquired forms and those deriving from functional disorders (achalasia) (1, 2). In congenital strictures, different subtypes have been described. The two most important are the fibromuscular subtype and the tracheal cartilaginous remnant subtype. In acquired forms, we can distinguish among caustic, anastomotic, peptic, actinic and neoplastic strictures. We can also identify strictures deriving from pathologies as epidermolysis bullosa and eosinophilic esophagitis (1). The most common causes are complications of surgical treatment of esophageal atresia, or esophageal burns due to caustic ingestion (3) that occurs especially in children of five years of age or younger (4), even though there are relevant variations from one country to another, especially be-

tween developed and developing countries in terms of incidence (2).

Failure to thrive is the most important consequence of this clinical condition, as is causes an impaired oral intake (5).

The endoscopic treatment of esophageal strictures has been reported to be the most frequent strategy in children (6). There is no universally accepted standard for the choice of the endoscopic technique in patients with esophageal strictures (3). Improvements in endoscopes and accessories have supported an increase in the number of patients who are conservatively treated with endoscopic dilations and a significant reduction of surgical treatments (6). Different dilators are now available. Fixed diameter push-type dilators as semirigid Savary-Giliard bougies and radial expanding balloon dilators that pass over a guide wire or through the channel of the endoscope are the most used devices, although there is still no consensus about which one has to be preferred (7). No prospective studies have directly compared the safety and efficacy of these types of dilators.

Esophageal dilation is associated with clearly defined morbidity and mortality and it should only be performed by experienced endoscopists, under general anesthesia (7). Perforation is the principal risk of this technique. The risk of this complication may be reduced by performing an accurate study of the stricture morphology and etiology, by choosing a correct type and size of the dilators and by performing dilations under fluoroscopic control (1).

The aim of this paper was to perform a review of the available literature on endoscopic dilations of esophageal strictures in pediatric age, with particular attention to possible complications and incidence to conversion to surgery.

Methods

In order to evaluate the efficacy and the safety of endoscopic dilations of esophageal strictures, we performed a literature search of PubMed database using the following key words "endoscopic dilations", "esophageal strictures", "children". Medline, Scopus, PubMed publisher and Google Scholar were searched as well. The entire databases were considered, without restrictions of time. We included only full text papers selected with two filters "humans" and "language" (English papers).

We included all papers related to a pediatric population even if not exclusively.

Exclusion criteria were:

- papers referred only to single etiology strictures dilations
- papers referred to adult population exclusively
- study referred to other gastrointestinal tract strictures
- literature-review articles

Each article was tabulated in chronological order from the oldest to the most recent as follows: author and year of the study, number of patients, demographic data, endoscopic technique, total number of dilations, dilations for each patient, serious complications and conversion to surgery (Table 1). Regarding endoscopic techniques, we considered two different types: fixed diameter push-type dilators (bougie dilators) and radial expanding balloon dilators. Different adjuvant treatments were not considered.

The publications were manually screened and reviewed to identify reports and data were extracted from the papers according to the predetermined criteria. Two investigators independently reviewed and extracted data from the papers according to the predetermined criteria.

Results

We found at first 324 papers. Including only full text papers we limited the research at 234 study. Finally selecting two filters "humans" and "language" and including only English papers, we obtained 104 papers. After manual screening according to established criteria, 17 retrospective articles from 1989 to 2018 were selected.

Study population size among papers was very different, from a small cohort of 5 patients (8) up to the most numerous one with 125 patients (9). Overall, 738 patients in pediatric age (less than 18 years) underwent esophageal dilation. Only one study (10) considered a not exclusively pediatric population including people from 10 to 80 years (mean age 58 years).

Table 1. Articles included in the literature review

Author, year	N° patients	Demographic data	Endoscopic technique	N° of dilations	Dilation/ patient	Serious Complications (total n° and %)	Conversion to surgery
Gandhi RP, 1989	12	<18 years	Tuckers	-	-	Yes 1 perforation (1%)	No
Shah, 1993	17	1 month- 15 years	Ballon dilation	132	7,7	Yes 1 perforation	Yes, 1
Jawad AJ, 1995	36	<18 years	Ballon dilation and Savary-Gilliard	-	-	Yes 1 perforation 1 anastomotic leak	Yes, 2
Wang YG, 2002	55 (40 M, 15 F)	10-80 years (median age 58)	Savary-Gilliard	401	7,2	No	No
Lan LC, 2003	77	2 months-20 years	Ballon dilation	260	3,3	Yes 4 perforation (1,5%)	Yes, 1
Bittencourt PF, 2006	125	1 month-16 years	Savary-Gilliard	-	-	Yes 5 perforation	No
Khanna S, 2008	5	4-12 years	Ballon dilation	-	-	No	No
Saleem MM, 2009	38	1 months- 10 years (median age 3,2)	Tuckers	801	21,1	Yes 2 perforation	Yes, 2
Alshammari J, 2011	49	<18 years	Ballon dilation	-	-	Yes 3 perforation	Yes, 6
Chang CF, 2011	10	1-50 months	Ballon dilation	-	-	No	Yes, 1
Lakhdar-Idrissi M, 2012	60	10 months-17 years	Savary-Gilliard	247	4,1	Yes 2 perforation	No
Shehata SM, 2012	38	5-22 months	Savary-Gilliard	654	17,2	Yes 1 perforation 2 small diverticulum	Yes, 3
Van der Zee D, 2014	19	1 month-15 years	Ballon dilation	87	4,5	No	No
Pieczarkowsky S 2016	106	1 month-18 years	Ballon dilation and Savary-Gilliard	347	3,2	Yes 1 perforation	No

(continued)

Table 1 *(continued)*. Articles included in the literature review

Author, year	N° patients	Demographic data	Endoscopic technique	N° of dilations	Dilation/ patient	Serious Complications (total n° and %)	Conversion to surgery
Cakmak M, 2016	38	0-14	Ballon dilation	-	-	Yes 4 perforation 1 fistula	No
Hsieh KH, 2017	10	<10 years	Ballon dilation	93	9,3	Yes 1 perforation (1%)	No
Al Sharkhy AA, 2018	43	2-17 years		180	4,1	Yes 3 perforation	No

Different endoscopic dilatation techniques were used: in 6 studies fixed diameter push-type dilators were preferred, in 2 Tuckers (2, 4) and in 4 Savary-Gillard were used (9-12); in 8 studies radial expanding balloon dilators were used (5, 8, 13-18); in 2 works (3, 4) a combination of two techniques was used, while in 1 study (19) the technique was not specified.

Even if in 7 papers (4, 5, 8, 9, 13, 14, 18, 20) the total number of dilations was not described, overall 3202 procedures were performed (median number 6,9/patient). Making a comparison between the two techniques, the median number of dilations with fixed diameter push-type dilators was 12,3/patient while it was 5,8/patient with radial expanding balloon dilators.

A total of 35 serious complications were recorded, 1 anastomotic leak, 2 small diverticulum formation, 1 fistula and 31 perforations. In 4 study complications were not described (8, 10, 14, 18).

Finally, in 10 studies (3, 5, 8-11, 15, 18-20) an eventual conversion to surgery was not described. In the other cases a total of 16 patients underwent surgical treatment, due to inefficacy of the dilation or for the management of the complication.

Discussion

Esophageal strictures in pediatric age are a quite common condition (1). In adults, the most common cause of strictures are esophageal tumors, while in children the etiological spectrum is broader (2). In the present review only Wang et al in 2002 studied a wide aged population from 10 to 80 years (with a median age of 58). All 55 unselected consecutive patients were treated with Savary-Gillard bougies achieving in all cases a relief of symptoms. No serious procedure-induced complications occurred.

There is no universally accepted standard of endoscopic treatment of patients with esophageal strictures (3). In our review Gandhi et al. in 1989 and Saleem et al. in 2009 reported their experience with Tucker's string guide dilators while Wang et al in 2002, Bittencourt et al in 2006, Lakhdar-Idrissi et al and Shehata et al in 2012 described their one with Savary-Gilliard bougies. Eight authors from Shah in 1993 to Hsieh in 2017 used expanding balloon dilators while Jawad in 1995 and Pieczarkowsky in 2016 reported both, balloon dilators and semirigid Savary-Gilliard bougies. Overall, literature data show that there is no substantial preference between the two endoscopic techniques.

Comparing the efficacy of these two techniques, balloon dilators can be more effective and less traumatic than traditional bougies, as they provide a uniform radial force (16). More obviously, balloon dilation is performed under direct vision, furthermore the insertion of multiple devices is not necessary (8). In addition, endoscopic and fluoroscopic guidance allow a direct placement of the balloon catheter and visualization of the balloon inflation, thereby decreasing the risk of perforation (16). The only disadvantage is

that a balloon is single-use, therefore it is far more expensive than a bougie (8). If we consider number of dilatation per patient it is possible to observe how the median number of dilations with fixed diameter push-type dilators is higher than with radial expanding balloon dilators. Saleem in 2009 described a median of 21 dilations with Tucker's string guide dilators and Shehata in 2012 a median of 17 dilation with Savary-Gilliard bougies. Wang in 2002 reported a median of 7,2/patient with Savary-Gilliard, while Lakhdar-Idrissi in 2012 reported a better result with 4,1/patient. On the other side Lan in 2003 and Pieczarkowsky in 2016 reported similar results with a median number of 3,2/patient. Van der Zee in 2014 and Al Sharkhy in 2018 found similar values with respectively 4,5 and 4,1 median dilations per patient. Hsieh in 2017 showed slightly more numerous dilations, with 9,3/patient. Overall, the present review of literature confirms the superiority of pneumatic dilations compared to bougies.

Currently, esophageal dilation in children are almost exclusively performed under general anesthesia (3). Endoscopic esophageal dilation is associated with low risk of complications. No significant prognostic factors could be determined (13). The most frequent potential complication is bleeding and perforation is the most serious. Esophageal perforation remains the most dreaded complication for dilatation of esophageal strictures. A higher perforation rate has been esteemed for bougienage than for balloon dilation (16). The use of antibiotics is advised to reduce the potential complication of infection and more frequent scar formation in absence of antibiotic therapy (4). In literature, Wang in 2002, Swagata in 2008, Chang in 2011 and Van der Zee in 2014 did not report complications. Shah in 1993, Lan in 2003 et Hsiehin 2017 reported a similar rate of perforations with balloon dilators of 1-1,5% while Saleem in 2009, Lakhdar-Idrissi in 2012 and Shehata in 2012 reported a very low rate of perforations. Probably, the very low rate of complications in pediatric age can be explained with the constant practice of operative endoscopy in the operating room and under general anesthesia, to maximize safety.

The resort to surgery is a possible, even if uncommon, eventuality. Therefore, it should be reserved for those patients in whom endoscopic dilation has failed and for those with complications caused by dilation (8) due to its association with high mortality rate and high complication rate.

Consecutive dilation procedures are recommended for at least 2 years before deciding their failure (2). Many authors recommend a six to 12-month period of conventional repeated esophageal dilatation (4) Determinant factors of success or failure vary in reported series and include: age, site of the stricture, tightness of stricture, length of stricture, number of strictures and failure to respond to dilatation (2).

In literature two studies, Alshammari and Chang both in 2011, needed surgery for dilation's failure. For the first author, 6 surgical interventions were described, 3 due to perforation and 3 for failure of the procedure, while for the second author a conversion to surgery was necessary in absence of complications.

Moreover, the review showed also a few surgical treatments of complications. Shah in 1993 described only a perforation treated by surgery while Jawad in 1995 and Saleem in 2009 reported two surgical treatment, for perforations and for anastomotic leak. Lan in 2003 had 4 perforation, but only in 1 case surgery was necessary, while Shehata in 2012 reported 3 surgical treatments, among whom, one perforation and 2 small diverticulum formations.

Overall, in literature a very low rate of need of surgery is reported and it is required mostly for the treatment of complications.

Conclusions

Esophageal dilatation represents a small percentage of pediatric endoscopic procedures (17) and it represents the first-choice treatment of esophageal strictures. Both, fixed diameter push-type dilators and radial expanding balloon dilators, showed positive outcomes in term of improvement of clinical conditions and cases converted to surgery, although the efficacy of pneumatic dilations seems to be superior compared to the use of bougies. Endoscopic esophageal dilation is associated with a low risk of complications. However, it is essential to perform these procedure in specialized Centers by experienced team, in order to reduce complications. Resort to surgery is a possible, even if

uncommon, eventuality and it should be reserved for failure and for complication's treatment.

References

1. Dall'Oglio L, Caldaro T, Foschia F, Faraci S, Federici di Abriola G, Rea F, et al. Endoscopic management of esophageal stenosis in children: New and traditional treatments. World J Gastrointest Endosc 2016; 8(4): 212-9.
2. Saleem MM. Acquired oesophageal strictures in children: emphasis on the use of string-guided dilatations. Singapore medical journal 2009; 50(1): 82-6.
3. Pieczarkowski S, Woynarowski M, Landowski P, Wilk R, Daukszewicz A, Toporowska-Kowalska E, et al. Endoscopic therapy of oesophageal strictures in children - a multicentre study. Przeglad gastroenterologiczny 2016; 11(3): 194-9.
4. Jawad AJ, Al-Samarrai AI, Al-Rabeeah A, Al-Rashed R. The management of esophageal strictures in children. Annals of Saudi medicine 1995; 15(1): 43-7.
5. Cakmak M, Boybeyi O, Gollu G, Kucuk G, Bingol-Kologlu M, Yagmurlu A, et al. Endoscopic balloon dilatation of benign esophageal strictures in childhood: a 15-year experience. Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus 2016; 29(2): 179-84.
6. Lew RJ, Kochman ML. A review of endoscopic methods of esophageal dilation. Journal of clinical gastroenterology. 2002; 35(2): 117-26.
7. Riley SA, Attwood SE. Guidelines on the use of oesophageal dilatation in clinical practice. Gut 2004; 53 Suppl 1: i1-6.
8. Khanna S, Khanna S. Management of benign oesophageal strictures in children. Indian journal of otolaryngology and head and neck surgery : official publication of the Association of Otolaryngologists of India 2008; 60(3): 218-22.
9. Bittencourt PF, Carvalho SD, Ferreira AR, Melo SF, Andrade DO, Figueiredo Filho PP, et al. Endoscopic dilatation of esophageal strictures in children and adolescents. Jornal de pediatria 2006; 82(2): 127-31.
10. Wang YG, Tio TL, Soehendra N. Endoscopic dilation of esophageal stricture without fluoroscopy is safe and effective. World journal of gastroenterology 2002; 8(4): 766-8.
11. Lakhdar-Idrissi M, Khabbache K, Hida M. Esophageal endoscopic dilations. Journal of pediatric gastroenterology and nutrition 2012; 54(6): 744-7.
12. Shehata SM, Enaba ME. Endoscopic dilatation for benign oesophageal strictures in infants and toddlers: experience of an expectant protocol from North African tertiary centre. African journal of paediatric surgery: AJPS 2012; 9(3): 187-92.
13. Alshammari J, Quesnel S, Pierrot S, Couloigner V. Endoscopic balloon dilatation of esophageal strictures in children. International journal of pediatric otorhinolaryngology 2011; 75(11): 1376-9.
14. Chang CF, Kuo SP, Lin HC, Chuang CC, Tsai TK, Wu SF, et al. Endoscopic balloon dilatation for esophageal strictures in children younger than 6 years: experience in a medical center. Pediatrics and neonatology 2011; 52(4): 196-202.
15. Hsieh KH, Soong WJ, Jeng MJ, Lee YS, Tsao PC, Chou YL. Flexible endoscopic diagnosis and treatment of esophageal stenosis in children with noninvasive ventilation support. Pediatrics and neonatology 2018; 59(1): 31-4.
16. Lan LC, Wong KK, Lin SC, Sprigg A, Clarke S, Johnson PR, et al. Endoscopic balloon dilatation of esophageal strictures in infants and children: 17 years' experience and a literature review. Journal of pediatric surgery 2003; 38(12): 1712-5.
17. Shah MD, Berman WF. Endoscopic balloon dilation of esophageal strictures in children. Gastrointestinal endoscopy 1993; 39(2): 153-6.
18. van der Zee D, Hulsker C. Indwelling esophageal balloon catheter for benign esophageal stenosis in infants and children. Surgical endoscopy 2014; 28(4): 1126-30.
19. Al Sarkhy AA, Saeed A, Hamid YH, Al Asmi MM, Altokhais TI, Ullah AA, et al. Efficacy and safety of endoscopic dilatation in the management of esophageal strictures in children. Saudi medical journal 2018; 39(8): 787-91.
20. Gandhi RP, Cooper A, Barlow BA. Successful management of esophageal strictures without resection or replacement. Journal of pediatric surgery 1989; 24(8): 745-9; discussion 9-50.

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Review

Diagnosis of GERD in typical and atypical manifestations

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Summary. The manifestations of gastroesophageal reflux disease (GERD) have been recently classified into either esophageal or extra-esophageal syndromes. Clinical history, questionnaire data and response to antisecretory therapy are insufficient to make a conclusive diagnosis of GERD. Endoscopy had a low sensitivity. Recently, the availability of multichannel intraluminal impedance and pH-monitoring (MII-pH) has modified the diagnostic approach towards atypical manifestations of GERD. There is a rising consensus that this technique should be considered as the gold standard for GERD diagnosis. Gastrin 17 (G-17) has been proposed as a non-invasive marker of GERD, due to the negative feedback between acid and the hormone. G17 levels seem able to identify patients with acid and non-acid reflux. (www.actabiomedica.it)

Key words: GERD, diagnosis, typical manifestations, atypical manifestations, pH impedance, gastrin 17

Introduction

Gastroesophageal reflux disease (GERD) is one of the most common gastrointestinal disorders in Western countries (1). The clinical features of GERD have been recently classified into either esophageal or extra-esophageal syndromes (2). Most common atypical manifestation of GERD may include ear, nose, and throat (ENT), pulmonary (chronic cough or asthma), or cardiac (noncardiac chest pain) symptoms (3). Therefore, GERD should be strongly considered in the differential diagnosis of patients presenting with atypical symptoms when alternative diagnoses have been excluded by other specialist (ENT surgeons, cardiologists, pneumologists, allergists).

The diagnosis of GERD is very difficult and is typically made by a combination of clinical symptoms, response to acid suppression, as well as objective testing with upper endoscopy and esophageal pH monitoring.

Empirical therapy

In patients with a history suggestive of uncomplicated GERD manifesting in typical symptom of heartburn and/or regurgitation can be offered empiric treatment (4). Typical symptoms that are responsive to acid suppression offer additional evidence for pathologic esophageal acid exposure and it's reasonable to assume a diagnosis of GERD in patients who respond to appropriate therapy. On the other hand, typical symptoms that do not improve warrant further tests to demonstrate the existence of GERD and evaluate for an alternate diagnosis. Similarly, patients with atypical manifestations or non-cardiac chest pain should be considered for esophageal function tests prior to empiric therapy (5).

However, this empirical test is contraindicated in patients with alarm symptoms such as dysphagia, weight loss and bleeding in according to the five recommendations of the Italian Association of Hospital Gastroenterologist (AIGO).

Upper endoscopy

Upper endoscopy allows to evaluate the esophageal mucosa in patients with GERD and obtains biopsies of concerning lesions (e.g. Barrett's metaplasia, strictures or masses). There are limitations with the use of upper endoscopy in the diagnosis of GERD. Erosive reflux disease (ERD) occurs in a minority of patients with GERD (<30%), whereas the majority of them are included in the non-erosive reflux disease (NERD) phenotype, characterized by typical reflux symptoms, mainly heartburn, without any esophageal mucosal lesion visible on upper endoscopy (6). Patients with atypical GERD symptoms usually have a low prevalence of endoscopic esophagitis (3). Therefore, an upper endoscopy is not required for the diagnosis and is mostly performed for evaluation of GERD associated complications and alternative diagnoses. Patients with alarm symptoms, such as anemia, weight loss and dysphagia, or history of chronic GERD and age 50 years or older should receive screening endoscopy for Barrett's esophagus (7,8).

Barium radiographs

Barium radiographs have been historically considered part of the potential diagnostic armamentarium in the patient with esophageal symptoms, including GERD. Although well-performed barium esophagrams with double contrast can detect signs of esophagitis, the overall sensitivity of this test is extremely low (9). The finding of barium reflux above the thoracic inlet with or without provocative maneuvers including the water siphon test does increase the sensitivity of the barium test; however, not sufficiently to be recommended as a diagnostic test without dysphagia (10).

Esophageal manometry

Esophageal manometry is currently considered the gold standard test for the diagnosis of esophageal dysmotility that may be responsible for symptoms like dysphagia and chest pain. However, it has shown limited capability in diagnosing GERD. With the advent of high-resolution manometry (HRM), more accurate evaluations of esophageal motility are now possible. Furthermore, new metrics have been developed to investigate esophagogastric junction (EGJ) morphology and function. In particular, the anti-reflux barrier function of EGJ can now be assessed evaluating the contraction integral of the junction. Also, transient lower esophageal relaxations can be defined more precisely with HRM. Neither a decreased lower esophageal sphincter pressure, nor the presence of a motility abnormality is specific enough to make a diagnosis of GERD. Manometry should be used to aid in placement of transnasal pH-impedance probes and is recommended before consideration of anti-reflux surgery primarily to rule out achalasia or severe hypomotility (scleroderma-like esophagus), conditions that would be contraindications to Nissen fundoplication, but not to tailor the operation (11).

24 hours bilimetry

Bilimetry allows spectrophotometric measurements of esophageal luminal bilirubin concentration due to duodenogastric reflux (DRGE).

Although the role of bile in the pathogenesis of esophageal mucosal damage is unknow and there is a high prevalence of both acid and non-acid refluxes, some Authors recommend simultaneous pH monitoring and bilimetry (12, 13).

The main indications for double monitoring are patients with typical GERD symptoms poorly responsive to PPI therapy.

Bilitec 2000 is a new spectrophotometric system. Unfortunately, this technology is only a semiquantitative measure for detecting DRGE. Validation studies found that this instrument underestimates bile reflux in an acid medium (pH < 3.5) (14). In solutions with pH < 3.5, bilirubin undergoes a monomer to dimer isomerization which is reflected by the shift in the absoption wavelength from 435 nm to 400 nm. Because Bilitec readings are based on the detection of absorption at 470 nm, this shift underestimates the degree of DRGE. Therefore, Bilitec measurements of DRGE must always be accompanied by the simultane-

ous measurements of acid exposure by pH monitoring. Furthermore, a variety of substances can cause false positive readings by the Bilitec, because it indiscriminately records any substance absorbing around 470 nm such as heme (i.e. during hematemesis), porphyrin, carotenoids, riboflavin and various foods such as tomatoes, bananas, carrots, beets, parmesan, cheese, meat, tea and coffee (15). In addition, solid food can obstruct the tip of the probe and reduce the accuracy of the recordings, for these reasons standardized liquid diets should prescribe to allow registrations. However, there is a limitation in the registration of DRGE patterns due to a different and a lower caloric content diet.

Despite the measurement of bilirubin adds valuable information on the chemical nature of the flowed material, there are several limitations that do not allow to accurately and accurately detect the onset and frequency of episodes of DGER.

Table 1. DeMeester score

Percent total time pH < 4
Percent Upright time pH < 4
Percent Supine time pH < 4
Number of reflux episodes
Number of reflux episodes ≥ 5 min
Longest reflux episode (minutes)

Ambulatory pH monitoring

Ambulatory reflux monitoring is the only modality allowing direct measurement of esophageal acid exposure (acid exposure time, AET), reflux episode frequency and association between symptoms and reflux episodes. It's typically used to evaluate patients without endoscopic evidence of GERD, in order to confirm the diagnosis. It can also be employed to monitor the control of reflux in those on therapy with persistent symptoms.

24 h pH-metry allows to monitor the presence of acid in esophagus recorded over 24 hours by means of a transnasal pH catheter positioned near the lower esophagus. When there is a the passage of acid gastric contents into the esophagus during the reflux it causes a decrease in the esophageal pH. The test is considered positive if the pH falls below 4 for a period longer than 5 seconds. A patient's tracing is analyzed, and the results are expressed using six standard components. Of these 6 parameters a pH score called DeMeester Score has been calculated, which is a global measure of esophageal acid exposure (Tab. 1) (16). A DeMeester score > 14.72 indicated reflux.

There are limitations with the use of 24 h-pH metry for the diagnosis of GERD. The frequency of symptoms it's variable. It's unlikely that symptoms will occur during a routine 24-hour monitoring session and therefore a single measurement may not be representative. Also, the pH monitoring cannot diagnose non-acid reflux (pH> 4) (17).

24 h esophageal pH-impedance monitoring is a technique used in the diagnosis of GERD, by monitoring both impedance and pH. An impedance pH probe is inserted into the nostril and advanced into the esophagus. The impedance pH probe will remain in place for 24 hours and is connected to a small recorder.

Impedance measurement permits the detection of anterograde and retrograde bolus (liquid, gas or mixed) flow in the esophagus and combined-pH monitoring allows the chemical characterization of the refluxate. pH-impedance monitoring can detect not only acid (pH < 4) but also weakly acid (4 < pH < 7) and non-acid (pH > 7) gastric contents. This increases the diagnostic yield of reflux monitoring in patients with GERD (18).

After completion of the impedance-pH study, data are analyzed using appropriate software and interpreted by the reporting physician. The software identifies individual reflux and swallow events, measures symptom-reflux association and distinguishes changes in impedance that are not clinically important. Automated analysis is adequate for acid reflux events but overestimates non-acid or weakly acid events. As consequence calculation of Symptom Index (SI) and Symptom Association Probability (SAP) might be affected. A manual review of the 2 minutes preceding each symptom event in pH-impedance studies is recommended (19).

Acid exposure time (AET) was calculated as the percentage of time the pH was less than 4 at the distal esophageal pH sensor. The Lyon Consensus proposes that AET < 4% be considered definitively normal (physiological) and > 6% be considered definitively abnormal. Intermediate values identify a "grey area" in which additional evidence from other tests may provide the presence of pathologic acid burden (19, 20). Furthermore, there is a considerable day-to-day variability in AET measurements so a clinical decision should never be made exclusively based on this parameter (21).

Some Authors have evaluated a correlation between numbers of reflux episodes and GERD. A clearly high number of reflux episodes (above 80) might be considered abnormal while a number of reflux episodes on pH-impedance of 40 or few are considered ad normal. However, number of reflux episodes alone is not predictive of treatment outcome but an adjunctive tool (19, 20).

Symptom reporting during ambulatory 24-hours reflux monitoring allows investigation of the temporal relationship between reflux and symptom. The pH-impedance allows to modify the diagnostic analysis for atypical GERD manifestations such as cough, asthma, laryngitis and non-cardiac chest pain (22-25). Only symptoms that can reasonably be related to reflux episodes such as cough, chest pain, heartburn, and regurgitation are considered for symptom reflux association analysis. It's not possible to perform reliable symptom reflux association analysis for symptoms that lack a crisp onset and are chronically present, such as dyspnea or hoarseness (26).

The relationship between symptomatic events and reflux episodes can be evaluated with SI and SAP. The SI is defined as the percentage of symptom events that are related to reflux episodes, thus number of reflux related symptomatic events divided by total number of symptomatic events times 100%. The most often used cut-off is 50%, which means that above 50% the SI is considered positive (27). There is not necessarily a correspondence between SI and the acid exposure in the esophagus. The major defect of SI is that it doesn't considered the total number of reflux episodes; as consequence, the probability that SI becomes positive increases with the increase in the number of reflux episodes. The SI presents another limit: this index doesn't integrate all the factor that determine the relationship between symptoms and reflux.

The SAP is a statistical parameter that express the strength of the relationship between symptom events and reflux episodes during measurement. The calculation is more complex than the SI and cannot be done manually but it calculated instead by the measurement software. The cut-off for the SAP is 95%, and a SAP above 95% (corresponding to $P<0.05$, applying Fisher's exact rest on a 2x2 table) is considered positive for a relationship between symptomatic events and reflux episodes (28).

These indices have some limitations, especially related to day-to-day variability of reflux burden and occurrence of symptomatic events during the monitoring day. The presence of positive SI and positive SAP together provides the best evidence of a clinically relevant association between reflux events and symptoms. If one test is positive and the other is negative, this represents a grey area and further interpretation with other parameters and clinical factors are necessary (19).

Non erosive reflux disease (NERD) represents the more common phenotypic presentation of GERD and these patients are markedly heterogeneous from a pathophysiological point of view and should be (correctly?) by means of 24 h impedance-pH monitoring. This technique is able to identify three subsects of NERD, so called "NERD umbrella" (29):

1. Patients with "true" NERD characterized by pathological AET;
2. Patients with Hypersensitive Esophagus (HE) characterized by normal AET and positive SI/SAP for acid or weakly acid reflux;
3. Patients with Functional Heartburn (FH) who do not have any kind of reflux underlying their symptoms and must be excluded from the realm of GERD.

According to Roma III, FH is not a GERD subcategory and it's classified as functional disorder (30). Patients of group 1 and 2 need to be treated with reflux inhibitor. Patients with functional heartburn shouldn't undergo therapy with PPI (31).

Recent studies showed the added diagnostic value of two new pH-impedance parameters, post reflux swallow-induced peristaltic wave (PSPW) index and mean nocturnal baseline impedance (MNBI).

Chemical clearance consists of a salivary swallow, elicited by a post-reflux esophago-salivary vagal reflex and delivering salivary bicarbonate and epidermal growth factor to the esophagus, this augments pH and hastening repair of mucosal damage. A PSPW was define as an antegrade 50% drop in impedance occurring within 30 s of a reflux event, originating in the most proximal impedance channel, reaching the most distal impedance sites, and followed by at least 50% return to the baseline. An index of chemical clearance, namely PSPW index, was obtained by dividing the number of PSPWs by the number of total reflux events.

Baseline impedance values reflect the permeability of the esophageal mucosa. Low baseline esophageal mucosal impedance has been linked to alteration in intercellular space and tight junction and to the reflux symptoms. MNBI was assessed form the most distal impedance channel during the nighttime recumbent period. Three 10-minute time periods (around 1.00 am, 2.00 am and 3.00 am) were selected, excluding swallows, refluxes and pH drops; and the mean of the three measurements was calculated to obtain the MNBI.

Previously established cut-off values for PSPW index and MNBI were 61% and 2292 R respectively (Fig 1). The PSPW index and MNBI increase the

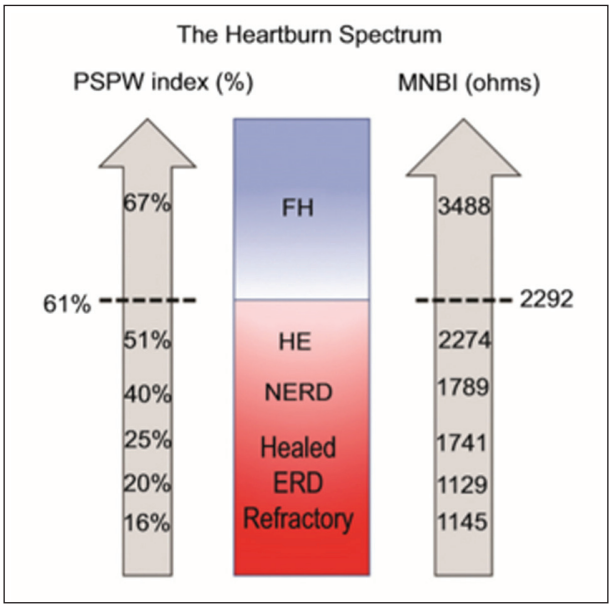

Figure 1. Median values of PSPW index and MNBI for the various diagnostic categories in the heartburn spectrum

diagnostic yield of impedance-pH monitoring in GERD patients as compared with healthy control. The PSPW index has lower values in ERD than in NERD patients and in both groups as compared with no-GERD subjects (32). MNBI distinguishes PPI-responsive from PPI-refractory heartburn patients with normal conventional impedance-pH variables and associated with greater probability of PPI response in patients with chronic cough. In clinical practice these novel impedance-detected parameters can distinguish reflux-related from reflux-unrelated heartburn in patients with normal AET. The very high sensitivity of both parameters allows excluding reflux disease when normal values are found.

PSPW index and MNBI have also a diagnostic value in patients on-therapy evaluated by impedance-pH monitoring. PSPW index and MNBI efficiently distinguish PPI-refractory NERD from FH.

Low MNBI (< 2292 R) independently predicts response to anti-reflux therapy. Frazzoni et al. hypothesize that abnormal PSPW index represents an independent predictor of PPI-refractory GERD, possibly due to a defective esophago-salivary vagal unaffected by surgical treatment. It is conceivable that persistent impairment of chemical clearance is rendered clinically latent after successful surgery owing to sub-total abolition of reflux events, which in turn determines restoration of mucosal integrity, as indicated by improved MNBI and then persistent heartburn remission (33).

Gastrin 17

Gastrin 17 (G-17) is a gastrointestinal peptide hormone and is involved in the control of gastric acid secretion. It's secreted almost exclusively by antral G cells. G-17 controls gastric acid secretion with a negative feedback mechanism. G cells are stimulated by high intragastric pH. High acidity in the stomach inhibits the secretion of G-17. So gastrin levels reflect indirectly intragastric acidity (Fig. 2) (34).

Sipponen et al. have evaluated that the serum levels of G-17 were lower in patients with Barrett's esophagus (BE) than in non-BE controls (34).

Franceschi et al. assessed the role of Gastropanel® (Biohit Oji, Finland), a non-invasive serological test,

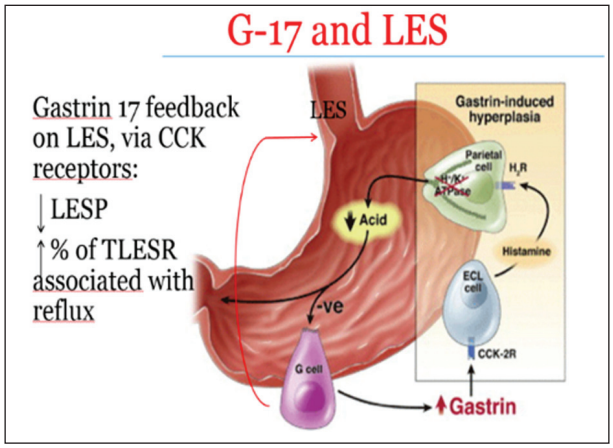

Figure 2. Role of G-17 in the control of gastric acid secretion

for the screening of chronic atrophic gastritis in a dyspeptic population. In this population people with GERD showed significant lower level of G-17 than other group of patients (35). Goni et al. confirmed that results and established that G-17 value < 1,9 pmol/L are useful for the diagnosis of GERD (36).

The role of G-17 in the diagnosis of GERD was assessed by pH-metry and pH-impedance in two different study. In both studies it was possible to conclude that the G-17 seemed to be able to identify patients with GERD and assess the nature of reflux (37, 38).

Low levels of G-17 are useful to identifying not only patients with typical symptoms but also those with atypical manifestations of GERD (39).

Therefore, he serum level of G-17 is proposed as promising and useful first level examination for the diagnosis of GERD even in atypical manifestations.

GastroPanel® Gastrin-17 is an enzyme-linked immunosorbent assay (ELISA) for the quantitative measurement of gastrin-17 (G-17) in human EDTA plasma samples.

Conclusions

GERD is a complex disease with heterogeneous symptoms and a multifaceted pathogenic basis that defies a simple diagnostic algorithm or categorical classification.

Ambulatory pH monitoring of the esophagus helps to confirm gastroesophageal reflux in patients with persistent symptoms (both typical and atypical) in the absence of esophageal mucosal damage, especially when a trial of acid suppression has failed.

The novel metrics from pH-impedance monitoring, MNBI and PSPW index, can distinguish GERD from No-GERD patients and predict PPI response.

Future studies are warranted to confirm the value of Gastrin-17 as non-invasive marker for GERD diagnosis, both in patients with typical and atypical symptoms.

References

1. El-Serag, Hashem B., et al. "Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review." Gut (2013): gutjnl-2012.
2. Vakil, Nimish, et al. "The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus." The American journal of gastroenterology 101.8 (2006): 1900.
3. Vaezi, Michael F. "Atypical manifestations of gastroesophageal reflux disease." Medscape General Medicine 7.4 (2005): 25.
4. Lacy, Brian E., et al. "The diagnosis of gastroesophageal reflux disease." The American journal of medicine 123.7 (2010): 583-592.
5. Aanen, M. C., et al. "Diagnostic value of the proton pump inhibitor test for gastro-oesophageal reflux disease in primary care." Alimentary pharmacology & therapeutics 24.9 (2006): 13771384.
6. Savarino, Edoardo, et al. "Drugs for improving esophageal mucosa defense: where are we now and where are we going?." Annals of gastroenterology 30.6 (2017): 585.
7. Shaheen, Nicholas J., Dawn Provenzale, and Robert S. Sandler. "Upper endoscopy as a screening and surveillance tool in esophageal adenocarcinoma: a review of the evidence." The American journal of gastroenterology 97.6 (2002): 1319.
8. Emami, Mohammad Hasan, Masoud Ataie-Khorasgani, and Nasim Jafari-Pozve. "Diagnostic value of alarm symptoms for upper GI malignancy in patients referred to GI clinic: A 7 years cross sectional study." Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences 22 (2017).
9. Johnston, Brian T., et al. "Comparison of barium radiology with esophageal pH monitoring in the diagnosis of gastroesophageal reflux disease." American Journal of Gastroenterology 91.6 (1996).
10. Katz, Philip O., Lauren B. Gerson, and Marcelo F. Vela. "Guidelines for the diagnosis and management of gastroesophageal reflux disease." The American journal of gastroenterology 108.3 (2013): 308.
11. Savarino, Edoardo, et al. "Practice guidelines on the use of esophageal manometry–A GISMADSIGE-AIGO medi-

cal position statement." Digestive and Liver Disease 48.10 (2016): 1124-1135.
12. Tack, Jan, et al. "Gastroesophageal reflux disease poorly responsive to single-dose proton pump inhibitors in patients without Barrett's esophagus: acid reflux, bile reflux, or both?." The American journal of gastroenterology 99.6 (2004): 981.
13. Stein, H. J., et al. "Bile reflux in benign and malignant Barrett's esophagus: effect of medical acid suppression and Nissen fundoplication." Journal of Gastrointestinal Surgery 2.4 (1998): 333-341.
14. Vaezi, Michael F., Richard G. Lacamera, And Joel E. Richter. "Validation studies of Bilitec 2000: an ambulatory duodenogastric reflux monitoring system." American Journal of Physiology-Gastrointestinal and Liver Physiology 267.6 (1994): G1050-G1057.
15. Tack, Jan, et al. "Dietary restrictions during ambulatory monitoring of duodenogastroesophageal reflux." Digestive diseases and sciences 48.7 (2003): 1213-1220.
16. Johnson, Lawrence F., and Tom R. DeMeester. "Development of the 24-hour intraesophageal pH monitoring composite scoring system." Journal of clinical gastroenterology 8 (1986): 52-58.
17. Vaesi, Michael F., Patrick L. Schroeder, and Joel E. Richter. "Reproducibility of proximal probe pH parameters in 24-hour ambulatory esophageal pH monitoring." American Journal of Gastroenterology 92.5 (1997).
18. Sifrim, Daniel, and F. Fornari. "Esophageal impedance–pH monitoring." Digestive and Liver Disease 40.3 (2008): 161-166.
19. Roman, S., et al. "Ambulatory reflux monitoring for diagnosis of gastro-esophageal reflux disease: update of the Porto consensus and recommendations from an international consensus group." Neurogastroenterology & Motility 29.10 (2017): 1-15.
20. Gyawali, C. Prakash, et al. "Modern diagnosis of GERD: the Lyon Consensus." Gut (2018): gutjnl-2017.
21. Zerbib, F., et al. "Normal values and day-to-day variability of 24-h ambulatory oesophageal impedance-pH monitoring in a Belgian–French cohort of healthy subjects." Alimentary pharmacology & therapeutics 22.10 (2005): 1011-1021.
22. Pauwels, Ans, et al. "Cough and gastroesophageal reflux: from the gastroenterologist end." Pulmonary pharmacology & therapeutics 22.2 (2009): 135-138. 127.
23. Savarino, Edoardo, et al. "Gastroesophageal reflux and pulmonary fibrosis in scleroderma: a study using pH-impedance monitoring." American journal of respiratory and critical care medicine 179.5 (2009): 408-413. 128.
24. Bigatao, Amilcar M., et al. "Chronic Obstructive Pulmonary Disease Exacerbations Are Influenced by Gastroesophageal Reflux Disease." The American Surgeon 84.1 (2018): 51-55. 129.
25. Prakash, Chandra, and Ray E. Clouse. "Wireless pH monitoring in patients with non-cardiac chest pain." The American journal of gastroenterology 101.3 (2006): 446.
26. Abdul-Hussein, Mustafa, Crystal Zhang, and Donald Castell. "Symptom Index or Symptom Association Probability?." Journal of clinical gastroenterology 52.1 (2018): e7-e10.
27. Wiener, G. J., et al. "The symptom index: a clinically important parameter of ambulatory 24hour esophageal pH monitoring." American Journal of Gastroenterology 83.4 (1988).
28. Weusten, Bas LAM, et al. "The symptom-association probability: an improved method for symptom analysis of 24-hour esophageal pH data." Gastroenterology 107.6 (1994): 1741-1745.
29. Savarino, Edoardo, Patrizia Zentilin, and Vincenzo Savarino. "NERD: an umbrella term including heterogeneous subpopulations." Nature Reviews Gastroenterology & Hepatology 10.6 (2013): 371
30. Savarino, Edoardo, et al. "The added value of impedance-pH monitoring to Rome III criteria in distinguishing functional heartburn from non-erosive reflux disease." Digestive and Liver Disease 43.7 (2011): 542-547.
31. Savarino, Vincenzo, et al. "Functional heartburn and non-erosive reflux disease." Digestive diseases 25.3 (2007): 172-17
32. Frazzoni, L., et al. "Postreflux swallow-induced peristaltic wave index and nocturnal baseline impedance can link PPI-responsive heartburn to reflux better than acid exposure time." Neurogastroenterology & Motility 29.11 (2017): e13116.
33. Frazzoni, M., et al. "The added diagnostic value of postreflux swallow-induced peristaltic wave index and nocturnal baseline impedance in refractory reflux disease studied with on-therapy impedance-pH monitoring." Neurogastroenterology & Motility 29.3 (2017): e12947.
34. Sipponen, Pentti, et al. "Low circulating levels of gastrin-17 in patients with Barrett's esophagus." World Journal of Gastroenterology: WJG 11.38 (2005): 5988.
35. Franceschi, Marilisa, et al. "Sa1749 Serological Diagnosis of Upper GI Diseases in Primary Care Setting." Gastroenterology148.4 (2015): S-322.
36. Goni, Elisabetta, et al. "Mo1135 Gastrin 17 As Non Invasive Marker of Reflux Disease." Gastroenterology 148.4 (2015): S-616.
37. Landi, S., et al. "P. 01.13: Gastrin-17 as a Non-Invasive Marker for Gerd: A Prospective Study on Sample of 777 Consecutive Patients." Digestive and Liver Disease 49 (2017): e137.
38. Savarino, Edoardo V., et al. "Gastrin 17 in Singling Out Patients with Different Patterns of Refluxate: A Pilot Study Using Impedance-pH as Reference Standard." Gastroenterology 152.5 (2017): S653.
39. de Bortoli, N., et al. "P. 06.20 Gerd diagnosis in 340 patients with atypical or extra-esophageal symptoms by using a non invasive surrogate test." Digestive and Liver Disease 50.2 (2018): e187.

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Review

Relationship between *Helicobacter pylori* infection and GERD

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Summary. Gastroesophageal reflux disease (GERD) is due to the chronic exposure of the esophageal mucosa to acid secretion from the stomach. *Helicobacter pylori* (H.p.) infection, is a risk factor for the development of peptic ulcer, atrophic gastritis and gastric cancer, and causes various effects on gastric function. The relationship between GERD and H.pylori infection is still subject of debate. *Background and aim:* In literature no clear causal relationship has been established between GERD and H. pylori infection, although some papers support the onset of esophagitis in patients in whom the infection has been cured. Aim of this work is to review the most recent literature data about the relationship between reflux disease and H. pylori infection. *Methods:* Articles reviewed were found through literature searches on PubMed, Google Scholar using keywords such as gastroesophageal reflux disease, *Helicobacter pylori*, acid-related disorders, GERD and esophagitis. (www.actabiomedica.it)

Key words: gastroesophageal reflux disease, *Helicobacter pylori*, acid-related disorders, GERD, esophagitis

Reflux disease and esophagitis, definition and pathophysiology

Gastroesophageal reflux disease (GERD) is one of the most common gastrointestinal conditions in the general population (1), but an universally accepted definition is lacking since 2006 (2). According to Montreal classification, GERD is defined as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications (3).

Probably a defective anti-reflux barrier and luminal clearance mechanisms are responsible for macroscopically detectable injury to the esophageal squamous epithelium (4), which concretizes in erosive esophagitis and Barrett's Esophagus. However, more than 70% of patients that experience heartburn do not have visible lesions at endoscopy (5) and they are termed as NERD (6) (Non Erosive Reflux Disease).

The pathophysiology of GERD is determined by a failure of the lower esophageal sphincter, that can be related to different factors such as hiatal hernia, obesity, pregnancy, drugs that act on the sphincter musculature, cigarette smoking. Other factors involved are a delay in gastric emptying, reduced oesophageal motility and an excessive stomach relaxation, but the variability of endoscopic findings depends on the different resistance and sensitivity of the individual patient's esophagus. The mucosa of GERD patients produces significantly larger amounts of various cytokines (4) that activate immune cell recruitment and migration, and are involved in the pathophysiology of the illness.

Helicobacter pylori

In 1983 two Australian researchers, B.J. Marshall and R. Warren published on Lancet a paper in

which they claimed the presence of "small curved and S shaped bacilli", later classified as *Helicobacter pylori* (7). Since that moment, *H. pylori* has been established as a major cause of chronic gastritis and peptic ulcer, being in fact involved in the pathogenesis of gastric cancer and gastric mucosa-associated lymphoid tissue (MALT) lymphoma.

H.pylori is a gram-negative microaerophilic bacterium, that generally colonizes the stomach in early life (8). It has the ability to reach the protective mucus layer at the surface of gastric mucosa and to survive the extreme acid content of the stomach thanks to its 4-6 flagella, and -by avoiding low pH areas using chemiotaxis- it first colonizes the antrum, where there are no acid-producers cells. Then it adheres to epithelial cells using the blood group antigen binding adhesin (BabA) that it binds to ABO/Leb (Leb) group antigens and fucosylated carbohydrates expressed by gastric epithelial cells (9). It produces a huge amount of urease, that metabolizes the urea present in the stomach in ammonia and carbon dioxide in order to produce a neutralized area where the bacteria can live (10). The virulence of the bacteria strains is linked to the presence of a pathogenicity island (cagPAI) locus of its genoma that encodes for the bacterial oncoprotein CagA (11), T4SS and to another factor encoded by a different locus, the vacuolating cytotoxin A (VacA). VacA causes massive vacuolation in epithelial cell lines forming pores in their membranes, determining the output of anions and urea (12).

H. pylori forges the stomach homeostasis inducing inflammation using proinflammatory cytokines and so influencing the activity of somatostatin-producing D cells, gastrin-producing G cells, and acid-producing parietal cells. *H. pylori* gastritis causes a reduction in somatostatin levels (13) and, since somatostatin negatively regulates gastrin, hypergastrinemia ensues (14, 15). Gastrin is a specific growth factor for *H. pylori* (16), so this potentially creates a positive-feedback loop. If not detected or cured, the bacterium or *H. pylori* continues its proliferation and inflammation of gastric mucosa causing the progressive loss of gastric glands. The atrophic changes markedly increase risk of gastric ulceration and non-cardia gastric adenocarcinoma (17, 18) but the lower acid production protects against duodenal ulceration, and probably against acid-induced complications of gastroesophageal reflux (19).

H. pylori and Reflux Disease

Knowledge on *H. pylori* has recently experienced a shift: the Kyoto Consensus Conference on *H. pylori* concluded that the bacteria should be defined as an infectious disease even in asymptomatic patients and *H. pylori*-infected subjects should receive eradication therapy (20). The World Health Organization published an IARC monograph in which is stated that *H. pylori* eradication represents the best strategy to prevent gastric cancer (21) and this was recently approved from high risk gastric cancer incidence countries such as Japan. In 1997, Labenz et al. have suggested the hypothesis that *H. pylori* eradication can lead to reflux disease (22) and nowadays the relationship between gastroesophageal reflux disease and H.pylori infection is still subject of debate.

On the other hand, the Maastricht V/Florence Consensus report claims that H.pylori eradication has not a clinical importance in acid production changes (23).

Epidemiological views

Some papers in literature claim that the prevalence in H.pylori infection has declined in parallel with a decrease of peptic ulcer and an increase of reflux esophagitis (24) but to understand better current data reported on this topic it's important to distinguish between GERD symptoms, erosive esophagitis, Barrett's Esophagus and adenocarcinoma (25). Gastric acid secretion is a key factor in the development of reflux disease. Nevertheless, it's unquestioned the role of the bacteria in the development of gastric atrophy, that is the most important mechanism that protects the esophagus from the excessive exposure of acid (26), since the atrophy of the corpus may undermine parietal cells secretion (27). Supporting this, a case-control study from Korea -that is a nation with high prevalence of atrophic gastritis- showed the association between H.pylori seropositivity and a reduced risk

for erosive esophagitis (OR: 0.44; 95% CI: 0.39-0.49) (28). On the other hand, in Western World there is an opposite time trend in peptic ulcer disease and distal gastric cancer, that are decreasing, and reflux esophagitis, which is increasing (29). In particular, cag-A positive strains of bacteria have been associated with a lower incidence of GERD (27). An Iranian study of 2017 showed that there was no difference of *H. pylori* prevalence in GERD patients compared with controls, but the prevalence of the cagA gene of *H. pylori* and the co-existence of cagA and cagE were significantly higher in the control group (30). Bor et al. investigated on this essay in a study conducted in Turkey, where the population is characterized with both Eastern and Western countries lifestyles, coming to the conclusion that there is no relationship between the infection and GERD (31).

Eradication therapy "consequences"

Several studies have shown the inverse relationship between the occurrence of GERD and H.p. infection, in particular an increased severity of the disease is documented in patients with pre-existing symptoms (32-34). McColl et al. showed a markedly resolution of dyspepsia in patients in whom the eradication therapy was successful when compared with subjects with a persistent infection. However, this study didn't show a correlation between GERD occurrence and H.p. cure in ulcer patients (35). Yaghoobi et al. instead, found that there was two folds increased risk of GERD development with successful eradication among patients with peptic ulcer compared to untreated controls, but this was not found in dyspeptic patients (36).

Conclusions

Relying to several population studies, is noticeable an inverse relationship between H.pylori and GERD (19, 37), but considering the single patient this relationship is difficult to explain, since GERD is a disease determined by several concomitant factors.

For example, mentioning a problem of the new era such as obesity, it's well known from literature that an elevate BMI can affect the development of the disease (38), regardless the presence of *H. pylori* but the role of weight loss is unclear.

Another known risk factor, that is important to consider in the single patient, is smoking habit, that is another well known risk factor for the developing of GERD. Several mechanisms are responsible of the association between smoking and reflux symptoms, although they mostly normalize after 3 to 8 minutes finishing a cigarette (39). However, recently the HUNT study reported that smoking cessation improves GERD symptoms only in patients with a normal BMI (40). Moreover, recent studies suggest a link between pro-inflammatory genotypes and less severity of GERD (41, 42) as well as H.p. infection. In conclusion, studies combining all these factors (including H.p. infection, host factors, life style habits) are needed to better define their effect on the onset of GERD.

References

1. El-Serag, H. B., Sweet, S., Winchester, C. C. & Dent, J. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut 63, 871-80 (2014).
2. Savarino, E. et al. The natural history of gastro-esophageal reflux disease: A comprehensive review. Diseases of the Esophagus 30, 1-9 (2016).
3. Vakil, N. et al. The Montreal definition and classification of gastroesophageal reflux disease: A global evidence-based consensus. American Journal of Gastroenterology 101, 1900-1920 (2006).
4. Altomare, A., Guarino, M. P. L., Cocca, S., Emerenziani, S. & Cicala, M. Gastroesophageal reflux disease: Update on inflammation and symptom perception. World J. Gastroenterol. 19, 6523-6528 (2013).
5. Altomare, A., Guarino, M. P. L., Cocca, S., Emerenziani, S. & Cicala, M. Gastroesophageal reflux disease: Update on inflammation and symptom perception. World J. Gastroenterol. 19, 6523-8 (2013).
6. Giacchino, M., Savarino, V. & Savarino, E. Distinction between patients with non-erosive reflux disease and functional heartburn. Ann. Gastroenterol. 26, 283-289 (2013).
7. Marshall, B. J. & Warren, J. R. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet 323, 1311-1315 (1984).
8. Thorell, K., Lehours, P. & Vale, F. F. Genomics of Helicobacter pylori. Helicobacter 22, e12409 (2017).
9. Camilo, V., Sugiyama, T. & Touati, E. Pathogenesis of Helicobacter pylori infection. Helicobacter 22, e12405 (2017).
10. Mobley, H. L., Mendz, G. L. & Hazell, S. L. Helicobacter

pylori. Helicobacter pylori: Physiology and Genetics (ASM Press, 2001).
11. Camilo, V., Sugiyama, T. & Touati, E. Pathogenesis of Helicobacter pylori infection. Helicobacter 22, e12405 (2017).
12. Iwamoto, H., Czajkowsky, D. M., Cover, T. L., Szabo, G. & Shao, Z. VacA from Helicobacter pylori : a hexameric chloride channel. FEBS Lett. 450, 101-104 (1999).
13. Kaneko, D. H. et al. Helicobacter pylori infection induces a decrease in immunoreactive-somatostatin concentrations of human stomach. Dig. Dis. Sci. 37, 409-416 (1992).
14. Dacha, S., Razvi, M., Massaad, J., Cai, Q. & Wehbi, M. Hypergastrinemia. Gastroenterol. Rep. 3, 201-8 (2015).
15. Fiddian-Green, R. G., Pittenger, G. & Kothary, P. Effect of luminal somatostatin on acid secretion and gastrin release. Scand. J. Gastroenterol. 15, 305-9 (1980).
16. Chowers, M. Y., Keller, N., Bar-Meir, S. & Chowers, Y. A defined human gastrin sequence stimulates the growth of Helicobacter pylori. FEMS Microbiol. Lett. 217, 231-236 (2002).
17. MichaelF.M.D.,F.R.C.Path;Genta,RobertM.M.D.;Yardley, J. M. D. ;Corre. Classification and Grading of Gastritis: the Updated Sydney System. Am. J. Surg. Pathol. 34, 434-434 (2010).
18. Polk, D. B. & Peek, R. M. Helicobacter pylori: gastric cancer and beyond. Nat. Rev. Cancer 10, 403-414 (2010).
19. Di Mario, F. & Goni, E. Gastric acid secretion: Changes during a century. Best Pract. Res. Clin. Gastroenterol. 28, 953-965 (2014).
20. Sugano, K. et al. Kyoto global consensus report on Helicobacter pylori gastritis. Gut 64, 1353-1367 (2015).
21. IARC Helicobacter pylori Working Group. Helicobacter pylori eradication as a strategy for preventing gastric cancer. IARC Working Group Reports, No.8 (WHO Press, 2014). doi:10.3748/wjg.v20.i19.5660
22. Labenz, J. et al. Curing Helicobacter pylori infection in patients with duodenal ulcer may provoke reflux esophagitis. Gastroenterology 112, 1442-7 (1997).
23. Malfertheiner, P. et al. Management of Helicobacter pylori infection-the Maastricht V/Florence Consensus Report. Gut 66, (BMJ Publishing Group, 2017).
24. McColl, K. E. L. Helicobacter pylori Infection. N. Engl. J. Med. 362, 1597-1604 (2010).
25. Vasapolli, R., Malfertheiner, P. & Kandulski, A. Helicobacter pylori and non-malignant upper gastrointestinal diseases. Helicobacter 21, 30-33 (2016).
26. Kandulski, A. & Malfertheiner, P. Helicobacter pylori and gastroesophageal reflux disease. Curr. Opin. Gastroenterol. 30, 402-407 (2014).
27. Loffeld, R. J. L. F. et al. Colonization with cagA-Positive Helicobacter pylori Strains Inversely Associated with Reflux Esophagitis and Barrett's Esophagus. Digestion 62, (S. Karger, 1968).
28. Chung, S. J. et al. Helicobacter pylori Serology Inversely Correlated With the Risk and Severity of Reflux Esophagitis in Helicobacter pylori Endemic Area: A Matched Case-Control Study of 5,616 Health Check-Up Koreans. J. Neurogastroenterol. Motil. 17, 267-73 (2011).
29. el-Serag, H. B. & Sonnenberg, A. Opposing time trends of peptic ulcer and reflux disease. Gut 43, 327-33 (1998).
30. Shavalipour, A. et al. Prevalence of cytotoxin-associated genes of Helicobacter pylori among Iranian GERD patients. Gastroenterol. Hepatol. from bed to bench 10, 178-183 (2017).
31. Bor, S., Kitapcioglu, G. & Kasap, E. Prevalence of gastroesophageal reflux disease in a country with a high occurrence of Helicobacter pylori. World J. Gastroenterol. 23, 525-532 (2017).
32. Ghoshal, U. C. & Chourasia, D. Gastroesophageal Reflux Disease and Helicobacter pylori: What May Be the Relationship? J. Neurogastroenterol. Motil. 16, 243-50 (2010).
33. Haruma, K. Review article: influence of Helicobacter pylori on gastro-oesophageal reflux disease in Japan. Aliment. Pharmacol. Ther. 20, 40-44 (2004).
34. Fallone, C. A. et al. Is Helicobacter pylori eradication associated with gastroesophageal reflux disease? Am. J. Gastroenterol. 95, 914-920 (2000).
35. McColl, K. E., Dickson M.A, A., El-Nujumi, A., El-Omar, E. & Kelman, A. Symptomatic benefit 1-3 years after H. pylori eradication in ulcer patients: impact of gastroesophageal reflux disease. Am. J. Gastroenterol. 95, 101-105 (2000).
36. Yaghoobi, M., Farrokhyar, F., Yuan, Y. & Hunt, R. H. Is There an Increased Risk of GERD After Helicobacter pylori Eradication?: A Meta-Analysis. Am. J. Gastroenterol. (2010). doi:10.1038/ajg.2009.734
37. Sharma, P. & Vakil, N. Helicobacter pylori and reflux disease. Aliment. Pharmacol. Ther. 17, 297-305 (2003).
38. Hampel, H., Abraham, N. S. & El-Serag, H. B. Meta-analysis: Obesity and the risk for gastroesophageal reflux disease and its complications. Annals of Internal Medicine 143, 199-211 (2005).
39. Stanciu, C. & Bennett, J. R. Smoking and gastro-oesophageal reflux. Br. Med. J. 3, 793-5 (1972).
40. Hallan, A., Bomme, M., Hveem, K., Møller-Hansen, J. & Ness-Jensen, E. Risk Factors on the Development of New-Onset Gastroesophageal Reflux Symptoms. A Population-Based Prospective Cohort Study: The HUNT Study. Am. J. Gastroenterol. 110, 393-400 (2015).
41. Queiroz, D. M. M. et al. IL1B and IL1RN polymorphic genes and Helicobacter pylori cagA strains decrease the risk of reflux esophagitis. Gastroenterology 127, 73-79 (2004).
42. Chourasia, D. et al. Genotypic and Functional Roles of IL-1B and IL-1RN on the Risk of Gastroesophageal Reflux Disease: The Presence of IL-1B–511*T/IL-1RN*1 (T1) Haplotype May Protect Against the Disease. Am. J. Gastroenterol. 104, 2704-2713 (2009).

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Review

A non-invasive method for the diagnosis of upper GI diseases

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Summary. Upper-GI diseases are one of the most relevant issue in primary care. Nowadays they are still responsible for about 100 million ambulatory care visits only in the US. The diagnosis of almost every upper-GI condition is still deputed to invasive tests such as upper gastrointestinal endoscopy, gastroesophageal manometry or radiography. The possibility of analysing serum markers like Pepsinogens I and II, produced by gastric mucosa, in order to assess the functional characteristics of the upper GI tract has spread itself since the 80's especially in the diagnosis of peptic ulcer. The discovery of *Helicobacter pylori* by Marshall and Warren in 1983 and the scientific consecration of its role in the pathogenesis of gastric cancer and peptic ulcer (crystallized in Peleo Correa's Cascade, 1992), led to an increase importance of non-invasive tests, raising the attention towards the assessment of both immunoglobulins anti-H.p. and Gastrin hormone produced by antral G cells, as an implementation of the panel of gastric markers. This narrative review aims to analyze the huge landscape of non-invasive tests for diagnosis of GI diseases, studying the literature of the recent years. (www.actabiomedica.it)

Key words: stomach, gastritis, diagnosis, Gastrin-17, pepsinogens, *Helicobacter pylori*, GERD

Introduction

It's widely known that upper-GI diseases are one the most important issue in primary care. The prevalence of upper-GI symptoms in primary care is still relevant: only in the U.S., up to now digestive diseases account for more than 100 million ambulatory care visits annually but comparatively less is known about the true burden of gastrointestinal (GI) symptoms. The most commonly reported symptoms are heartburn/reflux (30.9%), abdominal pain (24.8%), bloating (20.6%), diarrhoea (20.2%), and constipation (19.7%). Less common symptoms are nausea/vomiting (9.5%), dysphagia (5.8%), and bowel incontinence (4.8%) (1). Moreover, there is also an economical issue: in 2015, annual health care expenditures for gastrointestinal diseases in the U.S. totalled $135.9 million, being oesophageal disorders ($18.1 millions) one of the most expensive. Yearly, there were more than 54.4 million ambulatory visits with a primary diagnosis for a GI disease, 3.0 million hospital admissions, and 540,500 all-cause 30-day readmissions (2). In 2004, GERD was by far the most frequently first-listed digestive system condition at ambulatory care visits in the U.S., constituting 17.5% of all digestive system diagnoses, while there were about 700,000 ambulatory care visits with peptic ulcer as the first-listed diagnosis and an equal number in which it was a secondary diagnosis (3). Concerning upper-GI cancers, The Surveillance, Epidemiology, and End Results **(SEER)** program provides considerable information on cancer burden, as shown in figure 1. Between 2011 and 2015, approxi-

All Races

Site	Incidence[a] (2011-2015) Total	Males	Females	US Mortality[b] (2011-2015) Total	Males	Females	Survival[c] (%) (2008-2014) Total	Males	Females
All Sites	439.2	483.0	409.9	163.5	196.8	139.6	66.9	66.4	67.5
Oral Cavity & Pharynx:	11.3	17.1	6.3	2.5	3.9	1.3	64.8	64.0	66.9
Lip	0.7	1.1	0.3	0.0	0.0	0.0	88.4	88.2	89.3
Tongue	3.4	5.2	1.8	0.6	0.9	0.4	65.8	66.1	64.8
Salivary gland	1.3	1.7	1.0	0.3	0.4	0.1	71.6	64.0	82.1
Floor of mouth	0.5	0.7	0.3	0.0	0.0	0.0	52.9	51.9	55.2
Gum & other oral cavity	1.5	1.8	1.3	0.4	0.5	0.3	59.2	55.2	64.3
Nasopharynx	0.6	0.9	0.4	0.2	0.3	0.1	61.6	59.4	66.8
Tonsil	2.0	3.4	0.7	0.2	0.4	0.1	73.9	74.5	70.9
Oropharynx	0.4	0.7	0.2	0.3	0.4	0.1	45.8	47.1	40.8
Hypopharynx	0.6	1.0	0.2	0.1	0.2	0.0	32.9	32.9	32.5
Other oral cavity & pharynx	0.3	0.4	0.1	0.4	0.7	0.2	45.1	47.7	35.5
Digestive System:	81.1	98.8	66.3	41.3	53.0	31.7	43.5	41.2	46.3
Esophagus	4.2	7.2	1.7	4.0	7.2	1.5	19.2	18.9	20.0
Stomach	7.2	9.8	5.2	3.2	4.3	2.3	31.0	28.4	35.1
Small intestine	2.3	2.6	2.0	0.4	0.5	0.3	67.6	66.8	68.4
Colon & Rectum:	39.4	45.2	34.5	14.5	17.3	12.2	64.5	64.1	64.9
Colon	27.7	30.7	25.3	-	-	-	63.6	63.6	63.6
Rectum	11.7	14.6	9.2	-	-	-	66.6	65.2	68.6
Anus, anal canal & anorectum	1.8	1.5	2.1	0.3	0.2	0.3	67.4	60.8	71.4
Liver & intrahepatic bile duct	8.8	13.6	4.7	6.4	9.4	3.8	17.7	17.5	18.4
Gallbladder	1.2	0.9	1.4	0.6	0.5	0.7	18.2	18.4	18.1
Other biliary	1.9	2.3	1.5	0.4	0.5	0.4	17.5	18.8	16.1
Pancreas	12.6	14.4	11.2	10.9	12.6	9.5	8.5	8.8	8.3
Retroperitoneum	0.4	0.4	0.4	0.1	0.1	0.1	54.2	52.9	55.4
Peritoneum, omentum & mesentery	0.5	0.1	0.9	0.3	0.1	0.4	32.0	38.2	31.5
Other digestive system	0.7	0.8	0.6	0.3	0.4	0.3	8.6	7.1	10.2

Figure 1. Age-adjusted SEER Incidence and U.S. Death Rates and 5-Year Relative Survival (Percent) By Primary Cancer Site, Sex Time Period

mately 243,000 people were diagnosed with digestive system cancers, which represented 18% of all cancers and were second only to genital system cancers for the most commonly affected organ system. The most common cancer of the upper-GI tract was Gastric Cancer with a reported incidence of 7.2/100,000 followed by Oesophageal cancers (4.2/100,000). Concerning survival, despite the low incidence of these upper-GI neoplasms, compared with colorectal cancers, they were associated with lower 5-year survival rate (2008-2014), 31/100,000 for gastric neoplasms and 19.2/100,000 for oesophageal ones, against 64.5/100,000 for colorectal cancers (3, 4).

Upper gastrointestinal endoscopy

The increasing reliance by physicians on endoscopy and the appreciation by the general public that upper endoscopy (EGD) is useful for diagnosis, surveillance, treatment, or exclusion of important gastroduodenal diseases, led to an increasing demand for open-access endoscopy. Every year in the U.S. more than 6 million of EGD are performed against a total number of 17,800,000 endoscopies (2), as shown in figure 2. This allows physicians to directly schedule elective, common endoscopic procedures for their patients without prior consultation. Unfortunately, this has also resulted in a considerable increase in overall costs and waiting lists for EGD. Moreover, a substantial rate of inappropriateness of EGD indications has been reported, which has also been associated with a marked decrease of its diagnostic efficacy. An Italian prospective, multicentre study has evaluated the appropriateness rate of 6270 upper endoscopies and the indication for EGD was considered appropriate, according to ASGE criteria, in 77.1% of the cases, whereas it was judged inappropriate in the remaining 22.9% of the examinations. In detail, the inappropriateness rate widely ranged, from 2.8% to 59.1%, among the different centres taking into examination. This study assessed that the probability of endoscopic

Procedure	Number
Colonoscopy	10,964,034
Upper endoscopy	6,069,647
Flexible sigmoidoscopy	313,045
Upper endoscopic ultrasound	178,417
Endoscopic retrograde cholangiopancreatography	169,510
Lower endoscopic ultrasound	17,727
Total	**17,712,380**

Source: MarketScan Commercial Claims and Encounters and Medicare

Figure 2. Estimated Annual Number of Endoscopic Procedures in the United States, 2013

detection of a clinically relevant finding was distinctly higher when the procedure was performed for an appropriate, as opposed to an inappropriate indication (5). Therefore, it is clear how appropriateness is the key word for EGD in clinical practice, especially in relation to costs, quality of assistance and nonetheless in the relevance of findings.

Non-invasive approach

A renewed interest for a non-invasive approach to gastric diseases has been observed in the last 20 years. This is probably related to low specificity and sensibility of alarm symptoms, as well as to the above-mentioned limits of upper endoscopy. EGD is in fact bothersome and expensive; nonetheless sampling errors and pathologist intra-observer discrepancies can limit the findings of gastric biopsies. Furthermore, a negative EGD with no relevant histological alterations rule out organic lesions and premalignant conditions, but does not help the management of functional diseases, such as dyspepsia or the non-erosive reflux disease (NERD). Gastropanel® (Biohit Oyj, Helsinki, Finland) is a panel of the following biomarkers: *Pepsinogens I (PGI)* (n.v.: 30-160 μg/l), *Pepsinogens II (PGII)* (n.v.: 3-15 μg/l), *Gastrin-17 (G-17)* (n.v.: 1-7 pmol/l) and *Helicobacter pylori IgA and IgG antibodies* (n.v.: <30 EIU). It permits the indirect evaluation of both the secretory and morphological status of the gastric mucosa. PGI is produced only in the corpus-fundus of the stomach, while PGII it can be found also in the antrum, cardia and in the Brunner glands. Gastrin-17 is an endocrine hormone, produced by the antral G cells, which controls by negative feedback the acid production of the stomach. Lastly, the possibility to evaluate the presence of Anti-H.p. antibodies is crucial due to the widely known impact of H.p. infection on the functionality of gastric mucosa. Since the 80's, before the H.p. era, in the scientific world began to spread the idea of using serum pepsinogens as a "non-invasive gastric biopsy". Today, thanks to improvements in the knowledge of gastric physiology and physiopathology, the effectiveness of the evaluation of the above-mentioned serum gastric markers in a wide range of upper gastrointestinal diseases and conditions is proved.

Dyspepsia

The dosage of these markers finds his main indication in the so-called dyspeptic patients. Dyspepsia is a functional GI disorder consisting in a wide range of symptoms. The international Consensus Report "Rome III" tried to simplify the dyspeptic picture, focusing on two groups of symptoms: 1. The meal-induced symptoms such as *post-prandial fullness and early satiation*; 2. *Epigastric pain and epigastric burning*, excluding other symptoms such as nausea and vomiting (6). The main challenge in these patients has always been whether to perform an EGD or an abdominal US, since the principal worry of the physician has been to misunderstand an organic problem. In the Maastricht III Consensus Report was suggested an algorithm that contemplate to perform an EGD with biopsy sampling in dyspeptic patient older than 45 years, unless alarm features were

present (7a). Through years the possibility of avoiding EGD, with an improvement in the patient's management and a considerable economical saving, has spread leading up to the most recent Maastricht V Consensus Report (7b) in which the statement "An endoscopy-based strategy should be considered in patients with dyspeptic symptoms, particularly in low prevalence *H. pylori* populations." was rejected with a "very low" level of evidence and weak recommendation. Moreover, in the same Consensus it was assessed with a high level of evidence, that Pepsinogen serology is the most useful non-invasive test to explore the gastric mucosa status, making room for the implementation of GastroPanel® in management algorithm of dyspepsia (7, 8).

H. Pylori related gastritis

Several studies have been showing the role of PGI, PGII and PGI/PGII ratio in the determination of acute gastritis associated with *Helicobacter pylori* infection (11, 12). In a Chinese study on 395 subjects, it was assessed a statistically significant link between levels of PGI, PGII and the PGI/PGII ratio with age in healthy subjects and in H.p. infected ones. In particular, higher levels of PGI and above all PGII were found in subjects from the 65-year-old age group against the 35-44-year-old age group. It was nonetheless determined a positive correlation between H.p. IgG levels and PGI, PGII and G-17, while a negative correlation was found with PGI/PGII ratio (9). This inverse correlation between PGI/PGII ratio and acute gastritis seems to suggest the possibility of a slighter more rapid increase in PGII levels than PGI in presence of acute inflammation of gastric mucosa, such as the one caused by *Helicobacter pylori* infection. An Italian study (10) showed a clear increase in PGII levels in H.p.+ patients with active or chronic gastritis compared with lower levels in H.p.- patients. In addition, a slight lower increase in PGI levels resulting in a significant decrease of PGI/PGII ratio, was reported. To strengthen this correlation, has to be mentioned from the literature an American study on a model of acute H.p. infection, consisting of 18 H.p. negative volunteers who were orally inoculated with H.p. which showed PGII levels rising more rapidly than PGI levels, and within two weeks, 94% of inoculated patients showed PGII levels above normal cut-off value against only 72% of them showing elevated PGI values (13). Furthermore, it was assessed an important relation between PGII values and H.p. eradication, showing a relevant decrease of PGII values from 17.5 μg/ L to 8.2 μg /L in eradicated subjects compared with a statistically not significant decrease ($p<0.03$) of the same value in not eradicated subjects (9). These results suggest not only a role of PGII as a biomarker for inflammation but also in the assessment of H.p. eradication.

Gastro-oesophageal reflux disease and Barrett's oesophagus

As previously mentioned, GERD is the most diagnosed digestive condition in primary care. A recent review showed that GERD has a prevalence ranging from 9.8% to 18% in Europe, 18.1%-27.8% in Northern America, with the lowest incidence found in East Asia (2.5%-7.8%) (14). The first line treatment for GERD patients with typical symptoms such as heartburn and/or regurgitation is the PPI prescription, but in those patients, who suffer from NERD or that refer atypical GERD symptoms such as asthma, it can be difficult to prescribe PPI treatment or perform further examination (e.g. pH-metry or impedance-pH). Several studies have shown that fasting G-17 levels could be a surrogate marker of high basal acid output which predisposes to gastric acid reflux (17, 18). A recent Italian study confirmed that in a population of GERD/NERD patients, the ones with Los Angeles A esophagitis and B esophagitis as well as NERD patients showed a basal G17 value, which was significantly lower ($p=0.0001$) than that seen in the control group, by taking a cut-off <1.9 ng/dL (19). As we know from the physiopathology under the umbrella of NERD patients, there are numerous patterns of reflux, such as proper acid reflux, non-acid reflux or functional heartburn (FH). G-17 could be used in order to single out these patterns, that have been standardized by means of Impedance-Ph. An Italian study based on a pool of 35 patients suffering from heartburn, subdivided in 3 groups for 3 different patterns of reflux by Impedance-Ph, demonstrated that G-17 levels well

correlated with the three different categories of patients included in the NERD umbrella, suggesting its use as a surrogate marker of NERD, non-acid reflux disease or FH, without the need of performing invasive tests (20). A major concern in GERD is Barrett's Oesophagus (BO), a precancerous metaplastic lesion, strongly related with a higher risk of oesophageal cancer. A Finnish case-control study, for the first time, observed that low G-17 value could be a risk factor for BO (15), even if other studies seemed to exclude that serum gastric markers could correlate with the severity of GERD (16). Another Italian study (21) demonstrated a significant reduction in fasting G-17 levels in patients with both Erosive Esophagitis an BO in comparison to patients with a normal oesophagus, suggesting a predictive role of G-17 in the early prevention of oesophageal cancer.

Chronic Atrophic Gastritis

PGI levels decrease in corpus atrophic gastritis. Several studies have demonstrated that the decrease is proportional to the severity of atrophy. Furthermore, because of the acid-gastrin negative feedback, the presence of corpus atrophy is confirmed by high levels of Gastrin 17 (22, 23). An Italian study involving 287 patients with a histologically evaluated gastric mucosa, subdivided these patients into 5 groups: Normal (N), Non atrophic chronic gastritis (NCAG), Antrum atrophic gastritis (AAG), Multifocal atrophic gastritis (MAG) and Corpus atrophic gastritis (CAG). The aim of that study was to compare serological values of PGI and G-17 with histological evaluation. The study demonstrated a statistically significant ($p<0.001$) decrease of PGI levels in the CAG group versus N and NCAG group. On the opposite, the study showed a significant ($p<0.001$) increase of G-17 values in CAG patients compared to N and NCAG ones, in according with physiopathology (24). Even though production of G-17, as it's acknowledged, mainly by antral G cells, could suggest a role of this serum marker in the diagnosis of antral atrophy, several studies through years have not been capable of discriminating whether there is a statistically significant correlation between these tools. Some studies agree that G-17 could be used as a quite sensible marker for antral atrophy, due to its decrease caused by antral G cells loss (22, 26); on the other hand, studies still argue G-17 role in antral atrophy screening due to very low sensibility and specificity levels (25, 27). Nevertheless, the literature widely agrees that when atrophy involves both antrum and corpus, serum gastric markers (PGI, PGII, and G-17) fall down (22-24). In the last 15 years, many studies performed worldwide have analyzed the accuracy of PGI or a combination of PGI with other biomarkers such as GastroPanel® in order to detect atrophic gastritis. However, the results in the literature are often difficult to compare because of several differences:

1. Studies performed in different countries with different H. pylori and gastric lesions epidemiology
2. Types of cohort (asymptomatic or dyspeptic)
3. Different techniques to evaluate biomarkers (ELISA or RIA)
4. Different outcomes (CAG or Antrum predominant atrophic gastritis or APAG)

Despite all the above-mentioned differences, as shown in figure 3, low PGI or PGI/PGII ratio appear to have both moderate sensitivity and good specificity (23, 24, 29-31). A recent systematic review with metanalysis has evaluated 20 studies for a total of 4241 subjects, in order to assess the performance of serum panel test (GastroPanel®) for the diagnosis of atrophic gastritis regardless of the site in the stomach. The summary sensitivity was 74.7% (95% confidence interval (CI), 62.0-84.3) and the specificity was 95.6% (95%CI, 92.6-97.4). With a prevalence of atrophic gastritis of 27% (median prevalence across the studies), the negative predictive value was 91% (28).

Gastric Cancer

According to Lauren's classification (32, 34), both intestinal and diffuse types of gastric cancer are linked to gastric inflammation and several studies culminating in Peleo Correa's cascade (33), have confirmed the role of H.p. infection in the pathogenesis of cancer as a precancerous condition. GastroPanel® could be, for instance, a useful examination to select subjects with premalignant conditions (p.e. atrophy; H.p. infection),

Serological Test	Outcome	Population (n)	Sensitivity (CI 95%)	Specificity (CI 95%)	Authors
PGI/PGII Ratio	APAG	Asymptomatic (147)	55% (38-71)	68% (59-76)	Ricci et al.
G-17	APAG	Asymptomatic (147)	48% (32-65)	73% (64-80)	Ricci et al.
GastroPanel (postprandial G-17	ACG	Dyspeptic (404)	83% (74-92)	95% (92-97)	Vaananen et al.
GastroPanel (fasting G-17)	ACG	Dyspeptic (287)	64% (59-70)	93% (89-96)	Germanà et al.
GastroPanel (fasting G-17)	ACG	Dyspeptic (94)	57% (not reported)	95% (not reported)	Nardone et al.
GastroPanel (fasting G-17)	ACG	Asymptomatic (180)	0%	100%	Graham et al.

Figure 3. Sensitivity and Specificity values for serological tests form different works

potentially at risk of gastric cancer. An important Japanese prospective cohort study evaluated the incidence of gastric cancer, performing an EGD annually to 6983 participants of a health program. Gastric cancer development was significantly associated with low PGI levels, with Hazard Ratio's of 8 or 6 according to negative or positive IgG-H.p. antibodies, respectively (35). An important metanalysis (37), with the goal of assessing the availability of serum gastric markers in the follow-up of high-risk patients for gastric cancer (p.e. patients with precancerous lesions such as gastric dysplasia or atrophic gastritis), found that, as for the diagnosis of dysplasia, studies considering pepsinogen I <50 mg/L and pepsinogen I/II ratio <3 obtained sensitivity 65% and specificity ranging from 74%-85%, both with Negative Predictive Value >95%. Authors assumed that, from these data, further studies of this test in the management of high-risk patients seem to be worthwhile. Throughout the years, several studies confirmed the linkage between low serum PGI and higher risk of cancer especially together with the presence of H.p. infection (36, 38, 40, 41). In a Japanese cohort prospective study, serum Pepsinogens levels were assessed in a pool of 101,892 asymptomatic patients. Those with a positive PG test and those with a negative PG test took EGD every 2 and 5 years, respectively. Early-stage gastric cancers and intestinal-type intramucosal cancers accounted for 80% and 39% of all the detected cancers, respectively. Therefore, the authors were able to conclude that Serum PG measurement for mass screening of gastric cancer achieve high recruitment for EGD in intended individuals, a favourable detection rate of gastric cancer and an extremely high proportion of early-stage gastric cancer in all the detected cancers (39). A positive family history (having a first-degree relative with gastric cancer) is a risk factor for gastric cancer (42). The magnitude of the relative risk differs by country and study, ranging from 2 to 10 (43). Positive family history could be a risk factor as a result of shared environment, for example, passing of H. pylori from parents to children, or because of shared genetic factors (44). Considering

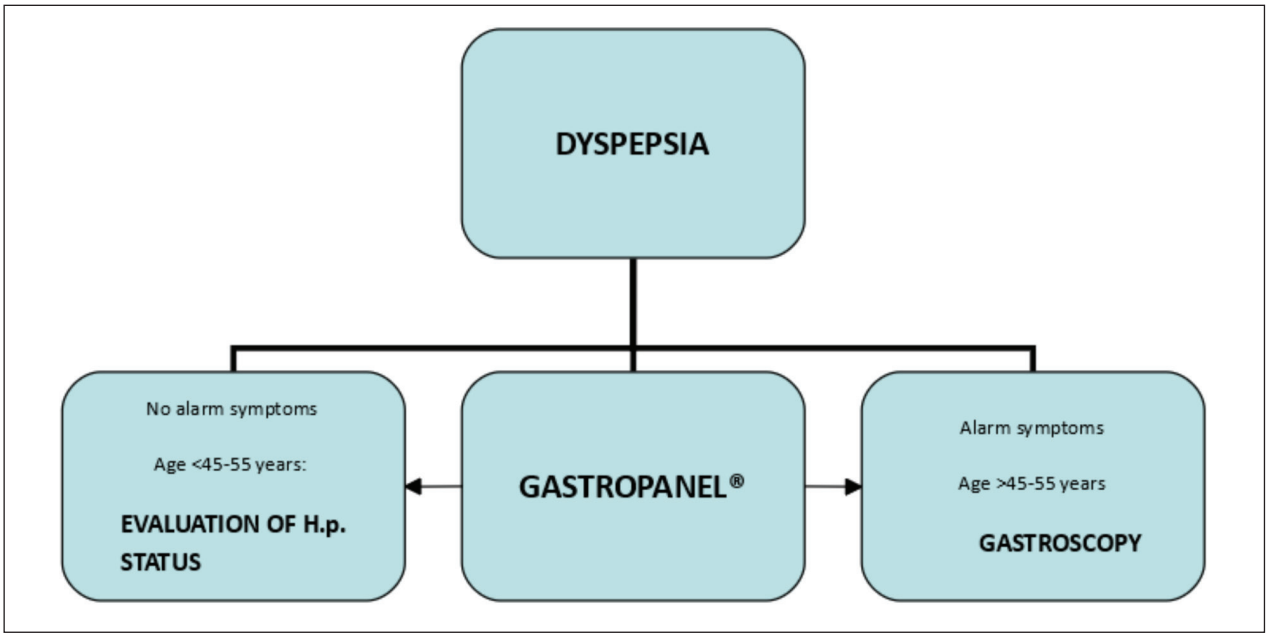

Figure 4. Management algorithm for dyspepsia

these assumptions, an Italian case control study evaluating dyspeptic patients with or without first degree relatives affected by gastric cancer, found interestingly that patients with a positive family history had lower PGI levels and a higher rate of pre-malignant histological alterations than ones with a negative family history (45).

Conclusions

In the last 15 years, plenty of studies on serum gastric markers as a non-invasive approach to the diagnosis of upper-GI diseases have showed that a more profound knowledge of the functionality and morph structural characteristics of the stomach are important in order to discriminate patients that actually need a more invasive diagnostic approach from those who don't. In fact, the implementation of non-invasive test like GastroPanel® in the diagnostic algorithm of upper-GI diseases could save, for example lots of EGD with a relevant improvement in costs and patient's quality of life. From the literature, GastroPanel®, thanks to the high specificity and negative predictive value, seems to be useful in a wide range of upper-GI conditions such as the diagnosis of NCAG, the follow-up of CAG, the evaluation of antrum atrophy, which is a risk stage for gastric cancer and peptic ulcer, in the stratification of patients with GERD and in the management of gastric cancer, with a special focus on familiarity as one of the main risk factors. Above all, the introduction of serum gastric markers evaluation seems to be central in the management algorithm of dyspeptic patients, as shown in figure 4.

References

1. Almario, Christopher V., et al. Burden of Gastrointestinal Symptoms in the United States: Results of a Nationally Representative Survey of Over 71,000 Americans. The American journal of gastroenterology (2018): 1.
2. Peery, Anne F., et al. Burden and Cost of Gastrointestinal, Liver, and Pancreatic Diseases in the United States: Update 2018. Gastroenterology (2018).
3. Everhart, James E., and Constance E. Ruhl. Burden of digestive diseases in the United States part I: overall and upper gastrointestinal diseases. Gastroenterology 136.2 (2009): 376-386.
4. National Cancer Institute SEER cancer statistics review 1975-200
5. Hassan, Cesare, et al. Appropriateness of upper-GI endoscopy: an Italian survey on behalf of the Italian Society of Di-

gestive Endoscopy. Gastrointestinal endoscopy 65.6 (2007): 767-774.
6. Tack, Jan, and Nicholas J. Talley. Functional dyspepsia—symptoms, definitions and validity of the Rome III criteria. Nature reviews Gastroenterology & hepatology 10.3 (2013): 134.
7a. Malfertheiner, Peter, et al. Current concepts in the management of Helicobacter pylori infection: the Maastricht III Consensus Report. *Gut* 56.6 (2007): 772-781.
7b. Malfertheiner, P., et al. Management of Helicobacter pylori infection—the Maastricht V/Florence consensus report. Gut66.1 (2017): 6-30.
8. Tack, Jan, et al. Functional gastroduodenal disorders. Gastroenterology 130.5 (2006): 1466-1479.
9. Shan, Jin-Hua, et al. Changes with aging in gastric biomarkers levels and in biochemical factors associated with Helicobacter pylori infection in asymptomatic Chinese population. World journal of gastroenterology 23.32 (2017): 5945.
10. Di Mario, Francesco, et al. Usefulness of serum pepsinogens in Helicobacter pylori chronic gastritis: relationship with inflammation, activity, and density of the bacterium. Digestive diseases and sciences 51.10 (2006): 1791-1795.
11. Wagner S, Haruma K, Gladziwa U, Soudah B, Gebel M, Bleck J, Schmidt H, Manns M (1994) Helicobacter pylori infection and serum pepsinogen A, pepsinogen A, and gastrin in gastritis and peptic ulcer: significance of inflammation and effect of bacterial eradication. Am J Gastroenterol 89:211-218
12. Plebani M, Basso D, Cassaro M, Brigato L, Scrigner M, Toma A, Di Mario F, Rugge M (1996) Helicobacter pylori serology in patients with chronic gastritis. Am J Gastroenterol 91:954-958
13. Nugalieva, Zhannat Z., Antone R. Opekun, and David Y. Graham. Problem of distinguishing false-positive tests from acute or transient Helicobacter pylori infections. Helicobacter11.2 (2006): 69-74.
14. El-Serag, Hashem B., et al. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut63.6 (2014): 871-880.
15. Sipponen, Pentti, et al. Low circulating levels of gastrin-17 in patients with Barrett›s esophagus. World Journal of Gastroenterology: WJG 11.38 (2005): 5988.
16. Monkemuller, K., et al. Serum gastrin and pepsinogens do not correlate with the different grades of severity of gastro-oesophageal reflux disease: a matched case-control study. Alimentary pharmacology & therapeutics 28.4 (2008): 491-496.
17. Landi, S., et al. P. 01.13: Gastrin-17 as a Non-Invasive Marker for Gerd: A Prospective Study on Sample of 777 Consecutive Patients. Digestive and Liver Disease 49 (2017): e137.
18. De Bortoli, N., et al. P. 06.20 Gerd diagnosis in 340 patients with atypical or extra-esophageal symptoms by using a non-invasive surrogate test. Digestive and Liver Disease 50.2 (2018): e187.
19. Goni, Elisabetta, et al. Mo1135 Gastrin 17 As Non-Invasive Marker of Reflux Disease. Gastroenterology 148.4 (2015): S-616.
20. Savarino, Edoardo V., et al. Gastrin 17 in Singling Out Patients with Different Patterns of Refluxate: A Pilot Study Using Impedance-pH as Reference Standard. Gastroenterology 152.5 (2017): S653.
21. Morana, E., et al. PA. 6 Gastrin-17 (G-17): a serological bio-marker for diagnosis of gastro-esophageal reflux disease (GERD). Digestive and Liver Disease 40 (2008): S77-S78.
22. Sipponen, P., et al. Atrophic gastritis serum levels of amidated gastrin-17 and pepsinogen i in atrophic gastritis: an observational case-control study. Scandinavian journal of gastroenterology 37.7 (2002): 785-791.
23. Väänänen, H., et al. Non-endoscopic diagnosis of atrophic gastritis with a blood test. Correlation between gastric histology and serum levels of gastrin-17 and pepsinogen I: a multicentre study. European journal of gastroenterology & hepatology 15.8 (2003): 885-891.
24. Germaná, B., et al. Clinical usefulness of serum pepsinogens I and II, gastrin-17 and anti-Helicobacter pylori antibodies in the management of dyspeptic patients in primary care. Digestive and liver disease 37.7 (2005): 501-508.
25. Leja, M., et al. Value of gastrin-17 in detecting antral atrophy. Advances in medical sciences 56.2 (2011): 145-150.
26. Agréus, Lars, et al. Rationale in diagnosis and screening of atrophic gastritis with stomach-specific plasma biomarkers. Scandinavian journal of gastroenterology 47.2 (2012): 136-147.
27. Leja, Marcis, et al. The validity of a biomarker method for indirect detection of gastric mucosal atrophy versus standard histopathology. Digestive diseases and sciences 54.11 (2009): 2377-2384.
28. Zagari, R. M., et al. Systematic review with meta-analysis: diagnostic performance of the combination of pepsinogen, gastrin-17 and anti-Helicobacter pylori antibodies serum assays for the diagnosis of atrophic gastritis. Alimentary pharmacology & therapeutics 46.7 (2017): 657-667.
29. Ricci, Chiara, et al. Serological markers for gastric atrophy in asymptomatic patients infected with Helicobacter pylori. The American journal of gastroenterology 99.10 (2004): 1910.
30. Nardone, G., et al. Diagnostic accuracy of the serum profile of gastric mucosa in relation to histological and morphometric diagnosis of atrophy. Alimentary pharmacology & therapeutics22.11-12 (2005): 1139-1146.
31. Graham, David Y., et al. Noninvasive versus histologic detection of gastric atrophy in a Hispanic population in North America. Clinical Gastroenterology and Hepatology 4.3 (2006): 306-314.
32. Lauren, Pekka. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma: an attempt at a histo-clinical classification. Acta Pathologica Microbiologica Scandinavica 64.1 (1965): 31-49.
33. Correa, Pelayo. Human gastric carcinogenesis: a multistep and multifactorial process—first American Cancer Society award lecture on cancer epidemiology and prevention. Cancer research 52.24 (1992): 6735-6740.

34. Fox, James G., and Timothy C. Wang. Inflammation, atrophy, and gastric cancer. The Journal of clinical investigation 117.1 (2007): 60-69.
35. Watabe, H., et al. Predicting the development of gastric cancer from combining Helicobacter pylori antibodies and serum pepsinogen status: a prospective endoscopic cohort study. Gut54.6 (2005): 764-768.
36. Miki, Kazumasa. Gastric cancer screening using the serum pepsinogen test method. Gastric cancer 9.4 (2006): 245-253.
37. Dinis-Ribeiro, M., et al. Meta-analysis on the validity of pepsinogen test for gastric carcinoma, dysplasia or chronic atrophic gastritis screening. Journal of Medical Screening 11.3 (2004): 141-147.
38. Karimi, Parisa, et al. Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention. Cancer Epidemiology and Prevention Biomarkers 23.5 (2014): 700-713.
39. Miki, Kazumasa, et al. Long-term results of gastric cancer screening using the serum pepsinogen test method among an asymptomatic middle-aged Japanese population. Digestive Endoscopy 21.2 (2009): 78-81.
40. Abnet, C. C., et al. Plasma pepsinogens, antibodies against Helicobacter pylori, and risk of gastric cancer in the Shanghai Women's Health Study Cohort. British journal of cancer 104.9 (2011): 1511.
41. Ren, Jian-Song, et al. Serum pepsinogens and risk of gastric and esophageal cancers in the General Population Nutrition Intervention Trial cohort. Gut (2009).
42. Bernini M, Barbi S, Roviello F, Scarpa A, Moore P, Pedrazzani C, et al. Family history of gastric cancer: a correlation between epidemiologic findings and clinical data. Gastric Cancer 2006;9:9-13.
43. La Vecchia C, Negri E, Gentile A, Franceschi S. Family history and the risk of stomach and colorectal cancer. Cancer 2006;70:50-5
44. Yaghoobi M, Bijarchi R, Narod S. Family history and the risk of gastric cancer. Br J Cancer 2009;102:237-42.
45. Di Mario, F., et al. 'Serological biopsy in first-degree relatives of patients with gastric cancer affected by Helicobacter pylori infection. Scandinavian journal of gastroenterology 38.12 (2003): 1223-1227.

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Review

Non-invasive method for the assessment of gastric acid secretion

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Summary. Methods for the measure of gastric acid secretion include invasive and non-invasive tests. The gold-standard to measure the acid output is the collection of gastric after in basal condition (Basal Acid Output, B.A.O.) and after an i.m. injection of pentagastrin (Maximal Acid Output, M.A.O.). However, direct measurement of gastric acid production is out of order in clinical practice, but many GI symptoms are claimed to be related with acid disorders and empirically cured. Hypochlorhydria is associated with precancerous conditions such as chronic atrophic gastritis (CAG). Acid measurement with non-invasive methods (pepsinogens) is supported by international guidelines. (www.actabiomedica.it)

Key words: acid measurement, atrophy, acid secretion, pepsinogens, aspiration test, maximal acid output

Introduction

Gastric acid secretion has a complex pathophysiological role in humans (1) being an important protective mechanism against ingested pathogens and being related to different diseases.

The measurement of acid secretion proves useful in the diagnostic workup and treatment of these conditions: increased gastric acidity is characteristic of duodenal ulcer (DU) and patients with Zollinger-Ellison syndrome; in contrast, low or even absent acid secretion is found in patients with pernicious anemia and atrophic gastritis (AG), which is the most important know risk condition for gastric cancer, and is characterized by a decrease of acid-producing parietal cells and the PG-secreting chief cells. Last but not least, AG is *per se* clinically silent but low acid secretion is also linked with non-neoplastic and "extra-gastric" diseases, even more important than the cancer burden from viewpoints of the public health, and frequent especially in the elder population; these "extra-gastric" conditions are for example risks of malabsorption of vitamin B12 and other micronutrients and the predisposition to enteric infections (e.g. E. coli, Clostridium difficile), being the stomach a natural defense against orale microbes (2-16). The overgrowth of bacteria and fungi in acid-free stomach results also in production of class I carcinogens (e.g. acetaldehyde and nitrosamines) that increase the likelihood of cancer promoting mutations in gastric epithelial cells (17, 18).

The importance of gastric acid in the 21st century, characterized by an evident decrease of peptic ulcer, is especially related to the possibility to detect precancerous conditions that result in a hypochlorhydric or acid-free stomach (19,20) and to the increasing use of proton-pump-inhibitors (PPIs). It could be useful an acid secretion examination prior the PPI medication, to ensure that the patient does not have atrophic gas-

tritis and hypochlorhydric or even achlorhydric stomach (21,22), and to detect people with a higher secretion, who could benefit from antisecretory therapy (23,24). Identification of hyperchlorhydria may have other significant clinical implications, even apart from extreme cases such as the Zollinger-Ellison syndrome. For example, some studies reported that individuals with hyperchlorhydria are at high risk of low-dose aspirin-induced gastropathy (25).

Furthermore, in daily clinical practice, a lot of symptoms, mainly aspecific, are claimed to be caused by an acid disorder and then empirically cured. This is the reason why the measurement of acid secretion remains highly relevant to practicing clinicians.

Methods of measuring gastric acid secretion

Aspiration tests

Methods for the measure of gastric acid secretion include invasive and non-invasive tests.

The gold standard for measuring gastric acid secretion remains the invasive method that is aspiration test (26), involving placing a tube (endoscopic or nasogastric tube) in the most lower part of the stomach. The right position of the tube is usually determined radiologically or with recovery test, which is performed administering 100 mL of water aspirated through the gastric tube.

After that, the basal acid output (B.A.O.) is measured using a pump with continuous suction at a subatmospheric pressure of 30 to 50 mmHg or manually by a syringe in 15 minutes periods. Pentagastrin, histamine or tetragastrin are used as stimulation to collect maximal acid output (M.A.O.), which is aspirated for four 15-minute intervals for a total of one hour. After collecting the samples, the volume and titratable acid are measured using alkaline solution and chemical indicators and the amount of acid in each specimen is calculated (27-31).

Gastric acid aspiration test may cause discomfort to the patient, is invasive and time consuming: for these reasons, it's no longer used in clinical practice, leaving a gap in the diagnostic possibilities: nowadays, considering the high prevalence of acid related diseases, the overuse of PPI (32) and the interest in detecting precancerous conditions such as AG, the absence of a validated tool to measure acid secretion is more evident than ever.

Intragastric pH measurement

A combined pH electrode (usually made of glass or antimony) is positioned transnasally in the gastric corpus and is connected with a recording device. Significant regional variations exist in intragastric pH, also related to post-prandial periods: therefore, it is necessary to check fluoroscopically that the intragastric electrode is maintained in a rather fixed position. This method was developed for esophageal pH studies but gained a popularity for its usefulness in the diagnosis and management of patients with acid-related disorders, in particular for the possibility to evaluate the effect of acid-suppressing drugs. However, this invasive technique gives a measure of intragastric pH and does not offer a quantitative measure of acid secretion.

Non invasive tests

Current interest lies in finding a rapid, reliable and inexpensive non-invasive test (33).

The determination of serum pepsinogen I (sPGI) is regarded as reliable gastric secretory parameter (34-36). sPGI has been reported by a lot of studies and comprehensive and high quality meta-analysis' as predictive of the histological status of the gastric mucosa (37-44), and has been proposed as marker of gastric atrophy and screening tool for gastric cancer, as recommended by international guidelines (45-46). Pepsinogens are aspartic proteinases from which derivate the active enzyme pepsin after exposure to hydrochloric acid, and they are responsible of initial protein digestion functioning between a pH of 1.5 and 5.0. Pepsinogens can be divided in two groups according to biochemical and immunological differences: pepsinogen I (PGA or PGI, pepsinogens 1-5) and pepsinogen II (PGC or PGII, pepsinogens 6,7). PGI is a product of the chief cells and the mucus neck cells in the fundus area (47-48) and reflects the structural and functional status of the stomach. PGI is stable in the individual but show differences based on some individual factors such as age, weight, gender, ethnicity, diet, and circadi-

an rhythm. Since high levels of this enzyme is present in the serum of duodenal ulcers patients (49-51) and it decreases in AG, it can be used in clinical practice as serum biomarker. In fact, the anatomical site of production of PGI underlies a large number of the studies on the relationship between serum pepsinogen levels and gastric acid secretion. PGI-II levels may change during different pathological conditions involving gastric mucosa and this reflects both functional and morphological status of stomach. If PGI/PGII ratio decreases, it might be an indication for precancerous disease such as atrophic gastritis. The plasma levels of fasting gastrin-17 are also able to give indirectly information of gastric acidity.

A diagnostic panel of biomarker tests, GastroPanel (including PGI, PGII, G17 and H. pylori serology) has been proposed to screen subjects at risk for gastric cancer, but also to evaluate patients with chronic stomach complaints. GastroPanel® provides a method to diagnose whether the stomach mucosa is healthy or not and if the atrophic gastritis is H. pylori positive or not (52).

The serologic profile of these atrophy markers in different combinations can be applied to population screening to detect individuals at risk for precancerous lesions to be further evaluated by endoscopy and biopsy (53). The usefulness of GastroPanel® has been demonstrated (54). A meta-analysis of 27 population-based screening studies (comprising 296,553 subjects) and 15 selected groups (with 4385 subjects) (55), indicated that pepsinogen test had a sensitivity of 77% in detecting GC, with negative predictive values ranging from 99.1 and 99.9%. It concludes that this method is useful in identifying high-risk subjects rather than cancer itself. A meta-analysis done in 2017 on 20 studies with a total of 4241 subjects assessed the performance of serum panel test for diagnosis of atrophic gastritis regardless the site in the stomach. It pointed out that sensitivity was 74.7%, specificity was 95.6% and negative predictive value was 91%.

Conclusions

Invasive and non-invasive tests are able to measure gastric acid secretion. Aspiration test is claimed to be the gold standard, but it's not currently used in clinical practice. Several studies recommend the measurement of serum PGI as a screening test for achlorydria (31-40), and as suggested in Kyoto (2014) and Maastricht V (2016) guidelines serological PGI levels are the best indicators of gastric atrophy. It is generally accepted that PGI serum levels reflects acid secretion, based on many studies assessing its correlation with histological findings of AG, which represents a hypochlorhydria of acid-free stomach.

The measure of serum PGI levels in gastric cancer screening and clinical practice is able to identify hypoclorhydria to figure out who of the patients are at high cancer risk and in whom the assessment of severe gastric disorders (such as ulcer disease) through the gastroscopy is mandatory. The possibility to evaluate gastric acid secretion levels by simple measurement a serum markers has significant clinical implications in daily practice.

References

1. Di Mario, F. and Goni, E. (2014). Gastric acid secretion: Changes during a century. Best Practice & Research Clinical Gastroenterology, 28(6), pp.953-965.
2. Cook GC. Infective gastroenteritis and its relationship to reduced gastric acidity. Scand J Gastroenterol Suppl 1985; 111: 17–23.
3. Giannella RA, Broitman SA, Zamcheck N. Influence of gastric acidity on bacterial and parasitic enteric infections. A perspective. Ann Intern Med 1973; 78: 271–6.
4. Sack GH Jr, Pierce NF, Hennessey KN, Mitra RC, Sack RB, Mazumder DN. Gastric acidity in cholera and noncholera diarrhoea. Bull World Health Organ 1972; 47: 31–6.
5. Martinsen, T. C., Bergh, K., & Waldum, H. L. (2005). Gastric juice: a barrier against infectious diseases. Basic & clinical pharmacology & toxicology, 96(2), 94-102.
6. Cavalcoli, F., Zilli, A., Conte, D., & Massironi, S. (2017). Micronutrient deficiencies in patients with chronic atrophic autoimmune gastritis: A review. World journal of gastroenterology, 23(4), 563.
7. Gonçalves C, Oliveira ME, Palha AM, Ferrão A, Morais A, Lopes AI. Autoimmune gastritis presenting as iron deficiency anemia in childhood. World J Gastroenterol. 2014;20:15780–15786.
8. Aditi A, Graham DY. Vitamin C, gastritis, and gastric disease: a historical review and update. Dig Dis Sci. 2012;57:2504–2515.
9. Ludden J, Flexner J, Wright I. Studies on ascorbic acid deficiency in gastric diseases: Incidence, diagnosis, and treatment. Am J Digest Dis. 1941;8:249–252.

10. Mowat C, McColl KE. Alterations in intragastric nitrite and vitamin C levels during acid inhibitory therapy. Best Pract Res Clin Gastroenterol. 2001;15:523–537.
11. Carmel R. Diagnosis and management of clinical and subclinical cobalamin deficiencies: why controversies persist in the age of sensitive metabolic testing. Biochimie. 2013;95:1047–1055.
12. Rush EC, Katre P, Yajnik CS. Vitamin B12: one carbon metabolism, fetal growth and programming for chronic disease. Eur J Clin Nutr. 2014;68:2–7.
13. Rébeillé F, Ravanel S, Marquet A, Mendel RR, Webb ME, Smith AG, Warren MJ. Roles of vitamins B5, B8, B9, B12 and molybdenum cofactor at cellular and organismal levels. Nat Prod Rep. 2007;24:949–962.
14. Stabler SP. Vitamin B12 deficiency. N Engl J Med. 2013;368:2041–2042.
15. Carmel R. Prevalence of undiagnosed pernicious anemia in the elderly. Arch Intern Med. 1996;156:1097–1100
16. Sipponen P, Härkönen M. Hypochlorhydric stomach: a risk condition for calcium malabsorption and osteoporosis? Scand J Gastroenterol. 2010;45:133–138.
17. Salaspuro, M. (2017). Key role of local acetaldehyde in upper GI tract carcinogenesis. Best Practice & Research Clinical Gastroenterology.
18. Salaspuro, M. P. (2003). Acetaldehyde, microbes, and cancer of the digestive tract. Critical reviews in clinical laboratory sciences, 40(2), 183-208.
19. EL-OMAR, EMAD M., et al. Helicobacter pylori infection and chronic gastric acid hyposecretion. Gastroenterology, 1997, 113.1: 15-24.
20. Hunt, R. H., Camilleri, M., Crowe, S. E., El-Omar, E. M., Fox, J. G., Kuipers, E. J., & Sonnenberg, A. (2015). The stomach in health and disease. Gut, gutjnl-2014.
21. Hagiwara, T., Mukaisho, K. I., Nakayama, T., Sugihara, H., & Hattori, T. (2011). Long-term proton pump inhibitor administration worsens atrophic corpus gastritis and promotes adenocarcinoma development in Mongolian gerbils infected with Helicobacter pylori. Gut, 60(5), 624-630.
22. Fox, J. G., & Kuipers, E. J. (2011). Long-term proton pump inhibitor administration, H pylori and gastric cancer: lessons from the gerbil. Gut, 60(5), 567-568.
23. Shiotani, Akiko, and David Y. Graham. "Pathogenesis and therapy of gastric and duodenal ulcer disease." Medical Clinics86.6 (2002): 1447-1466.
24. Phan, Jennifer, Jihane N. Benhammou, and Joseph R. Pisegna. "Gastric hypersecretory states: investigation and management." Current treatment options in gastroenterology 13.4 (2015): 386-397.
25. Iijima, K., et al. "Identification of a high-risk group for low-dose aspirin-induced gastropathy by measuring serum pepsinogen in H. pylori-infected subjects." Journal of gastroenterology 50.3 (2015): 305-312.
26. Ghosh T, Lewis DI, Axon ATR, Everett SM. Review Article: Methods of Measuring Gastric Acid Secretion. Alimentary Pharmacology and Therapeutics. 2011; 33(7):768–781.
27. Hassan, M. A., & Hobsley, M. (1970). Positioning of subject and of nasogastric tube during a gastric secretion study. Br Med J, 1(5694), 458-460.
28. Kovacs, T. O., & Walsh, J. H. (1990). Standard secretory tests: Methodology. In Clinical Investigation of Gastric Function (Vol. 17, pp. 2-12). Karger Publishers.
29. Lawrie JH, Forrest AP. The measurement of gastric acid. Postgrad Med J 1965; 41: 408–17.
30. Findlay JM, Prescott RJ, Sircus W. Comparative evaluation of water recovery test and fluoroscopic screening in positioning a nasogastric tube during gastric secretory studies. Br Med J 1972; 4: 458–61
31. Meeroff JC. The nomenclature of gastric acid output. Dig Dis Sci 1979; 24: 87–8.
32. Ladd AM, Panagopoulos G, Cohen J, Mar N, Graham R. Potential costs of inappropriate use of proton pump inhibitors. Am J Med Sci. 2014;347:446–51
33. Di Mario, F., & Cavallaro, L. G. (2008). Non-invasive tests in gastric diseases. Digestive and liver disease, 40(7), 523-530.
34. Iijima, K., Koike, T., Abe, Y., & Shimosegawa, T. (2014). Cutoff serum pepsinogen values for predicting gastric acid secretion status. The Tohoku journal of experimental medicine, 232(4), 293-300.
35. Samloff, I.M., Secrist, D.M. & Passaro, E. Jr. (1975) A study of the relationship between serum group I pepsinogen levels and gastric acid secretion. Gastroenterology, 69, 1196-1200.
36. Nakanome, C., Akai, H. & Goto, Y. (1983) Serum group I pepsinogen levels in patients with peptic ulcer and normal subjects. Tohoku J. Exp. Med., 139, 151-158.
37. Miki, K., Ichinose, M., Shimizu, A., Huang, S.C., Oka, H., Furihata, C., Matsushima, T. & Takahashi, K. (1987) Serum pepsinogens as a screening test of extensive chronic gastritis. Gastroenterol. Jpn., 22, 133-141.
38. Miki K: Gastric cancer screening using the serum pepsinogen test method. Gastric Cancer 9: 245-253, 2006
39. Haruma, K., Yoshihara, M., Sumii, K., Tari, A., Watanabe, C., Kodoi, A. & Kajiyama, G. (1993) Gastric acid secretion, serum pepsinogen I, and serum gastrin in Japanese with gastric hyperplastic polyps or polypoid-type early gastric carcinoma. Scand. J. Gastroenterol., 28, 633-637.
40. Kinoshita, Y., Kawanami, C., Kishi, K., Nakata, H., Seino, Y. & Chiba, T. (1997) Helicobacter pylori independent chronological change in gastric acid secretion in the Japanese. Gut, 41, 452-458.
41. Pizzi, M., Saraggi, D., Fassan, M., Megraud, F., Di Mario, F., & Rugge, M. (2014). Secondary prevention of epidemic gastric cancer in the model of Helicobacter pylori-associated gastritis. Digestive Diseases, 32(3), 265-274.
42. Agréus, L., Kuipers, E. J., Kupcinskas, L., Malfertheiner, P., Di Mario, F., Leja, M., ... & Rugge, M. (2012). Rationale in diagnosis and screening of atrophic gastritis with stomach-specific plasma biomarkers. Scandinavian journal of gastroenterology, 47(2), 136-147
43. Sipponen P, Graham DY. Importance of atrophic gastritis in diagnostics and prevention of gastric cancer: Application of plasma biomarkers. Scand J Gastroenterol 2007; 42:2-10.

44. Telaranta-Keerie A, Kara R, Paloheimo L, Härkönen M, Sipponen P. Prevalence of undiagnosed advanced atrophic corpus gastritis in Finland: an observational study among 4256 volunteers without specific complaints. Scand J Gastroenterol 2010; 45:1036-1041.
45. Malfertheiner, P., et al. "Management of Helicobacter pylori infection—the Maastricht V/Florence consensus report." Gut 66.1 (2017): 6-30.
46. Sugano, Kentaro, et al. "Kyoto global consensus report on Helicobacter pylori gastritis." Gut 64.9 (2015): 1353-1367.
47. Gritti I, Banfi G, Roi GS. Pepsinogens: physiology, pharmacology pathophysiology and exercise. Pharmacol Res 2000; 41: 265–81.
48. Samloff IM. Cellular localization of group I pepsinogens in human gastric mucosa by immunofluorescence. Gastroenterology 1971; 61: 185–8.
49. Vianello, F., Plebani, M., Piccoli, A., Tessaro, P., Di Mario, F., Naccarato, R., & Burlina, A. (1988). Role of serum pepsinogen in detecting ulcer disease. Clinica chimica acta, 172(2), 335-339.
50. Samloff, I. M. (1989). Peptic ulcer: the many proteinases of aggression. Gastroenterology, 96(2), 586-595.
51. Del Bianco, T., Borgonil, R., Del Bianco, P., Cedaro, P., Vianello, F., Danieli, G. A., & Di Mario, F. (2000). Peptic ulcer inheritance in patients with elevated serum pepsinogen group A levels and without infection of Helicobacter pylori. Digestive and Liver Disease, 32(1), 12-19.
52. Iijima K, Abe Y, Kikuchi R, Koike T, Ohara S, Sipponen P and Shimosegawa T. Serum biomarker tests are useful in delineating between patients with gastric atrophy and normal, healthy stomach. World J Gastroenterol. 2009 February 21; 15(7): 853–859
53. Rugge M, Genta RM, Di Mario F. Gastric Cancer as Preventable Disease. Clinical Gastroenterology and Hepatology 2017; 2-12.
54. Watabe H, Mitsushima T, Yamaji Y et al. Predicting the development of gastric cancer from combining Helicobacter pylori antibodies and serum pepsinogen status: a prospective endoscopic cohort study. Gut 2005;54:764–8.
55. Miki K. Gastric cancer screening by combined assay for serum anti-H. pylori IgG antibody and serum pepsinogen levels-"ABC method". Proc Jpn Acad SerB Phys Biol Sci 2011;87:405–14.

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Review

Non-invasive tests for the diagnosis of *helicobacter pylori*: state of the art

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Summary. Usually, non-invasive tests are the first methods for diagnosing *Helicobacter pylori (HP)* infection. Among these, serological test, stool antigen research and urea breath test are the most used. Antibodies anti-*HP* are not recommended in low prevalence population, moreover they cannot reveal an ongoing infection, but they only prove a contact with the bacterium. Also, they can persist for a long time after the eradication of the infection, therefore, they should not be used to verify the success of eradication therapy. Stool antigen research and Urea Breath Test (UBT) are useful both in diagnosis and during follow-up after eradication treatment. The stool antigen test is cheaper than Urea breath test with similar sensitivity and specificity. Non-invasive tests are not able to diagnose the associated complications to *HP* infection. (www.actabiomedica.it)

Key words: *Helicobacter pylori*, infection, urea breath test, antibodies, stool antigen, eradication, diagnosis

Introduction

Helicobacter pylori (HP) is a very motile, spiral or curved rod-shaped Gram-negative bacterium with multiple flagella that lives in the gastric mucous-coated lining and the gastric pits of the epithelial tissue of the stomach and/or duodenum. Usually, HP colonizes the human stomach during childhood (1) and survives in the human stomach for the lifetime of the carrier (2). In most of the individuals HP infection may be asymptomatic, causing chronic gastritis. Around 20 to 30% of the infected individuals may develop peptic ulcer disease, (3) and less than 2% may develop gastric cancer (4). Therefore, testing for HP infection has become a very important part of the diagnostic process for gastric and duodenal diseases, since the presence or absence of the infection determines the type of treatment to be applied. Testing is also useful for monitoring the effectiveness of anti-microbial treatment.

A number of different invasive and non-invasive diagnostic methods are currently available (1-3). Invasive tests include histological examination and culture of biopsy sample. These tests are considered to be highly specific, particularly histological examination, but its sensitivity is partly dependent on the accuracy of the biopsy procedure. Moreover, both histological examination and culture of biopsy samples are time-consuming and require specialized laboratory facilities with highly trained staff. For these reasons, several techniques for *HP* non-invasive diagnostic tests have been developed and are widely used. They belong to three main categories:

1. Laboratory Serological Assay
2. Helicobacter pylori Stool Antigen tests (HpSA)
3. Urea Breath Test (UBT)

The aim of the present review is to focus on the state of the art of non-invasive test for the diagnosis of HP.

1. Laboratory Serological Assay

Serological testing consists in the dosage of specific antibodies against HP or its toxins on serum samples.

Serological testing is the most widely available non-invasive test for the diagnosis of HP infection. These tests are rapid and cheap and may be helpful in screening populations or in confirming the presence of *HP* infection in case of equivocal results of the other diagnostic methods due to bleeding ulcers, antibiotic and/or antisecretory treatment (5). People infected with *HP* generally present specific circulating antibodies (IgG, IgA and IgM) and these can be detected by specific serological tests. At present, several commercially available tests have been developed, mostly based on IgG detection.

Infection by cytotoxin-associated gene A (CagA) positive strains (type I) is generally more likely to be associated with more serious gastroduodenal disease, as MALT lymphoma and gastric adenocarcinoma, compared with negative (type II) strains. The detection of a serological response to CagA antigen could, therefore, give clinically useful information about the infecting strain. This association, however, is not seen in all countries (6). Several different techniques are available for serum antibody detection, such as *enzyme-linked immunosorbent assay (ELISA)*, *latex agglutination techniques or immunochromatography* (5, 7).

The **ELISA test** is based on sandwich enzyme immunoassay technique with purified *H. pylori* bacterial antigen adsorbed on micro well plate and detection antibody labelled with an enzyme (i.e. horse radish peroxidase). In the final step, a solution containing the enzyme's substrate is added. The subsequent reaction produces a detectable signal, most commonly a color change in the micro well that is read using a spectrophotometer.

Rapid tests are also available. They can be applied at the point-of-care, either based on latex agglutination or on immunochromatographic technology.

The **latex agglutination** tests contain latex particles sensitized with *H. pylori* antigens. *H. pylon* if present in the serum samples will react with the sensitized latex resulting in visual detectable clumps. This assay is still used as a rapid test even if its interpretation (positive/negative result) is highly subjective. Latex agglutination tests are most suitable as near patient tests because they are technically simple to perform and provide a result within minutes rather than the hour or two for ELISA tests.

Immunochromatographic tests employ a combination of anti-human immunoglobulin dye conjugate and highly purified *H. pylori* proteins. As the sample flows through the adsorbent device, the anti-human immunoglobulin dyed conjugate bind to the human IgG antibodies present in positive sample forming an antigen antibody complex. This complex binds to *H. pylori* proteins fixed in the adsorbent device and produces a colored band. At present, this test is little used as laboratory serological assay for *H. pylori*.

Performance Characteristics of Serological Assays

A meta-analysis evaluated the performance of several commercially available quantitative serological assays and found an overall sensitivity and specificity of 85% and 79%, respectively, with no significant differences among assays (4). Three of the qualitative whole blood antibody kits were compared in another study demonstrating sensitivities ranging from 76% to 84% and specificities from 79 to 90 (5). In general, performance characteristics of qualitative tests have been more variable than those of the qualitative tests, which are more standardized.

Limitations of serology for Helicobacter pylori

Several factors limit the usefulness of antibody testing in clinical practice. Firstly, serological testing cannot be used to monitor the effectiveness of antimicrobial therapy, since patients may continue to carry serum antibodies specific to *HP* for several months after eradication. Qualitative tests remain positive for up 3 years after successful treatment and quantitative antibodies levels do not decline significantly for 6 to 12 months after treatment (7). Furthermore, false positive serology tests are more common in low prevalence population, since the positive-predictive-value of antibody testing is greatly influenced by the prevalence of *HP* infection in the considered area (6). Also the American College of Gastroenterology does not

recommend use of serology in low prevalence populations. Generally, the prevalence of elevated IgG in the population tends to be higher in developing countries than in developed ones (8). In case of positivity of a serological test for HP in low-prevalence populations, that positive result should be confirmed with a more reliable test such as the histological examination and culture of biopsy sample (invasive tests) or the urea breath test and the fecal antigen test (non-invasive tests) (2). Finally, antibody tests developed using antigens from one region of the world may not perform well when applied to patients in another part of the world, suggesting that local validation may be necessary (9, 10).

2. Helicobacter pylori Stool Antigen Tests (HpSA)

The evidence that *HP* is present in stools was the prerequisite for the development of non-invasive diagnostic immunoassay tests using mono or polyclonal antibodies, based on the direct identification of the bacterium antigen in stools (15, 16). Unlike other tests normally used for the diagnosis of the infection, *HP* stool antigen test (HpSA) detects the antigen of the bacterium and not the antibodies against it. HpSA is able to diagnose an ongoing infection, while the serological tests are limited to diagnose a contact with the bacterium, which can be current or lifetime. The stool antigen test has many positive aspects: it is non-invasive, quick, has good sensitivity, specificity and reliability (presents good replication standards). This test can be used both for diagnosis of the infection and for monitoring therapy effectiveness, already four weeks after the end of treatment. Its low cost, easy use and the possibility to collect samples and perform the test at home have increasingly widespread the use of this method.

HPsA tests can be divided in ***HpSA ELISA test*** and ***Rapid HpSA test***.

HpSA ELISA Test

HpSA ELISA test uses polyclonal or, more recently, monoclonal antibodies for anti-*HP* adsorbed in micro-wells (17-19). According to several studies and to the International Consensus Report, Urea Breath Test (UBT) and the stool antigen research are considered the first-line diagnostic methods with sensitivity and specificity above 90%. In the diagnosis of the infection, HpSA presents values of sensitivity and specificity only modestly lower than UBT, 93.3% and 93.2% respectively (15, 20-22). However, it is important to underline that a proper collection and storage of the sample are necessary, considering that the test sensitivity drops to 69% if the sample is kept at room temperature for 48-72 hours. Moreover, the method should not be applied on watery stools or diarrhea. In addition, the method loses in sensitivity in the early stage post-eradication therapy for the presence of false-positive responses, with the sensitivity varying from 88 to 92% and the specificity from 87 to 88%. It has been reported that the presence of a relatively higher number of false positives, after eradication therapy, can limit the use in this field for a poor positive predictive value (69% vs. 95% than UBT). It is hypothesized that the presence of false positives immediately after the eradication therapy could be linked to the physiological elimination of gastric cells containing the HP without real infectious capacity, but still recognized positive at the antigenic research (23, 24).

Rapid HpSA Test

Recently, a rapid, mono-phase test for the detection of HP bacteria in stools is available on the market, called Quick test. It consists of a reactive support ("card") utilizing an immunochromatographic technology able to determine the presence of antigens of HP in human feces in a rapid, high quality and easy to perform method (23, 25). To evaluate the performance of the test, the results were compared with the diagnosis of *HP* infection by the reference tests, UBT and by means of a true gold standard of reference, represented by 500 patients who underwent gastroscopy with multiple biopsies. The Quick test on stool is, when compared to the true gold standard (gastroscopy with multiple biopsies), not only accurate for the diagnosis of *HP*, but also to control the effectiveness of eradication therapy. Four weeks after discontinuation of treatment, all patients underwent gastroscopy again to have a true gold standard of reference (26, 27).

Studies published by Yang HR et al. (28) and Vaira D et al (29) show that, after 7 days of treatment, the majority of patients continue to experience symptoms and in theory have to wait the standard 4 weeks before performing the fecal test or the UBT (continuing to suffer for the symptoms). In contrast, if the rapid fecal test made after 7 days of therapy were positive, it would not be clinically appropriate to wait for the standard 4 weeks, and therefore the patient may either be submitted to another eradication therapy or be subjected to gastroscopy for antibiogram (28, 29).

Subsequent studies have shown the effectiveness of the HpSA Immuno-Card test both before and after eradication therapy (Table 1) (25).

As for all diagnostic tests, all results should be interpreted after an accurate clinical evaluation of the patient. If the test result is negative and clinical symptoms persist, it is recommended to investigate further. A negative result does not exclude the possibility of *HP* infection. As for the UBT, the positivity for HpSA can be affected by ongoing bleeding of the gastrointestinal tract, by the presence of atrophic gastritis or by use of proton-pump inhibitor (PPI) drugs, antibiotics, and preparations of bismuth that inhibit the growth of *HP*, for which the sample collection must be performed not earlier than two weeks after the last intake of inhibitors and/or preparations of bismuth and, in the case of taking antibiotics, four weeks after the end of treatment.

The test can be used, 30 days after the completion of eradication therapy, to evaluate the outcome.

It should be noted that the search of the fecal antigen does not allow any screening in depth about the heterogeneity of the strains, and their different pathogenicity, as the target antigens of the tests in use are common to all *HP* subtypes.

Compared with other non-invasive methods (Table 1), Rapid HpSA has been proven simple to perform, particularly useful for patients who have difficulty to undergo the breath test such as children and elderly patients, patients with asthma, after gastrectomy or in case of achlorhydria (28). These tests seem to be a valuable aid, immediate and precise, in guiding diagnosis.

3. Urea Breath Test (UBT)

Urea Breath Test (UBT) is a widely available test with high sensitivity and specificity (from 90 to 100%) for diagnosing *HP* infection. Moreover, its non-invasiveness, the simplicity of execution and safety, make it elective in the suspicion of the infection in adults, children, and in pregnancy (30-32). However, the test specificity of UBT decreases in young children (<6 years old) because it requires active cooperation of the patient (33, 34). *HP* is the only bacterium capable to resist to the gastric acidity, it is able to hide within the gastric mucosa and replicate therein. This characteristic is given by the distinct ability to produce urease, an enzyme that breaks down the urea in the stomach releasing carbonic acid and ammonia. Then, the urease neutralizes gastric acid, creating a favorable microenvironment for the replication of the bacterium. UBT uses the urease activity to detect the infection. Actually, it is based on the administration of urea labeled with a carbon isotope (13C or 14C) which, once ingested, is hydrolyzed by the urease produced by the bacterium into ammonia and carbon dioxide, that is subsequently absorbed across the lining of the stomach and into the blood. Then, this labeled molecule reaches the lungs through the bloodstream and is excreted in the breath.

Table 1. Comparison of sensitivity and specificity for diagnosis and eradication between all the non-invasive tests for HP infection

Test	Sensitivity for diagnosis (%)	Specificity for diagnosis (%)	Sensitivity for eradication (%)	Specificity for eradication (%)
Serological assay (4)	85	79	/	/
HpSA ELISA (15, 20-22)	93.3	93.2	88-92	87-88
Rapid HpSA (25)	91.3	93.5	92	100
UBT (46)	96	93	100	89

Samples of exhaled breath are collected, and the isotopic carbon in the exhaled carbon dioxide is measured. Urease activity is missing in the stomach of healthy subjects, therefore urea administered is absorbed and eliminated by urine. Instead, in *HP*-infected subjects, an amount of labelled carbon dioxide will be exhaled by the patients a few minutes after the ingestion. This indicates the presence of *HP* in the stomach. UBT should be performed at least 4 weeks after the use of antibiotics (the use of a single antibiotic seems not to interfere on the exam) and 2 weeks after the suspension of drugs such as PPIs and H2-receptor antagonists and sucralfate. If the contact time of urea with the gastric mucosa is short, then the hydrolysis doesn't occur and false negative results will be obtained. For this reason several meals have been proposed to administer together with the labelled urea trying to delay the gastric emptying. Therefore, the oral administration of citric acid 10 minutes before the urea administration seems to be the best procedure. UBT is an accurate test for diagnosing HP infection in patients with a healthy stomach, but the sensitivity and specificity of the UBT in subjects who underwent partial gastrectomy are variable because of the lower bacterial load (35-39).

Conclusion

Several non-invasive *HP* tests are established in clinical routine, but at present, there is no single method, among the non-invasive tests, that can be considered as the gold standard for the diagnosis of *HP* infection. Clinical conditions, availability and costs should be considered in choosing the most suitable test. Serological testing is the most available test used for the diagnosis of *HP* infection. In patients treated with PPIs, if it is not possible to stop them for at least 2 weeks, a validated IgG serology test may be used. Antibodies against *HP* and especially against its most specific antigen CagA, remain elevated despite transient decreases of the bacterial load and even for long periods (months, even years) after the eradication. In recent years, new formats of the HpSA using monoclonal antibodies instead of polyclonal antibodies, which lead to a constant quality of the reagents have been developed. A systematic review by Leal et al. demonstrated that stool antigen test using monoclonal antibodies is an efficient non-invasive test for the diagnosis of HP infection also in children (41). UBT is similar to gastroscopy and biopsies for diagnosing HP infection in terms of sensitivity and specificity, but it is not able to show the associated complications such as gastroduodenal ulcers/erosions, gastric intestinal metaplasia nor neoplastic lesions. The 13C-UBT has a high accuracy, is easy to perform, and remains the best test to diagnose HP infection, although it has shown a variable level of accuracy in pediatric age, mainly in young children (<6 years old) as confirmed in a meta-analysis by Leal and colleagues (42). In special cases, such as gastric ulcer or gastric MALT lymphoma, follow-up is necessary with upper digestive endoscopy and then biopsy-based tests should be performed for confirmation of HP eradication. In other situations, a non-invasive test is used. As the HP antibodies remain for months after suppression and even eradication of the infection, serology is not recommended in follow-up. However, stopping PPIs 2 weeks before testing, allows the bacteria to repopulate the stomach, preventing false negatives with UBT, HpSA, rapid urease test, histology and culture. Furthermore, no study has evaluated the washout period necessary after long-term PPI treatment. Regarding UBT, a study claimed that the use of an acidic test meal would overcome the problem of false-negative tests. Anti-H2 drugs may also lead to false-negative results but to a much lesser extent (43, 44) and it is not necessary to stop them before testing if using citric acid. The monoclonal HpSA tests are appropriate and widely available for the primary as well as for post-treatment diagnosis of *HP* infection (40), but there is now overwhelming evidence that the best test in order to assess the efficacy of eradication of *HP* is UBT (Table 1) (46). In fact the guidelines of the European group of *HP* recommend the UBT as the ideal method to confirm the eradication of infection and to ascertain the infection state in patients with recurrent symptoms after eradication treatment (45).

References

1. Parente JM, da Silva BB, Palha-Dias MP, Zaterka S, Nishimura NF, Zeit une JM, (2006). H. Pylori infection in children of low and high socioeconomic status in northeastern Brazil. Am. Trop. Med. Hyg., 75(3): 509-12.

2. Carroll IM, Ahmed N, Beesley SM, Khan AA, Ghousunnissa S, Morain CA, et al, 2004). Microevolution between paired antral and paired antrum and corpus H. Pylori isolates recovered from individual patients. J. Med Microbiol., 53: 669-77.
3. Marques SB. Sao Paoulo: University of Sao Paoulo; 2009. Prevalence of H. Pylori infection associated with clinical disorders diagnosed by upper gastrointestinal endoscopies, retrospective analysis of 1478 cases.
4. Kusters JG, van Vliet AH, Kuipers EJ, (2006). Pathogenesis of H. Pylori infection. Clin. Microbiol. Rev. 19(3): 449-90.
5. Kazu H, Tatsuhiro M, Sachiko N et al. (2003). Current consensus on the diagnosis and treatment of H. Pylori-associated gastroduodenal disease. Keio. J. Med, 52(3): 163-71
6. Vaira D, Holton J, Menegatti M et al. (1999). New immunological assays for the diagnosis of H. Pylori infection. Gut., 45(1): 123-7.
7. Chey WD and Wong BCY, (2007). American College of Gastroenterology Guideline on the Management of H. Pylori Infection. Am. J. Gastroenterol., 1808-1825.
8. Loy CT, Irwig LM, Katelaris PH et al. (1996). Do commercial serological kits for H. Pylori infection differ in accuracy? A meta-analysis. Am. J. Gastroenterol., 91(6): 1138-44.
9. Chey WD, Murthy U, Shaw S et al. (1999). A comparison of three finger stick, whole blood antibody tests for H. Pylori Infection: a Unite States multicenter trial. Gastroenterol., 94: 1512-6.
10. Ho B and Marshall BJ, (2000). Accurate diagnosis of H. Pylori. Serologic testing. Gastroenterol. Clin. N. Am., 29: 853-62.
11. Nurgalieva ZZ and Graham DY, (2003). Pearls and pitfalls of assessing Helicobacter, pylori status. Dig. Liver Dis., 35: 375-7.
12. Marshall BJ, Howat AJ, Wright PA, (1999). Oral fluid antibody detection in the diagnosis of H. Pylori infection. J. Med. Microbiol., 48: 1043-6.
13. Makristathis A,Hirschl AM, Lehourst P et al. (2004). Diagnosis of H. Pylori infection. Helicobacter., 9: 7-14.
14. Hoang TT, Wheeldon TU, Bengtsson C et al. (2004). Enzyme-linked immunosorbent assay for H. Pylori needs adjustment for the population investigated. J. Clin. Microbiol., 42: 627-30.
15. Gisbert JP, Pajares JM, (2004). Stool antigen test for the diagnosis of H. Pylori infection: a systematic review. Helicobacter., 9: 347-68.
16. Gatta L, Ricci C, Tampieri A, Vaira D, (2003). Non-invasive techniques for the diagnosis of H. Pylori infection. Clin. Microbiol. Infect., 9: 489-96.
17. Asfeldt AM, Lochen ML, Sstraume B, Steigen SE, Florholmen J, Goll R, Nestergard 0, Paulssen EJ, (2004). Accuracy of a monoclonal antibody-based stool antigen test in the diagnosis of H. Pylori infection. Scand. J. Gastroenterol., 39: 1073-7.
18. Veijola L, Oksanen A, Lofgren T, Sipponen P, Karvonen AL, Rautelin H, (2005). Comparison of three stool antigen tests in confirming H. Pylori eradication in adults. Scand. J. Gastroenterol., 40: 395-401.
19. Manes G, Zanetti MV, Piccirillo MM, Lombardi G, Balzano A, Pieramico 0, (2005). Accuracy of a new monoclonal stool antigen test in post-eradication assessment of H. Pylori infection: comparison with the polyclonal stool antigen test and urea breath test. Dig. Liver Dis., 37(10): 751-5.
20. Kazemi S, Tavakkoli H, Habizadeh MR, Emami MH, (2011). Diagnostic values of H. Pylori diagnostic tests: stool antigen test, urea breath test, rapid urease test, serology and histology. J. Res. Med. Sci., 16(9): 1097-1104.
21. Choi J, Kim CH, Kim D, Chung SJ, Song JH, Kong JM, et al. (2011). Prospective evaluation of a new stool antigen test for the detection of H. Pylori, in comparison with histology, rapid urease test, (13)C-urea breath test, and serology. J. Gastroenterol. Hepatol., 26(6): 1053-9.
22. Peng NJ, Lai KH, Lo GH, Hsu PI, (2009). Comparison of noninvasive diagnostic tests for H. Pylori infection. Med. Princ. Pract.,18(1): 57-61.
23. Gisbert JP, de la Morena F, Abraira V, (2006). Accuracy of Monoclonal Stool Antigen Test for the Diagnosis of H. Pylori Infection: A Systematic Review and Meta-Analysis. Am. J. Gastroenterol., 1922-1930.
24. Dominguez J, Forne M, Blanco S, Prat C, Gall N, Latorre I, Viver JM, Ausina V, (2006). Comparison of a monoclonal with a polyclonal antibody-based enzyme immunoassay stool test in diagnosing H. Pylori infection before and after eradication therapy. Aliment. Pharniacol. Ther., 15;23(12): 1735-40.
25. Gatta L, Perna F, Ricci C, Osborn J.F, Tampieri A, Bernabucci V, Miglioli M and Vaira D, (2004). A rapid immunochromatographic assay for H. Pylori in stool before and after treatment. Aliment Pharmacol. Ther., 20: 469-474.
26. Vaira D, Malfertheiner P, Megraud F, Axon AT, Deltenre M, Hirschl AM, Gasbarrini G, O'Morain C, Garcia JM, Quina M, Tytgat GN, (1999). Diagnosis of H. Pylori infection with a new non-invasive antigen-based assay. HpSA European study group. Lancet., 3;354(9172): 30-3.
27. Vaira D, Malfertheinner P, Megraud F, Axon AT, Deltenre M, Gasbarrini G, O'Morain C, Pajares-Garcia TM, Quina M, Tytgat GN, (2000). Noninvasive antigen-based assay for assessing H. Pylori eradication: a European multicenter study. The European H. Pylori HpSA Study Group. Am. J. Gastroenterol., 95(4): 925-9.
28. Yang HR, Seo JK, (2008). H. Pylori Stool Antigen (HpSA) Tests in Children Before and After Eradication Therapy: Comparison of Rapid Immunochromatographic Assay and HpSA ELISA. Dig. Dis. Sci., 53: 2053-2058.
29. Vaira D, Vakil N, Menegatti M, van't Hoff B, Ricci C, Gatta L, et al. (2002). The Stool Antigen Test for Detection of H. Pylori after Eradication Therapy. Ann.. Intern. Med., 136,280-287.
30. Calvet X, Sanchez-Delgado J, Montserrat A, Lario S, Ramirez-Lazaro MJ, Quesada M, et al. (2009). Accuracy of diagnostic tests for H. Pylori: a reappraisal. Gin. Infect. Dis., 48(10): 1385-91.

31. Vaira D, Gatta L, Ricci C, Miglioli M, (2002). Review article: diagnosis of H. Pylori infection. Aliment Pharmacol. Ther, 16(Suppl 1): 16-23.
32. Jonaitis LV, Kiudelis G, Kupcinskas L, (2007). Evaluation of a novel 14C-urea breath test "Heliprobe" in diagnosis of H. Pylori infection. Medicina (Kaunas)., 43(1): 32-5.
33. Imrie C, Rowland M, Bourke B, et al. (2001). Limitations to carbonl3-labeled urea breath testing for H. Pylori in infants. J. Pediatr., 139: 734-7.
34. Hino B, Eliakim R, Levine A, Sprecher H, Berkowitz D, Hartman C, Eshach-Adiv 0, Shamir R, (2004). Comparison of invasive and non-invasive tests diagnosis and monitoring of H. Pylori infection in children. Pediatr. Gastroenterot Nutr., 39(5): 519-23.
35. Dominguez-Munoz JE, Leodolter A, Sauerbruch T, Malfertheiner P, (1997). A citric acid solution is an optimal test drink in the 13C-urea breath test for the diagnosis of H. Pylori infection. Gut., 40(4): 459-62.
36. Kopacova M, Bures J, Vorisek V, Konstacky M, Rejchrt S, Zivny P, et al. (2005). Comparison of different protocols for 13C-urea breath test for the diagnosis of H. Pylori infection in healthy volunteers. Scand. I Clin. Lab. Invest., 65(6): 491-8.
37. Gisbert JP, Vazquez MA, Jimenez I, Cruzado AI, Carpio D, Del CE, et al. (2000). 13C-urea breath test for the diagnosis of H. Pylori infection before treatment: is citric acid necessary? Dig. Liver Dis., 32(1): 20-4.
38. Leodolter A, Dominguez-Munoz JE, Von AU, Malfertheiner P, (1999). Citric acid or orange juice for the 13C-urea breath test: the impact of pH and gastric emptying. Aliment. Pharmacol. Ther. 13(8): 1057-62.
39. Tonkic A, Tonkic M, Lehours P, Megraud F, (2012). Epidemiology and diagnosis of H. Pylori infection. Helicobacter., 17 (supp1.1): 1-8.
40. Malfertheiner P, Megraud F, O'Morain CA, Atherton J, Axon AT; Bazzoli F et al. (2012). Management of H. Pylori infection-the Maastricht IV/Florence Consensus Report. Gut., 61: 646-64.
41. Leal YA, Cedillo-Rivera R, Simon JA, Velazquez JR, Flores LL; Torres J, (2011). Utility of stool sample-based tests for the diagnosis of H. Pylori infection in children. J. Pediatr. Gastroenterol. Nutr., 52: 718-28.
42. Leal YA, Flores LL, Fuentes-Panand EM, Cedillo-Rivera R, Torres J, (2011). 13C-Urea Breath Test for the Diagnosis of H. Pylori Infection in Children: A Systematic Review and Meta-Analysis. Helicobacter., 16: 327-337.
43. Gisbert JP, Pajares JM, (2005).13C-urea breath test in the management of H. Pylori infection. Dig. Liver Dis. 37: 899-906.
44. Graham DY, Opekun AR, Jogi M, et al. (2004). False negative urea breath tests with H2-receptor antagonists: interactions between H. Pylori density and pH. Helicobacter., 9: 17-27.
45. Pellicano R, Fagoonee S, Palestro G, Rizzetto M, Figura N, Ponzetto A, (2004). The diagnosis of H. Pylori infection: guidelines from the Maastricht 2-2000 Consensus Report. Minerva. Gastroenterol. Dietol., 50(2): 125-33.
46. Sharma BC, Bhasin DK, Pathak CM, Sinha SK, Ray P, Vaiphei K, et al. [14C]-urea breath test to confirm eradication of Helicobacter pylori. Journal of gastroenterology and hepatology. 1999;14(4):309-12.

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Review

How and when investigating and treating *Helicobacter pylori* infection in children

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Summary. For thousands of years humans have lived in symbiosis with *Helicobacter pylori*. This infection is acquired mainly during childhood and, despite it represents one of the most common infections in humans, only a minority of infected people may develop health issues and life-threatening diseases. For diagnosing *Helicobacter pylori* infection in children we can use, at first, non-invasive diagnostic tests, if clinical pattern and/or history are of suspicion. Then, invasive tests i.e. gastroscopy are necessary to confirm the infection. As antibiotics are not widely available in children affected by *Helicobacter pylori* infection, they should be chosen based on individual antibiotic susceptibility testing obtained by gastric biopsy specimens or the local antibiotic resistance pattern, in empirical treatment is chosen. Test and treat strategy in children should be avoided. In this brief review we summarize how and in which children the infection should be investigate and which the most appropriate eradication treatment should be chosen. (www.actabiomedica.it)

Key words: *Helicobacter pylori*, children, antimicrobial susceptibility testing, antibiotic resistance, esophagogastroduodenoscopy

Introduction

Helicobacter pylori (*H. pylori*) has been belonging to humans at least for 58,000 years (1). The Italian ice mummy, called 'Otzi', which dates to 5,200 years ago, was affected too (2). Therefore, many authors have started considering *H. pylori* as a commensal organism and only an opportunistic pathogen (3). Anyway analyzing the gastric microbiota, when *H. pylori* is present, it tends to dominate the microbial gastric community and patients have lower bacterial richness and diversity compared to healthy people (4).

The prevalence of *H. pylori* infection is higher in non-industrialized countries, but it varies around the world and depends on numerous factors such as age, ethnicity, geographical and socioeconomic status, bacterial virulence, host characteristics and environmental factors (mainly hygienic conditions). The highest infection rates belong to South Korea (50.8%), Shanghai (71.7%) and South Africa (66.1%), while the lowest are in the USA (7.5%) and Australia (15.5%). The higher prevalence rate in children is in Ethiopia (48% in children aged 2-4 years), in Nigeria (82% in children aged 5-9 years) and in Mexico (43% in children aged 5-9 years); while Canadian children have a prevalence of 7.1% (in 5-18 years children). In Europe the most infected children come from Bulgaria (61.7%) and the least infected from the Netherlands (1.2%) (5).

H. pylori infection is predominantly acquired in early childhood and person-to-person contact within the same household appears to be a key route for the transmission, mainly the mother-child dyad. Siblings and grandparents too, specially grandmothers, can be a potential origin of the spreading (6, 7).

After the colonization of the gastric mucosa, *H. pylori* can cause chronic gastritis (usually asymptomatic, particularly in children), peptic ulcer, gastric mucosa-associated lymphoid tissue lymphoma, and gastric adenocarcinoma (8). Furthermore *H. pylori* was classified by WHO as a carcinogenic of first class; this means it has ascertained carcinogenicity in humans (9). Anyway, luckily, the carcinogenic development is quite rare in developed countries while adult or elderly people especially in low-income countries can be at high risk (10).

For these reasons, although many authors around the world have been trying to define and optimize the strategy against *H. pylori* infection in children, there is still not a uniformity of diagnostic and therapeutic approach in pediatrics.

When should we investigate the *H. pylori* infection in children?

H. pylori infection typically remains undetected at the onset because of its lack of specific symptoms (11). Since its discovery, many gastrointestinal and extra-gastrointestinal symptoms have been associated to *H. pylori* infection in children. Hence many children have been often treated simply by a 'test and treat strategy' with the purpose to avoid or reduce the future risk of development of severe complications. Most infected people have no significant symptoms and remain symptoms-free throughout life (12).

Approximately 10-20% of *H. pylori* infected people may develop gastric or duodenal ulcers, gastric atrophy, intestinal metaplasia, dysplasia, lymphoma, or gastric adenocarcinoma depending on virulence features of the bacteria, host characteristics and environmental factors (5).

We do not have pathognomonic symptoms of *H. pylori* infection in children, but recurrent abdominal pain (RAP), perhaps, has been representing the main symptom for which doctors investigate *H. pylori* infection in pediatric age. A recent study in Iran showed that children with RAP had higher *H. pylori* infection rate than controls, although the difference was not statistically significant (13) and a study by Sykora *et al* showed a positive correlation between *H. pylori* infection and functional abdominal pain disorders fulfilling the Rome III criteria (14). On the contrary, *H. pylori* infection was identified only in 52% of cases in Brazilian children investigated for chronic non-ulcer dyspepsia (15).

H. pylori infection can be also associated to several extra-gastrointestinal symptoms, mainly acute idiopathic thrombocytopenic purpura, iron-deficiency anemia, B12 deficiency and allergic diseases (5) and, although some studies suggest an association between *H. pylori* infection and short stature (16), its role on failure to thrive remains controversial (10, 17).

How to investigate

The last ESPGAHN/NASPGHAN guidelines recommend diagnosing *H. pylori* infection in children only when symptoms, which can usually vary among vomiting, persistent/recurrent abdominal pain and gastrointestinal bleeding, can justify esophagogastroduodenoscopy with histological examinations because it is important to determine the underlying cause of the symptoms and not solely focus on the presence of *H. pylori* infection (17).

Despite this, many non-invasive diagnostic exams are available and well validated even in children.

Serological testing is the most widely available non-invasive method for diagnosing *H. pylori* infection. Moreover serology is the only test that is not affected by local changes in the stomach mainly due to drug therapy (proton-pump-inhibitors (PPIs), antibiotics, Non-Steroidal-Anti-Inflammatory-Drugs (NSAIDs)) that could lead to false-negative results in other tests as Urea Breath Test and stool antigen test. Furthermore serological testing is rapid, cheap, and may help in screening populations or in confirming the presence of *H. pylori* infection in case of equivocal results of the other diagnostic methods. Nevertheless, it cannot be used to distinguish between ongoing or past infections neither to monitor the progress of antimicrobial therapy, nor the eradication. The sensitivity ranges from 76% to 84% and specificity from 79% to 90% (18).

H. pylori ***stool antigen test*** using monoclonal antibodies detects the antigen of the bacterium and not the

antibodies and it is able to diagnose an ongoing infection. Low cost, easy use and sample collection at home have increasingly widespread the use of this method. It has a good sensitivity (about 94.6%) and specificity (about 98.4%), only modestly lower than Urea Breath test (18).

Urea Breath Test (UBT) is a widely available test with high sensitivity and specificity (from 90% to 100%) for diagnosing *H. pylori* infection. Moreover, its non-invasiveness, the simplicity of execution and safety make it elective in the suspicion of infection in adulthood, childhood, and in pregnancy. However, the specificity of UBT decreases in young children (< 6 year old) because it requires active cooperation of the patient to avoid false negative results.

Both stool antigen and UBT must be performed at least 4-6 weeks after either PPIs or antibiotics or NASIDs therapy (18).

Another non-invasive approach is the detection of IgG ***antibodies*** anti-*H. pylori* in ***urine*** samples. This might represent a good alternative to blood-based antibody tests and has the major benefit that it can be easily applied in the doctor's office. Being a test based on antibodies title, it presents the same limits as the serological test.

The detection of *H. pylori* in saliva and dental plaque are not still standardized (19).

Molecular methods applied to gastric biopsy specimens have provided a valuable alternative for detecting antibiotic resistance. Among them, polymerase chain reaction (PCR) and fluorescence *in situ* hybridization (FISH) are the most preeminent ones. Although they are still unusual methods in clinical practice, they are gathering the medical community confidence (20).

There is no single test that can be considered as the gold standard for the diagnosis of *H. pylori* infection. The appropriate test for any specific situation will be influenced by the clinical circumstances, the pretest probability of infection, as well as the availability and costs of the individual diagnostic tests. Non-invasive tests are the most usual methods for routine *H. pylori* detection, but they fail to provide complementary information on the location of *H. pylori* in the stomach, on the histopathological lesions underlying the presence of the bacteria and on the antimicrobial profile of the infecting strain. Because of these limitations, it is generally assumed that invasive tests by upper gastrointestinal endoscopy provide a more complete diagnosis. Culture from gastric biopsies should be performed from 2 different locations (i.e. antrum and body) and put in the same jar, for increasing the sensitivity of antimicrobial susceptibility testing (17).

Who to treat

According to the main international guidelines, the primary indications for treating *H. pylori* infection in children are peptic ulcer disease and first-degree familiarity of patients with gastric cancer. Although the eradication is always recommended specially to avoid long-term complications, in children with RAP or functional abdominal pain the risk of not obtaining the complete resolution of symptoms after eradication or the absence of absolute certainty in achieving eradication should always be critically discussed with parents before starting therapy. For these reasons it is essential to perform upper gastrointestinal endoscopy not to misdiagnosis other possible underlying causes.

Furthermore, *H. pylori* eradication seems related to an increase of gastroesophageal reflux disease and allergic diseases. Iron deficiency anemia and idiopathic thrombocytopenic purpura represent the only extra-intestinal diseases where the cause-effect relationship with *H. pylori* infection was demonstrated (17.)

How to treat

A "test and treat strategy" is no longer recommended in children (17).

Although many efforts have been made in obtaining eradication, several difficulties remain to be overcome. For many years the standard triple therapy (PPIs + amoxicillin + clarithromycin or metronidazole) has been the first-line therapy recommended by the international guidelines for the eradication of *H. pylori* infection. During the last years, the widespread use/abuse of antibiotics, particularly for respiratory tract infections, has led to the emergence of increasing resistance of *H. pylori* infection to common antibiotics, mainly to clarithromycin. A recent study showed an evident

increase of clarithromycin resistance, though with no statistical significance, while metronidazole resistance has been reducing in children in our geographical area during the last 13 years. Furthermore, ampicillin resistance has been confirmed to be very rare (21).

Unlike more common pathogens, which can usually be managed with a wide variety of treatments, *H. pylori* is only sensitive to a few drugs. Moreover, the widespread use (and, sometimes, abuse) of antibiotics in children to treat common infections has led to a reduction in antibiotics efficacy against this bacterium. The situation is exacerbated by the fact that *H. pylori* itself generates pharmacological resistances that differ depending on the geographic area and compromise successive second and third-line therapies (22).

For achieving a successful eradication rate three strategic points should be considered:

a) The eradication rate by geographic area.

b) The systematic use of susceptibility testing.

c) Treatment compliance higher than 90% (23).

H. pylori antibiotic resistance varies among countries and among areas within the same country. It depends on the frequency of the antibiotics used for treating other infections, especially those of the respiratory system (5, 21).

The more recent pediatric international guidelines recommend setting up the eradication therapy based on susceptibility testing. Moreover, before starting an eradication therapy, doctors should emphasize the importance of a strict adherence to therapy (17).

Treatment choices if antibiotic susceptibility testing is available

Standard triple therapy (amoxicillin + clarithromycin or metronidazole) or sequential therapy are good options (Table 1). All drugs are administered twice a day. In case of failure, bismuth-quadruple therapy (when bismuth is available), concomitant therapy, triple therapy or sequential therapy with high dosage amoxicillin can be chosen as second choices. Triple therapy with amoxicillin at high dosage (75 mg/kg/day) can increase the eradication rate associating between clarithromycin or metronidazole the one that had not been used previously in the first-line choice (17). Even sequential therapy with high dosage of amoxicillin, if standard triple therapy was used as first-line, may represent a good second-choice, as we can benefit of the amoxicillin increase associated with the ability of sequential regimen to overcome antibiotic resistance (table 2) (24, 25).

Therapeutic options in empirical treatment

Standard triple therapy for 10-14 days or sequential therapy for 10 days are equivalent as first-line therapy, remembering that the use of clarithromycin is recommended if its resistance does not exceed 15% in the considered geographic area (see Table 3). All drugs are administered twice a day. (17) Then, in case of failure, the second-line therapy should be chosen based on antibiotic susceptibility testing.

Table 1: First-line therapy if antimicrobial susceptibility is available (PPIs proton pump inhibitors, CLA: clarithromycin, MET: metronidazole). All drugs are administered two times a day

Standard Triple Therapy with CLA susceptibility	PPIs 1-2 mg/kg/day amoxicillin 50 mg/kg/day clarithromycin 20 mg/kg/day	10-14 days
Standard Triple Therapy with CLA resistance and MET susceptibility	PPIs 1-2 mg/kg/day amoxicillin 50 mg/kg/day metronidazole 20 mg/kg/day	10-14 days
Sequential Therapy	PPIs 1-2 mg/kg/day amoxicillin 50 mg/kg/day metronidazole 20 mg/kg/day	5 days
	+	
	PPIs 1-2 mg/kg/day clarithromycin 20 mg/kg/day tinidazole 20 mg/kg/day	5 days

Table 2. Second-line therapy by using high dose of amoxicillin in empirical treatment (PPIs proton pump inhibitors, CLA: clarithromycin, MET: metronidazole). All drugs are administered two times a day

Standard Triple Therapy if MET susceptibility and CLA used previously	PPIs 1-2 mg/kg/day amoxicillin 75 mg/kg/day metronidazole 20 mg/kg/day	10-14 days
Sequential Therapy if Standard Triple Therapy used previously	PPIs 1-2 mg/kg/day amoxicillin 75 mg/kg/day metronidazole 20 mg/kg/day +	5 days
	PPIs 1-2 mg/kg/day clarithromycin 20 mg/kg/day tinidazole 20 mg/kg/day	5 days

Table 3. First-line therapy in empirical treatment based on local CLA resistance rate (PPIs proton pump inhibitors; CLA: clarithromycin). All drugs are administered two times a day

Standard Triple Therapy if local CLA resistance rate <15%	PPIs 1-2 mg/kg/day amoxicillin 50 mg/kg/day clarithromycin 20 mg/kg/day	10-14 days
Standard Triple Therapy if local CLA resistance rate > 15%	PPIs 1-2 mg/kg/day amoxicillin 50 mg/kg/day metronidazole 20 mg/kg/day	10-14 days
Sequential Therapy	PPIs 1-2 mg/kg/day amoxicillin 50 mg/kg/day metronidazole 20 mg/kg/day +	5 days
	PPIs 1-2 mg/kg/day clarithromycin 20 mg/kg/day tinidazole 20 mg/kg/day	5 days

Otherwise, sequential therapy may be an option even in children with clarithromycin and metronidazole resistance with a good eradication rate, as showed in a recent study (24). Standard triple therapy or sequential therapy with amoxicillin at high dosage (75 mg/kg/day) is another valid alternative in case of antimicrobial resistance or in second-line treatment (table 2).

Eradication monitoring

The success of eradication therapy should be monitored 4 to 8 weeks after the end of antibiotic therapy and 2 weeks after stopping PPIs or 4 weeks after stopping antibiotics and NSAIDs by using either fecal antigen or UBT.

Probiotic use seems to be beneficial in *H. pylori* eradication in children (23). A mixture of probiotics can also be useful in improving side effects due to antibiotics in adult-affected patients. (26).

However, further studies are needed to identify the optimal dose and probiotic combination.

Discussion

H. pylori infection in children often has *pauci*-or asymptomatic clinic presentation.

The recent pediatric international guidelines recommend investigating *H. pylori* only by using upper gastrointestinal endoscopy because it is important to determine the cause underlying symptoms and not

merely focus on *H. pylori* infection. Researchers stress the concept that "test and treat strategy" should no longer be recommended in children. During esophagogastroduodenoscopy, additional biopsy specimens for rapid urease test and culture with susceptibility testing are recommended, but if *H. pylori* infection is an incidental finding during endoscopy, eradication therapy may be considered following careful discussion with parents (17).

In children with iron deficiency anemia and idiopathic thrombocytopenic purpura, *H. pylori* infection should be investigated and if positive, it should be treated after other causes have been excluded. Eradication therapy in persistent or functional abdominal pain is not expected to systematically improve symptoms in children (17).

Because the best results of *H. pylori* eradication are obtained after the first treatment, subsequent therapies using the same antibiotics should be avoided. The effectiveness of the eradication treatments depends on the sensitivity of *H. pylori* strains, the duration of the therapy and patients' compliance. Nowadays, it is essential to tailor eradication therapy based on the antibiotic susceptibility of *H. pylori* strains specific for the considered geographic area.

Hence, clarithromycin should not be used in empirical treatment of *H. pylori* infection in children if its local resistance rate is higher than 15%. Otherwise its use should be limited only to children with known antimicrobial susceptibility (21).

Treatment failure increases the percentage of second-line and third-line therapies, raising the costs of treatments and the number of patients who undergoing numerous antibiotic treatments. So, while choosing between two therapies, it is illogical and unethical to advise using the one with the lower eradication rate as the initial therapy. Considering the restrict choice of antibiotic in children affected by *H. pylori* infection, sequential therapy could be a good treatment option even in case of antimicrobial resistance (24). Equally, increasing the dose of amoxicillin could represent a good alternative option in presence of antibiotic resistance.

Therefore, the best eradication therapy of *H. pylori* infection should be based on individual antimicrobial susceptibility. With regards to this, molecular methods from biopsies (real-time PCR and FISH) have become one of the most promising techniques, even preferable to culture by gastric specimens (20).

Alternatively, if antimicrobial susceptibility tests are not available, empirical therapy based on local antibiotic resistance still remains the best therapeutic option (27).

Finally, since all antibiotic therapies generate unpleasant (but usually not serious) side effects, we believe that the combination with probiotics helps the patient withstand therapy which may easily result in unpleasant ailments (especially of the gastrointestinal tract) (26).

References

1. Linz B, Balloux F, Moodley Y, et al. An African origin for the intimate association between humans and *Helicobacter pylori*. Nature 2007; 445: 915-918.
2. Megraud F, Lehours P, Vale FF. The history of *Helicobacter pylori*: from phylogeography to paleomicrobiology. Clin Microbiol Infect 2016; 22: 922-927.
3. Li J, Perez-Perez GI. *Helicobacter pylori* the latent human pathogen or an ancestral commensal organism. Front Microbiol 2018; 3; 9: 609. doi: 10.3389/fmicb.2018.00609.
4. Llorca L, Perezs-Perez GI, Urruzuno P, et al. Characterization of the gastric microbiota in a pediatric population according to *Helicobacter pylori* status. Pediatr Infect Dis J 2017; 36: 173-178.
5. Iwanczak BM, Buchner AM, Iwanczak F. Clinical differences of *Helicobacter pylori* infection in children. Adv Clin Exp Med 2017; 26: 1131-1136.
6. Urita Y, Watanabe T, Kawagoe N, et al. Role of infected grandmothers in transmission of *Helicobacter pylori* to children in a Japanese rural town. J Paediatr Child Health 2013, 49: 394-398.
7. Manfredi M, Iuliano S, Gismondi P, et al. *Helicobacter pylori* infection: we should always verify the intrafamilial transmission. Biol Med (Aligarth) 2016; 9.1. DOI: 10.4172/0974-8369.1000366.
8. Hsu PI, Yamaoka Y, Goh KL, et al. *Helicobacter pylori* infection. Biomed res Int 2015; 2015: 278308. doi: 10.1155/2015/278308.
9. Schistosomes, liver fllukes and *Helicoobacter pylori*: IARC Working Group on the Evaluation of Carcinogenic Risks to Humans; Lyon, 7-14 June 1994. IARC Monogr Eval Carcinog Risks Hum 1994; 61: 1-241.
10. Sierra MS, Hastings EV, Goodman KJ. What do we know about benefits of *H. pylori* treatment in childhood? Gut Microbes 2013; 4: 549-67.
11. Torres J, Pérez-Pérez GI, Goodman KJ, et al. A compre-

hensive review of the natural history of *Helicobacter pylori* infection in children. Arch Med Res 2000; 31: 431-69. PMID: 11179581; http://dx.doi.org/10.1016/S0188-4409(00)00099-0.
12. Laszewicz W, Iwanczak F, Iwanczak B, Task Force of the polish Society of Gastroenterology. Seroprevalence of *Helicobacter pylori* infection in Polish children and adults depending on socioeconomic status and living conditions. Adv Med Sci 2014; 59: 147-150.
13. Alimohammadi H, Fouladi N, Salehzadeh F, et al. Childhood recurrent abdominal pain and *Helicobacter pylori* infection, Islamic Republic of Iran. East Mediterr Health J 2017; 22: 860-864.
14. Sykora J, Huml M, Siala K, et al. Pediatric Rome III criteria-related abdominal pain is associated with *Helicobacter pylori* and not with Calprotectin. J Pediatr Gastroenterol Nutr 2016; 63: 417-422.
15. Correa Silva RG, Machado NC, Carvalho MA, Rodrigues MA. *Helicobacter pylori* infection is high in paediatric non-ulcer dyspepsia but not associated with specific gastrointestinal symptoms. Acta Paediatr 2016; 105: e228-e231.
16. Goodman KJ, Correa P, Mera R, et al. Effect of *Helicobacter pylori* infection on growth velocity of school-age Andean children. Epidemiology 2011; 22: 118-126. doi: 10.1097/EDE.0b013e3181fe7e31.
17. Jones NL, Koletzko S, Goodman K, et al. Joint ESPGHAN/NASPGHAN Guidelines for the management of *Helicobacter pylori* in Children and Adolescents (Update 2016). J Pediatr gastroenterol Nutr 2017; 64: 991-1003.
18. Aloe R, Bonaguri C, de'Angelis GL, Fornaroli F, et al. Non-Invasive Methods - Common techniques: serological, stool antigen, and Urea Breath Tests. In "*Helicobacter pylori*: Detection Methods, Diseases and Health Implications", Marco Manfredi and Gian Luigi de'Angelis eds, NOVA Publishers, 2013, Chapter 1, pag. 5-18.
19. Horemans T, Boulet G, Delputte LM, Cos P. Non-Invasive Methods - Unusual techniques: Stool and Dental Plaque PCR, Urinary antibodies. In "*Helicobacter pylori*: Detection Methods, Diseases and Health Implications", Marco Manfredi and Gian Luigi de'Angelis eds, NOVA Publishers, 2013, Chapter 2, pag. 19-38.
20. Almeida C, Azevedo NF, Joao Vieira M. Invasive Methods - Unusual techniqes - Identification of H. pylori from biopsies: culture, PCR and FISH. In "*Helicobacter pylori*: Detection Methods, Diseases and Health Implications", Marco Manfredi and Gian Luigi de'Angelis eds, NOVA Publishers, 2013, Chapter 4, pag.69-81.
21. Manfredi M, Gismondi P, Maffini V, et al. Primary Antimicrobial Susceptibility Changes in Children with *Helicobacter pylori* Infection over 13 Years in Northern Italy. Gastr Res Pract 2015; Article ID 717349, 5 pages. http://dx.doi.org/10.1155/2015/717349.
22. Manfredi M, de'Angelis GL. Eradication of *Helicobacter pylori*: in search of a better therapy. Clin Microbial 2013, 1:1. http://dx.doi.org/10.4172/cmo.1000e101.
23. Kalach N, Bontems P, Raymond J. *Helicobacter pylori* infection in children. Helicobacter 2017; 22 (Suppl. 1): e12414. https://doi.org/10.1111/hel.12414.
24. Gaiani F, Manfredi M, Iuliano S, et al. Can Sequential Therapy Overcome Antimicrobial Resistance in Children with *Helicobacter pylori* Infection? Biomed J Sci &Tech Res 2018; 4(5). doi:10.26717/BJSTR.2018.04.001111.
25. Tong JL, Ran ZH, Shen J, Xiao SD. Sequential therapy vs. standard triple therapies for *Helicobacter pylori* infection: a meta-analysis. J Clin Pharm Ther 2009; 34: 41–53.
26. Manfredi M, Bizzarri B, Sacchero RI, et al. *Helicobacter pylori* Infection in Clinical Practice: Probiotics and a Combination of Probiotics + Lactoferrin Improve Compliance, But Not Eradication, in Sequential Therapy. Helicobacter 2012; 17: 254-263. doi: 10.1111/j.1523-5378.2012.00944.x
27. Manfredi M, Bizzarri B, Manzali, et al. Which treatment in *Helicobacter pylori* infection? Clin Exp Pharmacol 2013, 3:4 http://dx.doi.org/10.4172/2161-1459.1000139

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Review

Helicobacter pylori, transmission routes and recurrence of infection: state of the art

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Summary. Helicobacter pylori (*H. pylori*) infection is one of the most common infection in humans, affecting more than half of the population. The prevalence of the infection varies widely in rural developing areas (more than 80%) compared to urban developed ones (less than 40%), as a consequence of different socioeconomic and hygienic conditions. *H. pylori* infection is usually acquired during childhood; infected people usually remain asymptomatic, but about 30% of individuals may develop mild to severe upper gastrointestinal diseases such as gastritis, peptic ulcer, gastric cancer or MALT lymphoma. The transmission route is not clear yet; the person-to-person transmission, especially within the same family appears to be prevalent, but also environmental contamination is possible. The eradication without a specific therapeutic regimen is very unlikely and the reinfection rate after an effective eradication therapy is quite rare. The reinfection rate will increase if there are family members affected. (www.actabiomedica.it)

Key words: Helicobacter pylori, epidemiology, prevalence, transmission, reinfection, recurrence

Introduction

Helicobacter pylori (H. pylori) is an organism that has been intimately associated with humans for many centuries, even though it was discovered only in the early 1980s (1). *H. pylori* infection is a significant cause of morbidity and mortality in humans as it has a crucial role in the development of chronic gastritis, gastroduodenal ulcer, and gastric cancer which may seriously affect the quality of life of the patients (2). Since 1994 *H. pylori* has been classified in the first group of carcinogenic agents by WHO (3). For these reasons, the eradication of *H. pylori* infection remains a worldwide public health concern. All features implicated in the pathogenesis of *H. pylori*-related diseases are not completely understood and epidemiological data in certain countries are discordant, as in the so-called "African enigma". African enigma describes the discordance between the prevalence of *H. pylori* infection and *H. pylori*-related gastric cancer: despite the prevalence of *H. pylori* infection is high, there is no expected correlation with related gastric disease. Similar observations have now been made in other geographical areas. These data are of great interest in relation to the pathogenesis of *H. pylori*-related diseases and should lead to a careful examination of host, environment and *H. pylori* virulence (4, 5). *H. pylori* infection is predominantly acquired during childhood, usually persists throughout life without a specific treatment and interpersonal contact seems to be the main route of infection. In countries where the socio-economic conditions have been improving, there is evidence that the prevalence of *H. pylori* infection is declining. However, large proportions of adult populations remain infected so the burden of infection manifesting as peptic ulcer disease and gastric cancer continues to be relevant (6).

Anyway, also in more developed countries infection rates are heterogeneous, with well-defined high-risk groups. These groups include the elderly, those who live in poor hygienic conditions, migrants from high prevalence areas, the institutionalized and possibly rural dwellers in some areas. For these reasons, effective eradication treatments are needed, with the aim to prevent complications. Furthermore, intrafamilial transmission should also be considered, screening all the parents of infected subjects (7).

The aim of the present review is to focus on transmission routes and recurrence of infection of *H. pylori*.

Transmission routes

The route of transmission of *H. pylori* is not completely understood. The only known reservoir is the human stomach (8) and since *H. pylori* appears to have a narrow host range, new infections are thought to occur as a consequence of direct human-to-human transmission or environmental contamination. Person-to-person transmission can be subdivided in two main categories: vertical and horizontal transmission. The vertical mode is infection spread from ascendant to descendent within the same family, while horizontal transmission involves contact with individuals outside the family or environmental contamination (9). Several studies in the literature focus on the relation between *H. pylori* infection and familial exposure. Most of them (10, 11) support the concept of intrafamilial clustering of *H. pylori* infection. They suggest that person-to-person transmission occur in the same family possibly because of close interpersonal contacts, moreover, family members share a genetic predisposition to *H. pylori* infection, finally, family members are exposed to a common source of infection and share the socio-economic status. Instead, in developed countries with low *H. pylori* prevalence, the infected mother is likely to be the primary source of infection in the children (12). In population with high *H. pylori* prevalence and poor socio-economic conditions, infected mothers are less involved in the transmission inside the family, while transmission among siblings as well as outside acquisition appears to play a major role in the transmission pathway. The person-to-person transmission may occur by three possible pathways: the gastro-oral, the oral-oral and the fecal-oral routes, but no predominant mechanism of transmission has been yet identified.

Gastro-Oral Transmission

H. pylori is acquired in early life and the vomiting of achlorhydric mucus may serve as a vehicle for transmission. The transmission route could be via gastric juice, especially as a result of vomiting in childhood (13). Studies reported data about isolation percentage of *H. pylori* from gastric juice of symptomatic patients: the microbe appears to survive outside the human body in unbuffered gastric juice and is often present in high quantities in vomit. These results support the gastro-oral transmission, especially during childhood, in association with poor hygienic conditions.

Oral-Oral Transmission

The saliva is another possible source of *H. pylori*, since the gastric microbiome can reach and colonize the mouth after regurgitation or vomiting. *H. pylori* has been cultured directly from saliva and the DNA has been frequently amplified from saliva, subgingival biofilm and dental plaque (14). Based on these reports, the mouth might be a reservoir of *H. pylori* (15). The oral-oral transmission involves especially the mother-child transmission: the oral secretions of the mother, which may be contaminated with *H. pylori*, can be directly transmitted to the infant. Negative arguments against the oral-oral transmission include the discordance of strains type between mother and child (16, 17), although this is controversial, as other reports demonstrate the presence of common strains infecting couples (18). These data suggest that although saliva might work as a vehicle of transmission, the oral-oral transmission is not the main modality of transmission of *H. pylori*, at least in adults.

Fecal-Oral Transmission

H. pylori DNA has been frequently detected in human feces (19, 20) but attempts to culture *H. pylori* from feces have had limited success because the bacterium persists there predominantly in a non-culturable (coccoid) form.

Transmission by water

The exact way by which *H. pylori* gains access to the human stomach is unknown and also environmental contamination should be considered. When hygienic conditions are poor, household contamination of treated water cannot be ruled out. Some authors hypothesize that water plays a role both as an environmental reservoir of infection and as a medium in the fecal-oral transmission of *H. pylori* infection. It was demonstrated that children living in houses with an external water supply, or those consuming raw vegetables, which are often irrigated with untreated sewage water, had a higher prevalence of *H. pylori* infection (21, 22). The association of serum antibodies against *H. pylori* with serum antibodies against two known waterborne pathogens (*Hepatitis A virus*) (23) and *Giardia* (24), suggests that the infection may be waterborne or related to poor hygienic conditions.

Transmission by Food

As it happens with water, food products may also be contaminated while being handled under poor hygienic conditions. Several studies address the role of food in the transmission of *H. pylori*. Food products analyzed are mainly milk, meat and vegetables. Among these milk products are the most studied, probably because the infection is mainly acquired during childhood and milk is mostly consumed during this period (25).

Recurrence of infection

Recurrence of *H. pylori* is thought to occur via two distinct mechanisms: recrudescence and reinfection. Recrudescence reflects the reappearance of the original strain of *H. pylori* following its temporary suppression rather than successful eradication. Instead, true reinfection occurs when, after successful eradication, a patient becomes infected with either the original strain or a new strain of *H. pylori* (26). Many investigators have found that recurrence rates during the first 3-12 months after cure are due to late recrudescence. A documented *H. pylori* negativity for 1 year after treatment is a reliable indicator of successful eradication without recrudescence. It seems that low-efficacy therapy does not actually cure *H. pylori* infection in the gastric mucosa, but only temporarily suppresses it without eradicating it completely from the host (27-29).

H. Pylori reinfection after successful eradication is an important problem in the management of this disease. Recrudescence rather than reinfection is likely to be responsible for most recurrent cases because the recurrences decrease with time, declining sharply after the first year, and identified strains (before and after therapy) are usually genetically identical. Reported "true" reinfection rates in adults generally varied from 0 to 23.4%. The annual "true" reinfection rates were much lower than the reported annual recurrence rates within the first years after eradication (26). Intrafamilial transmission could be also involved in the reinfection of H. pylori; its presence among asymptomatic family members may facilitate the transmission within households (7). The reinfection rate after eradication therapy for *H. pylori* is extremely low in developed countries such as Europe and the USA. The annual reinfection rates reported by Zendehdel et al. were around 1% (29). In contrast to the low rates of *H. pylori* reinfection reported in western populations, high recurrence rates have been reported in developing countries (30-33). Therefore the high prevalence of *H. pylori* infection may possibly be associated with high recurrence of infection after eradication because of the high risk of re-exposure (34). Genetic factors may also play a role, susceptible individuals who have eradicated *H. pylori* may be prone to reinfection when they are exposed to *H. pylori*-positive people (7).

Several articles dealing with the occupational risk of infection by *H. Pylori* have been published. Matysiak-Budnik (35) showed an association between occupational exposure and an increased risk of infection. Williams (36), too, stated that there were increased occupational risks for endoscopy personnel.

Conclusion

The prevalence of *H. pylori* is closely related to socio-economic conditions and accordingly, this infection is more common in developing than in developed countries. Intrafamilial transmission is a modality of

infection and reinfection, which should never be forgotten. The close contact among family members appears to be a key route responsible for the transmission of *H. pylori* (37, 38). Therefore, all family members of infected people should always be screened, regardless of their symptoms. In this way, by reducing the undiagnosed patients, the risk of development of the *H. pylori*-related diseases could be reduced, decreasing the risk of reinfection within the family and then limiting the spread of *H. pylori*. Its recurrence in the first year after eradication therapy is likely due to a mixture of recrudescence of infection and reinfection. The reinfection is predominant in the subsequent years after eradication while the risk of recurrence tends to decrease. Since the early age at acquisition of *H. pylori* infection may result in more intense inflammation and the early development of atrophic gastritis and subsequent risk of gastric ulcer, gastric cancer, or both, health education programs within the family (washing of hands and mouth, brushing teeth, no sharing of food plates or drinking glasses, no sharing of spoons in feeding children) should be implemented. Then, to optimize eradication rate of *H. pylori* infection, not only the choice of antibiotics should be considered, possibly based on culture and antibiogram, but also the geographic site, the demographic factors, and the local infection recurrence rate should be analyzed.

References

1. Linz B, Balloux F, Moodley Y, et al. (2007). An African origin for the intimate association between humans and H. Pylori. Nature., 445:915-8.
2. Malfertheiner P, Megraud F, O'Morain CA, Atherton J, Axon ATR, Bazzoli F, Gensini GF, Gisbert JP, Graham DY, Rokkas T, El-Omar EM, Kuipers EJ, The Eur°P,wi Helicobacter Study Group (EHSG), (2012). Management of Helicobacter 01 infection — the Maastricht IV/ Florence Consensus Report. Gut., 61:646-664.
3. IARC Working Group on the Evaluation of Carcinogenic Risks to ti.„"onogr Schistosomes, liver flukes and H. Pylori 7-14 June 1994, Lyon MK IV' Eval. Carcinog. Risks Hum., 61:1-241.
4. Ghoshal U, Chaturvedi R, Correa P. The enigma of H. Pylori and gastric cancer. Indian J. Gastroenterology 2010.29- 95-100.
5. Agha A, Graham I), (2005). Evidence-based examination of the African enigma in n relation to H. Pylori infection. Scand. J. Gastroenterol. 40:523-529.
6. Fock KM, Talley N, Moayyedi P, Houn. st R, Azuma T, Sugano K, Xiao SD, Lam SK, Goh KL, Chiba T, Uemura N, Kim JG, Kim N, An TL Mahachai V Mitchell H Rani AA, Liou JM, Vilaichone RK, Sollano J, (2008). Asia-Pacific consensus guidelines on gastric cancer prevention. J. Gastroenterol. Hepatol, 23: 351-65.
7. Ryu KH, Yi SY, Na YJ et al. (2010). Reinfection rate and endoscopic changes after successful eradication of H. Pylori. World. J. Gastroenterol., 16:251-255.
8. Schwarz, S., Morelli, G., Kusecek, B., Manica, A., Balloux, F., Owen, R.J., Graham, D.Y., van der, M.S., Achtman, M., Suerbaum, S., (2008). Horizontal versus familial transmission of H. Pylori. PLoS Pathogens 4, el 000180.
9. Rothenbacher D, Bode G,Berg Get al. (1999). H. Pylori among preschool children and their parents: evidence of parent-child transmission. J. Infect. Dis., 179:398-402.
10. Parente F, Maconi G, Sangaletti 0 et al. (1996). Prevalence of H. Pylori infection and gastroduodenal lesions in spouses of H. Pylori positive patients with duodenal ulcere. Gut., 39:634-638.
11. Weyermann M, Rothenbacher D, Brenner H., (2009). Acquisition of H. Pylori infection in early childhood: independent contributions of infected mothers, fathers, and siblings. A. J. Gastroenterol., 104,182-189.
12. Axon AT, (1995). Review article: is H. Pylori transmitted by the gastro—oral route? Aliment. Pharmacol .Ther., 9,585-588.
13. Burgers R, Schneider-Brachert W, Reischl U, Behr A, Hiller KA, Lehn N, Schmalz G, Ruhl S, (2008). H. Pylori in human oral cavity and stomach. Eur. J. Oral. Sci., 116,297-304.
14. Gebara EC, Faria CM, Pannuti C, Chehter L, Mayer MP, Lima LA, (2006). Persistence of H. Pylori in the oral cavity after systemic eradication therapy. I Clin. Periodont., 33,329-333.
15. Gisbert JP, Arata IG, Boixeda D, Barba M, Canton R, Plaza AG, Pajares JM, (2002). Role of partner's infection in reinfection after H. Pylori eradication. Easy. Gastroenterol. flepatol., 14,865-871.
16. Vale FF, Vitor JM, (2007). Genomic methylation: a 1001 for typing Helicobucter pylori isolates. Appl. Env iron. Microbiol., 73,4243-4249.
17. Kivi M, Tindberg Y, Sorberg M, Casswall TH, Befrits R, Hellstrom PM, Bengtsson C, Engstrand L. Granstrom M, (2003). Concordance of H. Pylori strains within families. J. Clin. Microbiol., 41,5604-5608.
18. Queralt N. Bartolome R, Araujo R, (2005). Detection of H. Pylori DNA in human faeces and water with different levels of faecal pollution in the north-east of Spain. J. Appl. Microbiol., 98,889-895.
19. Klein PD, Graham DY, Gaillour A, Opekun AR, O'Brian Smith E, the Gastrointestinal Physiology Working Group, (1991). Water source as risk factor for H. Pylori infection in Peruvian children. Lancet., 337:1503-6.
20. Oderda G, Rapa A, Ronchi B, et al. Detection of Helicobacter pylori in stool specimens by non-invasive anti-

gen enzyme immunoassay in children: multicentre Italian study. *BMJ*. 2000;320(7231):347-8.
21. Hopkins RJ, Vial PA, Ferreccio C et al. (1993). Seroprevalence of H. Pylori in Chile: vegetables es may serve as one route of transmission. J. Infect Dis., 168:222-6.
22. Bizri AR, Nuwayhid IA, Hamadeh GN, Steitieh SW, Choukair AM, Musharrafieh UM, (2006). Association between hepatitis A virus and H. Pylori in a developing country: the saga continues. J. Gastroenterol. Hepatol., 21,1615-1621.
23. Moreira Jr ED, Nassri VB, Santos RS, Matos JF, de Carvalho WA, Silvani CS, Santana S, (2005). Association of H. Pylori infection and giardiasis: results from a study of surrogate markers for fecal exposure among children. World. J. Gastroenterol., 11, 2759-2763.
24. Vale FF, Vitor JMB, (2010).Transmission pathway of H. Pylori: Does food play a role in rural and urban areas? Int. J. Food. Microbiol., 138: 1-12.
25. Zhang YY, Xia HHX, Zhuan ZH, Zhong J, (2009). Review article: "True" re-infection of H. Pylori after successful eradication: worldwide annual rates, risk factors and clinical implications. Aliment Pharrnacol Ther., 29(2):145-60.
26. Sachs G, Scott DR. H. Pylori: eradication or preservation? F1000 Medicine Reports 2012; 4:7.
27. Adachi M, Mizuno M, Yokota K, Miyoshi M, Nagahara Y, Maga T, Ishiki K, Inaba T, Okada H, Oguma K, Tsuji T, (2002). Reinfection rate following effective therapy against H. Pylori infection in Japan. J Gastroenterol. Hepatol., 17: 27-31.
28. Cameron EA, Bell GD, Baldwin L, Powell, KU Williams SG, (2006). Long-term study of re-infection following successful eradication of H. Pylori infection. Aliment Pharmacol Ther., 23: 1355-1358.
29. Zendehdel N, Nasseri-Moghaddam S, Malekzadeh R, Massarrat S, Sotoudeh M, , Siavoshi F 2005). H. Pylori reinfection rate 3 years after successful eradication. J. Gastroenterol. Hepatol., 20: 401-404.
30. Wheeldon TU, Hoang TT Phung DC, Bjorkman A, Granstrom M, Sorberg M, (2005). Long-term follow-up of H. Pylori eradication therapy in Vietnam: reinfection and clinical outcome. Aliment Pharmacol Ther., 21: 1047-1053.
31. McMahon BJ, Bruce MG, Hennessy TW, Braden DL, Sacco F, Peters H, Hurlburt DA, Morris JM, Reasonover AL, Dailide G, Berg DE, Parkinson AJ, (2006). Reinfection after successful eradication of H. Pylori: a 2-year prospective study in Alaska Natives. Aliment. Pharmacol. Ther., 23: 1215-1223.
32. Soto G, Bautista CT, Roth DE, Gilman RH, Velapatiño B, Ogura M, Dailide G, Razuri M, Meza R, Katz U, Monath TP, Berg DE, Taylor DN, (2003). H. Pylori reinfection is common in Peruvian adults after antibiotic eradication therapy 188: 1263-1175.
33. Seo M. Okada M, Shirotani T, Nishimura 11, Maeda K, Aoyagi K. Sakisaka S, (1001). Recurrence of H. Pylori infection and the long-term outcome of peptic ulcer after successful eradication in Japan. J. ain. Gastroenterol., 34: 129-134.
34. Parsonnet J, Harris RA, Hack HM. Owens DK, (1996). Modelling cost-eliectiveness of H. Pylori screening to prevent gastric cancer: a mandate for clinical trials. Lancet.. 348:150-4.
35. Matysiak-Budnik T, Megraud F. Epidemiology of Helicobacter pylori infection with special reference to professional risk. J Physiol Pharmacol. 1997;48(Suppl 4):3–17.
36. Williams CL. Helicobacter pylori and endoscopy. J Hosp Infect. 1999;41:263–268.
37. Goodman KJ, Correa P, (1995). The transmission of H. Pylori. A critical review of the evidence. Int. J. Epidemiol., 24:875-887.
38. Nahar S Kibria KMK, Hossain E et al. (2009). Evidence of intra-familial transmission of He pylori by PCR-based RAPD fingerprinting in Bangladesh. Eur. J. Clin. Microbiol. Infect. Dis., 28:767-773.

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Review

Usefulness of intraoperative endoscopy in pediatric surgery: state of the art

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Summary. *Introduction:* Intraoperative endoscopy is a procedure that supports open and laparoscopic surgery, helping the surgeon to identify the presence of endoluminal gastrointestinal lesions which need to be treated, with a correct diagnosis and an adequate therapy. *Material and methods:* A search on PubMed was performed using "intraoperative esophagoscopy", "intraoperative duodenoscopy", and "intraoperative enteroscopy" as Mesh terms. The applied exclusion criteria were: papers written before 2000, not concerning pediatric or gastrointestinal pathology, literature-review articles, language different from English. *Results:* Sixteen studies from 2000 to 2018 were included. Overall, 1210 patients were treated. Different pathologies were considered. Complications were observed in a range of 0.3-14%. The most frequent complications were perforation, bleeding and mucosal tear. Mortality ranged between 0.7% and 1,2%. *Conclusion*: Intraoperative endoscopy is an indispensable tool for gastrointestinal surgery. In the hands of experienced endoscopists, intraoperative endoscopy can be performed safely, in time-efficient manner, facilitating diagnosis and treatment. (www.actabiomedica.it)

Key words: intraoperative endoscopy, pediatric gastroenterology, esophagogastroduodenoscopy, enteroscopy

Introduction

As well as the surgeon could be helpful to the pediatric endoscopist in case of complications during a diagnostic or operative endoscopy, the contribution of the endoscopist could be important for the surgeon, in several types of procedures. Although in the surgical practice laparoscopy is considered one of the most important innovations in the last 30 years, its big limitation still remains the impossibility to palpate the tissues directly, causing the loss of precision in some procedures, especially in those where the identification of solid endoluminal lesions is needed. Intraoperative gastrointestinal endoscopy allows increasing precision and sensitivity of both open and laparoscopic surgery, helping the surgeon to locate exactly endoluminal lesions of the digestive system which have to be treated (1). The operative maneuverability of current endoscopes makes every portion of the gastrointestinal tract accessible to direct visualization by the operating surgeon and by the endoscopist (2).

Intraoperative endoscopic procedures include:

Intraoperative esophagoscopy. It has different applications, mostly in case of Gastro-Esophageal Reflux Disease (GERD), as it allows the direct localization of the gastroesophageal junction (GEJ) and can recognize typical GERD's complications as ulcers, stenosis, Barrett's esophagus and short esophagus (3) and, in case of achalasia, where it allows to evaluate mucosal conditions that could change certain decisions as, for example, the type of fundoplication, the width of myotomy and eventually a postponement of the operation (4).

Intraoperative duodenoscopy. The main duodenal pathological conditions of surgical interest include atresia, annular pancreas and congenital stenosis in pediatric patients (5). Practising an intraoperative duodenoscopy in those cases could be helpful to accurately identify the position of the obstruction and to clarify the etiology.

Intraoperative enteroscopy. Despite the improvement of the tools, enteroscopy still presents several difficulties, mainly due to the length and small bowel's natural anatomic tortuosity (6). Both in adult and pediatric patients the main diagnostic and therapeutic conditions are gastrointestinal idiopathic bleeding, Crohn disease, localized lesions out of reach of upper and lower endoscopy, incomplete information gathered with TC and/or RM and Peutz-Jeghers syndrome. In particular, in this last case, intraoperative enteroscopy enhances polyps' resection without the necessity of additional enterotomy and intestinal resections and can help in reducing number of laparotomies (7).

Intraoperative colonoscopy. Taking advantage from the direct help f the surgeon in reducing colonic curves, it is faster than the standard colonoscopy and fundamentally it doesn't add any risk to the procedure (2). The most common indication concerns intestinal bleeding and the localization of tumors when palpation is not enough to achieve the purpose (8, 9).

Materials and methods

In order to verify the utilities of intraoperative gastrointestinal endoscopy, a research of the literature was performed by using Pubmed, Medline, Embase databases.

Cochrane database and google Scholar were searched as well, using the following mesh terms: "intraoperative esophagoscopy", "intraoperative enteroscopy", "intraoperative duodenoscopy". Additional articles were selected reviewing the references of the papers identified using these mesh terms.

Exclusion criteria were: papers written before 2000, not concerning pediatric or gastrointestinal pathology, literature-review articles, language different from English. Each article was tabulated as follows: authors; year of the study, number of patients, surgical technique, follow-up time and complications.

Results

We identified 518 full-text articles; 502 did not meet inclusion criteria. Sixteen studies published from 2000 to 2018 were included (Table 1). Five were case reports and 12 were retrospective studies. Overall, 1210 patients underwent surgical procedures under intraoperative endoscopic control. Different surgical procedures were analysed: 4 studies concerning Achalasia disease (10-13); 4 studies concerning GERD (14-17); 6 studies concerning Peutz-Jeghers syndrome (18-23); 1 case report of GI hemorrhage (24); 1 study concerning duodenal obstruction (25). Regarding achalasia, 303 patients underwent a laparoscopic Heller's myotomy under intraoperative endoscopic control. All patients complained of dysphagia, although heartburn, regurgitation/emesis, postprandial chest pain. The diagnosis of achalasia was confirmed by barium esophagogram, upper GI endoscopy and, in some cases, esophageal manometry studies. The average

Table 1. Studies included

Authors	Year	N° patients included	Disease requiring the procedure
Fernandez et al.	2001	81	Acalasia
Adikibi et al.	2009	5	Acalasia
Chapman et al.	2004	139	Acalasia
Bloomston et al.	2002	78	Acalasia
Oelschlager et al.	2002	142	GERD
Becerril et al.	2006	277	GERD
Chang et al.	2002	40	GERD
Del Genio et al.	2007	380	GERD
Ricco' et al.	2003	33	DO
Lin et al.	2000	1	PJ
Ross et al.	2006	3	PJ
Edwards et al.	2003	25	PJ
Lee et al.	2014	1	PJ
Pennazio et al.	2000	3	PJ
Chui et al.	2006	1	PJ
Jolley et al.	2001	1	GI Bleeding

time of surgical procedure was 50-300 minutes with a range of hospital stay of 1.9-6 days. Follow-up period ranged from 1.5 months to 91 months. Patients were asked to list their symptoms, grade their heartburn, if present, and grade their outcome compared with their preoperative status as: excellent (complete resolution of symptoms), good (greatly improved symptoms), fair (slightly improved symptoms), or poor (no improvement or worsened symptoms). In particular, Adikibi et al. (2009) (11) used the modified Visick symptom scale for evaluating the postoperative outcome, including 1) no symptoms (80% of patients), 2) better than before surgery (20% of patients), 3) no modifications, and 4) new symptoms or complications. Chapman et al. (2004) (12) used a questionnaire based on the quality of life with a score of 0-6, depending on the ability to eat, swallow, sleeping lying down etc. Around 90-96% of all patients had an improvement in their symptoms. Mortality occurred in a range of 0.7-1.2%, because of esophageal perforation in the post-operative period or because of other diseases not concerning the surgical procedure. From 2 to 3.8% cases, it was required a conversion to open-surgery; from 6 to 14% cases, esophageal perforation occurred.

Regarding GERD, 839 patients performed intraoperative endoscopy undergoing laparoscopic anti-reflux procedures. All patients had been evaluated preoperatively with esophageal manometry, 24-h pH monitoring, esophagogram and upper endoscopy. Hiatal hernia, esophagitis, and Barrett's esophagus were present in a range of 73.9-76%, 39.2%, and 3.9-12.5%, respectively. The average time of surgical procedure ranged from 38 to 139 minutes. The location of the laparoscopic GEJ was found to be the same as that of the endoscopic GEJ in a range of 65-90% and different in a range of 10-35%, appearing proximal or distal to the endoscopically identified GEJ. In particular, Becerril-Martinez et al. (2006) (15) noticed that intraoperative endoscopy permitted the correction of the fundoplication in 27.79% of cases: in 88.3% of those, because of the angulation of the fundoplication; in 1.3% of cases the gastric fundus was redundant; in 9.1% of cases it was necessary a switch of the procedure from a complete fundoplication to a partial one. There were no deaths; complications occurred in a range of 0.3%-1.4%, such as bleeding, perforation, anesthesiologic complications, mucosal tear. Mean postoperative hospital stay was 2.9±0.9 days. Patients had a follow-up of 1-13 years.

In case of congenital duodenal obstruction (DO), we report surgical records (25) of 33 patients with intraoperative diagnosis of DO, studied retrospectively. Surgical management required 26 bypass-procedure, 4 web excisions and 3 excisions of the Ladd. There were no signs of biliopancreatic tract lesions and no operative deaths. Outcome was considered excellent or good by patients or parents in all cases.

In case of GI bleeding in pediatric age, we present a case report (24). A 15 years old adolescent with Turner's syndrome was evaluated for GI bleeding, before the experience of 2 previous episodes of hemorrhage. She had undergone esophagogastroduodenoscopy as well as colonoscopy, abdominal CT scan with no source of bleeding identified. Laparoscopy was performed to identify any possible bleeding sites: several dilated vessels were noted on the surface of the small bowel as was an intestinal malrotation. Ladd's procedure was performed noticing the presence of dilated vessels from the ligament of Treitz to the ileocecal valve. The small bowel then was intussuscepted over a neonatal size endoscope, appreciating tortuous and dilated submucosal vessels and well-circumscribed hemangiomas in the ileum and in the jejunum, with evidence of recent bleeding and several of the vascular lesions. The patient has had no further evidence of bleeding in the 20 months since the initiation of estrogen therapy.

Regarding Peutz-Jeghers syndrome, 34 patients underwent laparoscopic-assisted enteroscopy. All patients had undergone upper and lower gastrointestinal endoscopy with polypectomy before surgery. Surgical procedures were required if intestinal obstruction occurred. Symptoms reported before the procedures were: abdominal pain, fullness, hematochezia. The entire procedure lasted with a range of 60-265 minutes, 506 PJS polyps were found (10-25 polyps per patient) without evidence of dysplasia, except for one case. No serious complications occurred. In 1 patient, a limited laceration of the mucosa of the small bowel was found together with some small submucosal hematomas, both of a traumatic nature. The majority of polyps were 5-8 mm (range: 0.5-4 cm). Postoperative hospital stay was

5-18 days. After procedure, the patient did not exhibit any gastrointestinal symptoms and could tolerate an oral diet. No patient required operative polypectomy within 4 years of polyp clearance by intraoperative enteroscopy. The median follow-up was 53 months (13-133 months).

Further analysis of the studies showed many critical points. Firstly, most of the studies took into account a small number of patients with a high variability (from 1 to 380 patients). Only six collected studies took into account more than 40 patients. The follow-up time was not homogeneous among the different studies. In most of the articles, comorbidities of patients were not taken into account. It was not possible to identify a statistically significant correlation between technique and complication rate. Each author in fact described the use of his personal surgical technique and clinical results, without uniformity.

Discussion and conclusion

In case of GERD, accurate identification of the GEJ is essential to the construction of an effective fundoplication. In fact, a wrap created around the stomach ("slipped") is a common cause of failure. Another cause of failure is hiatal herniation. To avoid this complication, the GEJ must first be identified precisely so the length of intraabdominal esophagus can be accurately determined. This will help to identify an otherwise unrecognized short esophagus and prevent these potential postoperative problems (16).

Regarding Achalasia, intraoperative endoscopy during Heller myotomy guides the extent and adequacy of myotomy, minimizing the postoperative dysphagia and allowing the possibility to evaluate intraoperatively the mucosal integrity (10, 13). It also allows evaluating the mucosal hermeticity, identifying eventual perforations that can occur (4).

In case of DO, intraoperative endoscopy did not change surgical management and duodeno-duodenostomy was the first-choice technique; endoscopy allowed accurate identification of obstruction position and etiology and recognized the Vater papilla making the surgical approach easier, avoiding biliary tract lesions and reducing post-operative morbidity and mortality (25). Regarding GI bleeding, this report describes the successful use of intraoperative endoscopy to identify the source of bleeding, that was, in this case, beyond the reach of standard endoscopic attempts (24).

In case of Peutz-Jeghers syndrome, the distribution of PJS polyps throughout the GI tract makes surveillance and treatment challenging, particularly for polyps located within the small intestine. This approach offers a single, minimally invasive approach to the diagnosis and the treatment of small-bowel PJS polyps (19). A combined endoscopic and operative polypectomy achieves a clean intestine and may allow relatively long asymptomatic periods, reducing the need for emergency surgery with extensive intestinal resection (21,22).

In conclusion, intraoperative endoscopy is an indispensable tool for GI surgery. With experienced endoscopist surgeon and operating room staffs, intraoperative endoscopy can be done without added morbidity in time-efficient manner, while providing value in diagnosis and treatment (8).

The literature about intraoperative endoscopy demonstrates that this combined procedure is becoming an increasingly valuable tool in the operating room. Clearly, intraoperative endoscopy can be of significant benefit in solving a wide variety of gastrointestinal tract problems, independently from their complexity.

References

1. Justo JJ, Garcia Coral MA, Chang AE, et al. Endoscopia Gastrointestinal Transoperatoria, VII congresso national de tecnologia aplicada a ciencias de la salud, 2016.
2. Bombeck CT. Intraoperative Esophagoscopy, Gastroscopy, Colonoscopy and Endoscopy of the Small Bowel. Surgical Clinics of North America 1975; 55 (1): 135-142.
3. Goldberg-Dryjanski, Navarro-Vargas. Utilidad De La Endoscopia Transoperatoria De Rutina En Cirugìa Antirreflujo Por Laparoscopia. Cirugìa Endoscòpica 2012; 13 (1): 42-44.
4. Oliva OJ, Mata Quintero C, Chuc Baeza G, et al. Puntos clave en el control endoscòpico de la miotomia de Heller por vìa laparoscòpica. Cir End 2013; 14: 73-77.
5. Marsha Kay RW. Pediatric Gastrointestinal Disease, Second Edition.
6. de'Angelis GL, Ferrozzi F, de'Angelis N, et al. L'endoscopia digestiva in età pediatrica e giovanile. Ed. G.L. de'Angelis. EMSI Roma 2002.

7. Kopacova M, Bures J, Vykouril L, et al. Intraoperative enteroscopy, Ten years experience at a single tertiary center. Surg Endosc 2007; 21: 1111-1116.
8. Arcila E, Shin J. Utility and techniques of intraoperative endoscopy and interventions. Seminars in Colon and Rectal Surgery 2017; 28: 30-33.
9. Podmanicky D, Stefanov V, Harustiakova D, et al. Intraoperative endoscopy is safe and helps to determine the resection extent in Chron's disease. Gastroent Hepatolog 2017; 71 (1): 24-28.
10. Fernandez A, Ruiz J, Diaz-Canell O, et al. Endoscopia transoperatoria en la Cirurgìa Laparoscòpica de la Acalasia. Rev Gastroent Perù 2001; 21(1): 31-35.
11. Adikibi BT, MacKinlay GA, Munro FD, et al. Intraoperative Upper GI Endoscopy Ensures an Adequate Laparoscopic Heller's Myotomy. Journal Of Laparoendoscopic & Advanced Surgical Techniques 2009; 19 (5): 687-689.
12. Chapman D, Muruyama J. Tratamiento de la acalasia. Arch Surg 2004; 139(5): 508-513.
13. Bloomston M, Brady P, Rosemurgy AS. Videoscopic Heller Myotomy with Intraoperative Endoscopy promotes optimal outcome. Journal of the Society of Laparoendoscopic Surgeons 2002; 6: 133-138.
14. Oelschlager BK, Pellegrini CA. Advancements in the Use of Endoscopy for GERD. Department of Surgery, University of Washington, Seattle. Disclosures, 5 April 2002.
15. Becerril Martinez G, Decanini Teràn C, Spaventa Ibarrola A, et al. Endoscopia transoperatoria en funduplicatura laparoscópica. Cir Ciruj 2006;74:95-99.
16. Chang L, Oelschlager BK, Barreca M, et al. Improving accuracy in identifying the gastroesophageal junction during laparoscopic antireflux surgery. Surg Endosc 2003; 17: 390-393.
17. Del Genio G, Rossetti G, Brusciano L, et al. Laparoscopic Nissen-Rossetti Fundoplication with Routine Use of Intraoperative Endoscopy and Manometry: Technical Aspect of a Standardized Technique. World J Surg 2007; 31: 1099-1106.
18. Lin BC, Lien JM, Chen RJ, et al. Combined endoscopic and surgical treatment for the polyposis of Peutz-Jeghers syndrome. Surg Endosc 2000; 14: 1185–-1187.
19. Ross AS, Dye C, Prachand VN. Laparoscopic-assisted double-balloon enteroscopy for small-bowel polyp surveillance and treatment in patients with Peutz-Jeghers syndrome. Gastrointestinal Endoscopy 2006; 64(6): 984-988.
20. Edwards DP, Khosraviani K, Stafferton R. Long-Term Results of Polyp Clearance by Intraoperative Enteroscopy in the Peutz-Jeghers Syndrome. Dis Colon Rectum, January 2003; 46(1): 48-50.
21. Lee DH, Shin HD, Cho WH, et al. Polyp Clearance via Operative and Endoscopic Polypectomy in Patients With Peutz-Jeghers Syndrome After Multiple Small Bowel Resections. Intest Res 2014; 12(4): 320-327.
22. Pennazio M, Rossini F.P. Small bowel polyps in Peutz-Jeghers syndrome: management by combined push enteroscopy and intraoperative enteroscopy. Gastrointestinal Endoscopy 2002; 51(3): 304-308.
23. Chui CH, Jacombsen AS. Transumbilical Approach to Intraoperative Enteroscopy in a Child with Intussusception and Peutz-Jeghers Syndrome. Journal Of Laparoendoscopic & Advanced Surgical Techniques 2006; 16(5): 543-545.
24. Jolley C, Langham MR, Dillard R, et al. Intraoperative Endoscopy in a Child With Turner's Syndrome and Gastrointestinal Hemorrhage: A Case Report. Journal of Pediatric Surgery 2001; 36(6): 251-252.
25. Riccò M, Del Rossi C, Casolari E, et al. Congenital Duodenal Obstruction (DO) and Intraoperative Endoscopy. Digestive and Liver Disease 2003; 35: 1-3.
26. Bowden TA. Intraoperative Endoscopy of the Gastrointestinal Tract: Clinical Necessity or Lack of Preoperative Preparation? World J Surg 1989; 13: 186-189.

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Review

Epidemiology of gastric cancer and risk factors

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Summary. Gastric cancer is, still nowadays, an important healthcare problem worldwide. In Italy, it represents the fifth tumour by frequency in both men and women over 70 years old. A crucial point is represented by the percentage of early gastric cancers usually found, which is actually very low, and it carries to a worse morbidity and mortality. The most important focus in this oncological disease, is to perform an effective detection of the most common precancerous lesion linked with this neoplasia, chronic atrophic gastritis, in order to avoid the future outcome of gastric cancer itself. (www.actabiomedica.it)

Key words: gastric cancer, diagnosis, risk factors, epidemiology

About gastric adenocarcinoma (ADK), irrespective of histological classification, it is possible to divide the whole set in two main groups: ADK arising from the cardia (cardia gastric cancer or cardia GC) and from all other parts of stomach but cardia (no cardia gastric cancer or no cardia GC), as they have different epidemiologic patterns and causes (1).

Each year approximately 990.000 people are diagnosed with GC worldwide, of whom about 738.000 die from this disease. Concerning Italy, ISTAT (Istituto Superiore della Sanità, Higher Institute of Health) has elaborating interesting data about morbidity and mortality for cancer in Italy. Cancer is now the second cause of death (29%), right after cardiovascular diseases (37%). Concerning GC, in 2014 ISTAT reported 9,557 deaths caused by this disease (60% were men).

The 5-year survival in Italy for gastric cancer has a medium value of 31.8% with evident variations between young people (39.8%) and over 75 years old (21.6%).

Data provided by the Italian Association of Tumours Register (AIRTUM) in 2017 showed that GC is the fifth tumour by frequency (5%), in both men and women over 70 years old. Among patients with neoplasia, 6% of men between 50-69 years old and 7% over 70 years old dies because of GC; women over 70 years old are 7%.

In Italy the prevalence of GC varies from Southern Country (70 cases per 100,000 people) and Northern-Central Country (137 cases per 100,000 people), according with data given by AIRTUM.

GC incidence rates have been on decline in most part of the world (2,3). Despite this, there is a major exception: cardia GC rates have remained stable or increased (4,5), in Western Countries. Such contrasting trends between cardia and no cardia GC may result from different aetiologies. For example, Helicobacter Pylori doesn't seem to be a risk factor for cardia GC in Western Countries (6), so its declining prevalence would not be expected to affect cardia GC rates. Conversely, obesity and gastroesophageal reflux disease (GERD), seem to be risk factors only for cardia GC. This is a very important notion because obesity has been increasing in prevalence in Western Countries

(7) and GERD is an increasing pathology in our reality.

Comparing nations, the highest incidence rates are in East Asia, East Europe and South America, meanwhile the lowest rates are observed in North America and most parts of Africa (8). For example, the annual age-standardized GC incidence rates per 100.000 in men is 65.9 in Korea versus 3.3 in Egypt (9). Particular indigenous populations just like Inuits (in the circumpolar region) and Maoris (in New Zealand), suffer from high rates of GC (10).

This kind of cancer is more common in men (rates are 2 to 3 folds higher in men compared to women) (11).

Early gastric cancer (Early GC) is an invasive cancer confined to mucosa and/or submucosa, with or without lymph node metastases, irrespective of the tumour size (12). Most Early GC are small (up to 5 cm in size), and those are usually located at lesser curvature around angularis. Some Early GC are multifocal, often indicative of a worse prognosis. It is possible to divide Early GC into: type I (for a tumour with protruding growth), type II (superficial growth), type III (excavating growth), and type IV (infiltrating growth with lateral spreading).

The prognosis of Early GC is excellent, with a 5 years survival rate of 90% (13).

In contrast, the advanced gastric cancer (Advanced GC), that invades into muscularis propria or beyond, has a much worse prognosis, with a 5 years survival rate at about 60% or less (14). The appearance of Advanced GC can be exophytic, ulcerated, infiltrative or combined. Based on Borrmann's classification, the appearance of this kind of cancer can be divided into type I (polypoid growth), type II (fungating growth), type III (ulcerating growth) and type IV (diffusely infiltrating growth).

Intestinal type adenocarcinoma is the most frequent GC. It develops through a cascade of precancerous lesions such as atrophic gastritis, intestinal metaplasia and dysplasia (Correa's cascade of gastric carcinogenesis) (15) (figure 1).

Chronic gastritis is the result of a chronic inflammation of the mucosa, where the appropriate native gastric glands can be replaced by fibrous tissue, giving shape to non-metaplastic atrophic gastritis, and/or by pyloric type glands or, more often, by intestinal

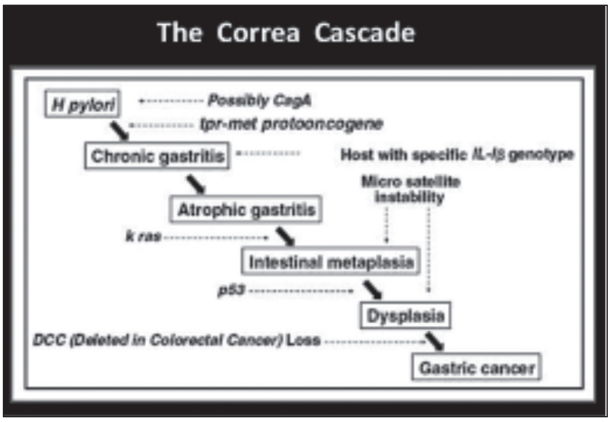

Figure 1. Correa's cascade

type glands that indicates the presence of a metaplastic atrophic gastritis (16).

Atrophic gastritis and intestinal metaplasia associate with an increased risk of developing gastric cancer as they constitute conditions in which dysplasia develops.

Risk factors

Several different risk factors are involved. It is possible to identify two different groups: not modifiable (older age, male sex, ethnicity, familiar history and presence of predisposing syndromes) and modifiable risk factors (voluptuous habits such as tobacco smoking, alcohol abuse, exposure to radiations, Helicobacter Pylori infection, etc…).

Moreover, is possible to identify risk factors that are typically linked with cardia gastric cancer, others linked with no cardia gastric cancer or linked with both kinds of neoplasia.

Common risk factors include:

Age: the incidence rate of GC rises progressively with age. Among all cases diagnosed between 2005 and 2009 in the USA, approximately 1% of those occurred in young patients (age between 20 and 34 years), meanwhile 29% occurred in old patients (age between 75 and 84 years). The median age at diagnosis of GC was 70 years (17).

Male sex: males have higher risk of both cardia and no cardia (5-fold) and no cardia (2-fold) GC (18).

The exact reason is not actually clear. In past, men were more likely to smoke tobacco, and this could have been important, but this data is now of a lesser importance in most countries because smoking is nowadays, a very common habit in both sexes.

Tobacco smoking: in 2002 IARC (international agency for research on cancer) establish that smoking has a role as a risk factor in GC onset, saying that there is a "sufficient evidence of causality between smoking and GC (19).

Race: in white people, cardia GC is about twice as common as in the other racial groups, but no cardia GC is half as common (20). The association of race with incidence of GC seems to be mediated by environmental effects, rather than genetic variations.

Radiations: long-term follow up on Hiroshima and Nagasaki disaster established radiations as risk factor for GC (21). Even more recent studies were done on survivors of Hodgkin's lymphoma and also showed that radiation to the stomach has a dose-response association with higher risk of GC. This effect is particularly evident in patients that at the same time received procarbazine.

Cardia gastric cancer risk factors include:

Obesity: this is a growing problem in our society and it has been linked with several different diseases, including GC. People with a BMI of 30 to 35 have two-fold risk compared with people with BMI of <25 and those with a BMI > 40 have a three-fold risk of cancers of the esophagogastric junctional, including the cardia GC (22).

Gastro-esophageal reflux disease (GERD): this pathology is strictly connected with risk of onset of esophageal adenocarcinoma with a 5-7-fold increase risk (23). Several studies have reported statistically significant association between GERD and cardia GC (24), with increased risks of 2-4 folds, in most of studies.

No cardia gastric cancer risk factors include:

Helicobacter Pylori: H. Pylori is a sure cause of GC (23) with relative risks of approximately 6 for no cardia GC (25). The H. Pylori that are positive for the virulence factor cytotoxin-associated gene A (Cag A), are more likely to cause GC (26, 27). It is not sure how H. Pylori causes the cancer onset. Two potential pathways are mostly considered: indirect action of the bacteria on gastric epithelial cells by causing inflammation and direct action: H. Pylori could also directly modulate epithelial cells function through bacterial agents, such as Cag A. Nevertheless, the relation between the two pathways is still unclear, both ones seem to work together to promote GC development.

H. Pylori is estimated to cause from 65% to 80% of all GC cases, about 660.000 new cases each year (28, 29).

Intake of salty and smoked food: the American Institute for Cancer Research (AICR) has concluded that "salty and salt-preserved foods are probably cause of GC (30). Large cohort studies were done in Korea, they had shown that people who tend to prefer salty food have higher risk of GC (31). Salt may increase the risk of GC through direct damage to gastric mucosa conducing to gastritis or other mechanisms (32).

Genetic risk factors also exist:

Only 1-3% of GC cases are result of inherited syndromes (33).

Those syndromes include hereditary diffuse gastric cancer (HDGC), which is a rare disease. It is an autosomal dominant inherited form of GC usually with an highly invasive diffuse type cancer.

It has a late presentation and a poor prognosis. In this kind of cancers there is a loss of expression of cell adhesion protein: E-caderin. Furthermore, about 25% of families with HDGC have inactivating CDH1 germline mutations.

Another syndrome is FAP (familial adenomatous polyposis), an autosomal dominant colorectal cancer syndrome caused by a mutation in the adenomatous polyposis coli gene. Those patients have a risk of 100% of colorectal cancer by the age of about 40 as well as an high risk of other neoplasia, including GC.

Peutz-Jeghers syndrome: is a rare autosomal dominant condition, linked with hamartomatous gastrointestinal polyposis and melanin spots on the lips and buccal mucosa. The cause is mutation of LKB1 gene, which encodes a serine/threonine kinase that acts as a suppressor.

Single nucleotide polymorphisms (SNPs): before the advent and use of genome-wide scans, a lot of case-control studies examined in deep candidate polymor-

phisms (mostly chosen based on biologic plausibility) in relation to GC.

Although some of those associations showed promise, quite all failed to replicate. For example, the initially exciting associations among polymorphisms in inflammatory genes (especially IL-1B), were not replicated in future studies (34), including in genome wide association studies.

Significant associations between SNPs at 1q22, located in Mucin 1 gene (MUC1), and GC were reported in the GWAS of Japan and Korean studies. Meta-analysis of the results identified several other SNPs in MUC1 that were significantly associated with GC risk (35). The mechanism of action is not clear for any of those polymorphisms. However, these findings will lead to mechanistic insight into gastric carcinogenesis.

Concerning Helicobacter pylori infection, in a systematic review and meta-analysis, we associated eradication of H pylori infection with a reduced incidence of gastric cancer. The benefits of eradication vary with baseline gastric cancer incidence, but apply to all levels of baseline risk (36).Real world data showed that large-scale eradication therapy has been performed mostly for benign conditions in Japan. Since eradication effects in preventing gastric cancer are conceivably greater there, GC incidence may decline faster in Japan than expected from the previous meta-analyses data which were based on multi-national, mixed populations with differing screening quality and disease progression (37).

Concerning early diagnosis worldwide, an accurate review carried out in 2014 pointed out that its rate is actually very low and this state is also due to the lack of early symptoms and the high difficulty to make a proper endoscopic diagnosis (even because it often shows only subtle changes) (38).

Further evaluations were recently carried out on some Italian areas. The situation in northern Italy shows a very poor early diagnosis percentage in two different populations that have been studied since 2011, Altovicentino (nearby Vicenza) and Parma district.

Early diagnosis rate in Parma district was of 10,5% and in Altovicentino of 6% (figure 2).

Conclusion: As as it is possible to understand from the evaluated information, gastric cancer is, still nowadays, an important healthcare burden worldwide. Even if the global incidence is decreasing, the mortality rates among those patients are unfortunately high. Several different risk factors exist but the main recognized risk factor for no cardia GC is the H.pylori infection. Those data underline the effectiveness of H.pylori eradication in order to avoid further gastric lesions, especially in countries with an high rate of gastric cancer outset just like East Asia ones. The importance of early diagnosis of precancerous lesions (such as atrophic gastritis) is underlined too, even through non-invasive serological tests such as Gastropane®, trying to effectively prevent the onset of neoplasia, an even more decisive point in the oncological field than the diagnosis of early stage gastric cancer itself.

Figure 2. Early diagnosis rates in Altovicentino and Parma district study groups.

References

1. Karimi P, Islami F, Anandasabapathy S, Freedman ND, Kamangar F. Gastric cancer: descriptive epidemiology, risk fac-

tors, screening and prevention. Cancer epidemiol biomarkers prev. 2014 May; 32 (5): 700-13.
2. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. In J Clin. Oncol. 2006;24: 2137-50.
3. Bosetti C, Bertuccio P, Malvezzi M, Levi F, Chatenoud L, Negri E et al. Cancer mortality in Europe, 2005-2009and an overview of trends since 1980. Ann Oncol. 2013; 24:2657-71.
4. Devesa SS, Blot JW, Fraumeni JF. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. Cancer. 1998;83:2049-53.
5. Powell J, McConkey CC. Increasing incidence of adenocarcinoma of the gastric cardia and adjacent sites. Br J Cancer. 1990; 62: 440-3.
6. Cavaleiro-Pinto M, Peleteiro B, Lunet N, Barros H. Helicobacter Pylori and gastric cardia cancer: systematic review and meta-analysis. Cancer Causes Control. 2011; 22:375-87.
7. Shields M, Carroll MD, Ogden LO. Adult obesity prevalence in Canada and the United States. National Center for Health Statistics; Hyattsville, MD. 2011. Data brief, no 56.
8. Forman D, Burley V. Gastric cancer: global pattern of the disease and an overview of environmental risk factors. Best Pract Res Clin Gastroenterol. 2006; 20: 633-49.
9. Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. Cancer Epidemiol Biomarkers Prev. 2010; 19:1893-907.
10. Arnold M, Moore SP, Hassler S, Ellison-Loschmann L, Forman D, Bray F. The burden of stomach cancer in indigenous populations: a systematic review and global assessment. Gut. 2014; 63:64-71.
11. FerlayJ, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010; 127: 2893-917.
12. Hamilton R, Aatonen LA. Tumors of Digestive System. Lyon:IARC; 2000:39-52.
13. Everett SM, Axon AT. Early gastric cancer in Europe. Gut 1997;41:142-50.
14. Yoshikawa K, Maruyama K. Characteristics of gastric cancer invading to the proper muscle layer--with special reference to mortality and cause of death. Jpn J ClinOncol 1985;15:499-503.
15. Correa P. Human gastric carcinogenesis: a multistep and multifactorial process- first American Cancer Society award lecture on cancer epidemiology and prevention. Cancer Research. 52.24 (1992); 6735-6740.
16. Dinis-Ribeiro M, Areia M, de Vries AC, Marcos-Pinto R et al. Management of precancerous conditions and lesions in the stomach (MAPS): guideline from the European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter Study Group (EHSG), European Society of Pathology (ESP), and the Sociedade Portuguesa de Endoscopia Digestiva (SPED). Endoscopy 2012; 44:74-94.
17. Maehara Y, Kakeji Y, Koga T, et al. Therapeutic value of lymph node dissection and the clinical outcome for patients with gastric cancer. Surgery. 2002;131(suppl):S85–91.
18. Howlader N, Noone A, Krapcho M, Neyman N, Aminou R, Waldron W, et al. SEER cancer statistics review, 1975-2088. National Cancer Institute; Bethesda, MD: 2011. P. 19
19. Brown LM, Devesa SS. Epidemiologic trends in esophageal and gastric cancer in the United States. Surg Oncol Clin N Am. 2002; 11:235-56.
20. IARC monographs on the evaluation of carcinogenic risks to humans. Ingested nitrate and nitrite, and cyanobacterial peptide toxins. IARC Monogr Eval Carcinog Risks Hum. 2010; 94:1-412.
21. El-Serag H, Mason A, Petersen N, Key C. Epidemiological differences between adenocarcinoma of the oesophagus and adenocarcinoma of the gastric cardia in the USA. Gut. 2002; 50:368-72.
22. Preston DL, Ron E, Tokuoka S, FunamotoS, Nishi N, Soda M, et al. Solid cancer incidence in atomic bomb survivors:1958-1998. Radiat Res. 2007; 168:1-64.
23. Hoyo C, Cook MB, Kamangar F, Freedman ND, Whiteman DC, Bernstein L, et al. Body mass index in relation to oesophageal and oesophagogastric junction adenocarcinomas: a pooled analysis from the international BEACON Consortium. Int J Epidemiol. 2012; 41: 1706-18.
24. Rubenstein JH, Taylor JB. Meta-analysis: the association of oesophageal adenocarcinoma with symptoms of gastro-oesophageal reflux. Aliment Pharmacol Ther. 2010; 32:1222-7.
26. Kamangar F, Sheikhattari P, Mohebtash M. Helicobacter Pylori and its effects on human health and disease. Arch Iran Med. 2011; 14: 192-9.
27. Gastric cancer and H. Pylori: a combined analysis of 12 case control studies nested within prospective cohorts. Gut. 2001; 49: 347-53.
28. Huang JQ, Zheng GF, Sumanac K, Irvine EJ, Hunt RH. Meta-analysis of the relationship between Cag A seropositivity and gastric cancer. Gastroenterology. 2003; 125: 1636-44.
29. Shiota S, Suzuki R, Yamaoka Y. The significance of virulence factors in H. Pylori. J Dig Dis. 2013; 14: 341-9.
30. De Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol. 2012; 13: 607-15.
31. Wiserman M. The second world cancer research fund/ American Institute for Cancer Research expert report. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Proc Nutr Soc. 2008; 67: 253-6.
32. Kim J, Park S, Nam BH. Gastric cancer and salt preference: a population-based cohort study in Korea. Am J Clin Nutr. 2010; 91: 1289-93.
33. Tsugane S, Sasazuki S, Kobayashi M, SasADKi S. Salt and salted food intADKe and subsequent risk of gastric cancer among middle-aged Japanese men and women. Br J Cancer. 2004; 90: 128-34.

34. Lynch HT, Grady W, Suriano G, Huntsman D. Gastric cancer: new genetic developments. J Surg Oncol. 2005; 90: 114_33.
35. Shi Y, Hu Z, Wu C, Dai J, Li H, Dong J et al. A genome wide association study identifies new susceptibility loci for non-cardia gastric cancer at 3q13.31 and 5p13.1. Nat Genet. 2011; 43: 1215-8.
36. Lee YC1, Chiang TH2, Chou CK et al. Association Between Helicobacter pylori Eradication and Gastric Cancer Incidence: A Systematic Review and Meta-analysis. Gastroenterology. 2016 May;150(5):1113-1124.e5. doi: 10.1053/j.gastro.2016.01.028. Epub 2016 Feb 2.
37. Sugano K. Effect of Helicobacter pylori eradication on the incidence of gastric cancer: a systematic review and meta-analysis. Gastric cancer. 2018 Sep 11. Doi:10.1007/s10120-018-0876-0.
38. Pasechnikov V, Chukov S,Fedorov E et al. Gastric cancer: prevention, screening and early diagnosis. World J Gastroenterology. 2014 October 14

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Review

Clinical manifestations of chronic atrophic gastritis

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Summary. Although the actual prevalence of chronic atrophic gastritis is unknown and it is probable that this entity goes largely underdiagnosed, patients in whom diagnosis is established usually present advanced stages of disease. Destruction of parietal cells, either autoimmune-driven or as a consequence of Helicobacter pylori infection, determines reduction or abolition of acid secretion. Hypo/achloridia causes an increase in serum gastrin levels, with an increased risk of the development of neuroendocrine tumors. Microcytic, hypochromic anemia frequently precedes the development of megaloblastic, vitamin B12-associated anemia. Moreover, vitamin B12 deficiency,may cause elevation of homocysteine, with an increase in the cardiovascular risk, and may be associated with neurological manifestations, mainly characterized by spinal cord demyelination and atrophy, with ensuing sensory-motor abnormalities. Gastrointestinal manifestations seem to be associated with non-acid reflux and tend to be non-specific. (www.actabiomedica.it)

Key words: gastritis, pernicious anemia, neuropathy, megaloblastic

Chronic atrophic gastritis (CAG) is the final consequence of an inflammatory process that ultimately leads to loss of appropriate mucosal glands. This histological alteration may be due to an autoimmune-mediated reaction directed towards parietal cells or their components, or may be associated to infection with *Helicobacter pylori* (1). To date, no universally accepted criteria are available to define autoimmune gastritis and to definitively distinguish this clinical entity from chronic, *H. pylori*-driven, multifocal atrophic gastritis. Features traditionally used to distinguish either etiology, such as positivity to intrinsic factor and parietal cell antibodies, presence of enterochromaffin-like cells, and absence of active *H. pylori* infection, have all been reported to be present in similar proportions in patients with body-restricted atrophic gastritis (the classical histological feature of autoimmune gastritis) and those with antral and body atrophic gastritis (more commonly attributed to *H. pylori* infection) (2, 4) thus, the specific features associated with autoimmune gastritis are far from being well defined.

There are two principal methodological approaches to assess this condition, namely serological studies using markers of gastric function (pepsinogen I, or pepsinogen I/pepsinogen II ratio, with or without the addition of gastrin-17 and antibodies against *H. pylori*) or invasive studies requiring histological analysis of biopsy samples taken in the course of upper esophagogastroduodenoscopy, the latter constituting the gold standard for establishing the diagnosis.

A standardized and validated method to stratify and grade severity and distribution of atrophy, the Operative Link on Gastritis Assessment (OLGA) system, allows the classification of patients in 5 groups from stage 0 to stage IV (5). More severe stages of atrophy (OLGA III and IV), characterized by extensive atrophy of the antrum and/or of the oxyntic mucosa, are associated with an increased risk of developing gastric

neoplasms(6). Notwithstanding a reduction in the incidence of this tumor, it remains an important cause of death associated with cancer, with a 5-year survival of 32.4% in Italy. (7, 8) Due to its high mortality and its silent presentation, the identification of a subgroup of patients who are at higher risk is important, as in these patients endoscopic surveillance is warranted. Thus, early identification of patients with CAG and their follow-up according to the risk of progression allows for early identification of neoplasms and reduction in gastric cancer mortality.

Destruction of parietal cells in CAG leads to a reduction or abolition of acid secretion, which can lead to the development of clinical extra-digestive manifestations that might aid in the identification of these patients, including iron deficiency, which can be associated with microcytic anemia. Vitamin B12 deficiency, due to a reduction of intrinsic factor produced by parietal cells may determine a megaloblastic form of anemia, but may also be associated with low platelet counts and peripheral neuropathy. Elevated levels of homocysteine, which constitute a risk factor for cardiovascular events, may be observed associated to reduction of levels of Vitamin B12.

Moreover, hypo/achloridia determines an increase in serum gastrin levels; this hormone stimulates the proliferation of enterochromafin-like cells (ECL), with a possible development of hyperplasia, which is in turn considered a precursor lesion of neuroendocrine tumors of the gastric mucosa (figure 1).

Vitamin B12 deficiency

Vitamin B12 (cobalamin) deficiency (9) may be associated with various cytological effects due to its key role as a cofactor within several metabolic pro-

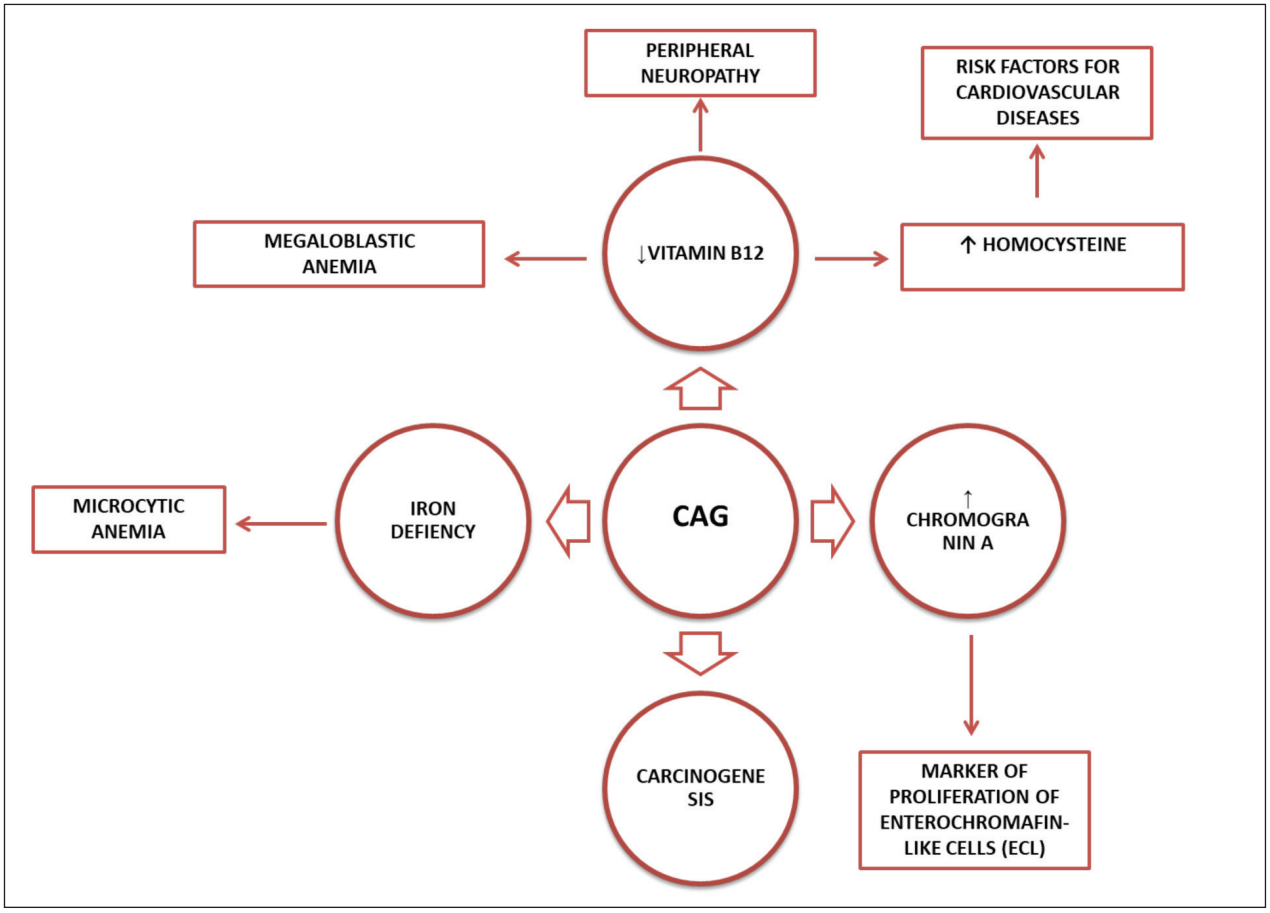

Figure 1. Clinical manifestations of chronic atrophic gastritis (CAG)

cesses, the most important of which implies the conversion of homocysteine in methionine by the enzyme homocysteine-methyltransferase, with a negative impact on the synthesis of nitrogenous compounds and consequently on DNA synthesis. This explains the repercussions of Vitamin B12 deficiency on hematopoiesis, with development of megaloblastic anemia (with mean corpuscular volume >90 fl), defined as pernicious anemia (antibodies against parietal cells of gastric mucosa, intrinsic factor, proton-pump, and or gastrin receptors).

As gastroenterological, neurological and hematological symptoms arise slowly and insidiously, patients frequently seek medical advice when the disease is already at an advanced stage. Anemia is often associated with tachycardia, vertigo, and dyspnea on exertion, while digestive manifestations of CAG may include post-prandial discomfort, diarrhea, and anorexia. Paleness of anemia is often combined with a very mild jaundice, the latter due to intramedullary hemolysis, resulting in a characteristic lemon-color complexion. Hunter's atrophic glossitis is also frequently encountered, with a dry, reddened, beefy and smooth tongue.

Another important consequence of Vitamin B12 deficiency is neuropathy; injury to the central nervous system has been found in nearly three fourths of all florid pernicious anemia patients, and may be present even in the absence of hematological alterations (10). Neurological alterations might constitute the cardinal and/or presenting clinical form (11). The spinal cord is mainly involved, with demyelination and atrophy, occasionally followed by axonal loss. These alterations lead to spastic paraparesis, sensory ataxia, visual disturbances, unsteady gait, and altered nervous reflexes. Cognitive disturbances may also be seen including memory loss, apathy, depression, and ultimately more complex behavioral changes. Sensory-motor peripheral polyneuropathy, or symmetric glove-and-stocking ("numb hands and feet syndrome") may present acutely, with tingling in the distal aspect of the toes, numbness, coldness, a pins-and-needles feeling, and occasional feelings of swelling or constriction (12).

Hematological alterations aside from macrocytic anemia may include hypersegmented polymorphonuclear neutrophils, increased platelet volume and thrombocytopenia. Serum levels of bilirubin, ferritin and lactate dehydrogenase may be elevated due to ineffective erythropoiesis (7).

Iron deficiency

Microcytic, hypochromic anemia, with all its clinical manifestations, frequently precedes the development of megaloblastic anemia in patients with CAG (13, 14). The pathophysiology of iron deficiency seems to be linked to four mechanisms: *(1)* chronic occult bleeding from gastric microerosions, *(2)* competition with *H. pylori* for dietary iron, *(3)* hypochlorhydria, and *(4)* upregulation of inflammatory hepcidin. Whether megaloblastic anemia or microcytic anemia develops seems to be dependent, at least in part, upon genetic factors. A genetic variant of transcobalamin II, related to lower Vitamin B12 levels, was more frequently associated with pernicious anemia in a cohort of patients with atrophic gastritis(15).

CAG has been reported in approximately 20-30% of cases of iron-deficiency anemia refractory to iron supplementation. Parietal cell atrophy and the ensuing hypochlorhydria negatively affect intestinal iron absorption. Moreover, up to 50% of patients with unexplained iron-deficiency anemia refractory to therapy has an active *H. pylori* infection. This association between *H. pylori* infection is further supported by the fact that eradication of the infection leads to resolution of anemia. In fact, according to several guidelines and the Maastricht V consensus on *H. pylori*, its eradication is advised in patients with iron deficiency anemia of unknown cause which is refractory to iron supplementation (16).

Hyperhomocysteinemia

Homocysteine, a sulphur-containing amino acid derived from methionine, is principally metabolized via methionine-synthase as the remethylation cycle, which is dependent on the presence of both Vitamin B12 and folate as co-factors. Elevated plasma homocysteine concentrations are now recognized as independent risk factors for cardiovascular diseases, and also seem to play an important role in the development of dementia, diabetes mellitus, and renal disease. By direct toxicity to endothelial cells and impairment

of endothelium-dependent vasodilation, hyperhomocysteinemia leads to progressive damage of the intima of the vascular wall.

Vitamin B12 and folate deficiencies constitute common causes of hyperhomocysteinemia, the former being a feature of chronic atrophic gastritis. Moreover, *H. pylori* infection per se, irrespective of atrophy of the gastric mucosa, has been associated with reduced plasmatic levels of Vitamin B12 and epidemiological studies have reported an association between *H. pylori* infection and coronary heart disease (17). Atrophic gastritis, rather than *H. pylor*i infection, is possibly a contributing factor to hyperhomocysteinemia, via Vitamin B12 malabsorption.(9)

Gastrointestinal symptoms

CAG has traditionally been considered silent from a gastrointestinal perspective. However, if sought, symptoms are usually present in a conspicuous portion of these patients. It has been reported that heartburn and regurgitation are present in approximately 24% and 12% of patients, respectively, while other frequent symptoms include postprandial fullness and early satiety in 7.1% and 10.1%, respectively (18). Another recent study showed that 56.7% of CAG patients presented one or more gastrointestinal symptoms; dyspepsia, subtype postprandial distress syndrome was the most frequent symptom, affecting more than half of symptomatic patients (4). A small, but interesting study in which 24 h multichannel intra-luminal impedance pH was performed in 41 patients with autoimmune CAG showed that acid reflux rarely occurred whereas increased non-acid reflux was found, and it correlated to symptoms in some patients. This group also observed that psychopathological profile plays a role in the occurrence of symptoms, and that the use of antisecretory drugs was generally inappropriate and clinically ineffective (19).

Postprandial related symptoms and epigastric pain syndrome (20) was significantly more prevalent in male patients with atrophy of the corpus and females with atrophy of the antrum, compared to patients with different topography of atrophy (20). Thus, authors conclude that the extent of atrophic gastritis appears to determine the predominant symptoms in a gender-dependent manner.

Coexisting autoimmune diseases

Autoimmune diseases tend to cluster, and autoimmune gastritis is more frequent in patients with autoimmune thyroid disease, vitiligo, and type 1 diabetes mellitus,. However, it is also true that anti-parietal cell antibodies, which are not specific for pernicious anemia and can be present in 7.8-19.5% of the general healthy adult population, are more prevalent in the serum of patients affected by these conditions, without necessarily having actual autoimmune gastritis (21). Prevalence of concomitant autoimmune diseases in patients with CAG has been reported to be as high as 40% (4), with the most frequent disorders being thyroid disease, vitiligo, alopecia, diabetes, hemolytic anemia, rheumatoid arthritis, psoriasis, autoimmune hepatitis, myasthenia gravis, and Sjögren's syndrome.

References

1. W. L. Neumann, E. Coss, M. Rugge, and R. M. Genta, "Autoimmune atrophic gastritis-pathogenesis, pathology and management," Nature Reviews Gastroenterology and Hepatology. 2013.
2. E. Lahner et al., "Occurrence and Risk Factors for Autoimmune Thyroid Disease in Patients with Atrophic Body Gastritis," Am. J. Med., 2008.
3. E. Lahner et al., "Reassessment of intrinsic factor and parietal cell autoantibodies in atrophic gastritis with respect to cobalamin deficiency," Am. J. Gastroenterol., 2009.
4. M. Carabotti, E. Lahner, G. Esposito, M. C. Sacchi, C. Severi, and B. Annibale, "Upper gastrointestinal symptoms in autoimmune gastritis A cross-sectional study," Med. (United States), 2017.
5. M. Rugge et al., "Gastritis staging in clinical practice: The OLGA staging system," Gut, 2007.
6. M. Rugge et al., "Gastritis OLGA-staging and gastric cancer risk: A twelve-year clinico-pathological follow-up study," Aliment. Pharmacol. Ther., 2010.
7. M. Sant et al., "EUROCARE-4. Survival of cancer patients diagnosed in 1995-1999. Results and commentary," Eur. J. Cancer, 2009.
8. G. Gatta et al., "Cancer survival in Europe 1999-2007 by country and age: Results of EUROCARE-5 - A population-based study," Lancet Oncol., 2014.
9. L. Santarelli et al., "Atrophic gastritis as a cause of hyperhomocysteinaemia," Aliment. Pharmacol. Ther., 2004.
10. G. T. Yang, H. Y. Zhao, Y. Kong, N. N. Sun, and A. Q. Dong, "Correlation between serum vitamin B12 level and

peripheral neuropathy in atrophic gastritis," World Journal of Gastroenterology. 2018.
11. B. Gökçe Çokal, H. N. Güneş, S. K. Güler, and T. K. Yoldaş, "Visual and somotosensory evoked potentials in asymptomatic patients with vitamin B12 deficiency.," Eur. Rev. Med. Pharmacol. Sci., 2016.
12. M. Campagnolo, C. DallaTorre, M. Cacciavillani, M. Lucchetta, and C. Briani, "Reversible peripheral neuropathy due to cobalamin deficiency," J. Peripher. Nerv. Syst., 2010.
13. C. M. Rojas Hernandez and T. H. Oo, "Advances in mechanisms, diagnosis, and treatment of pernicious anemia.," Discov. Med., 2015.
14. C. Hershko, A. Ronson, M. Souroujon, I. Maschler, J. Heyd, and J. Patz, "Variable hematologic presentation of autoimmune gastritis: Age-related progression from iron deficiency to cobalamin depletion," Blood, 2006.
15. E. Lahner, G. Gentile, F. Purchiaroni, B. Mora, M. Simmaco, and B. Annibale, "Single nucleotide polymorphisms related to vitamin B12serum levels in autoimmune gastritis patients with or without pernicious anaemia," Dig. Liver Dis., 2015.
16. J. F. rederi. Dahlerup et al., "Diagnosis and treatment of unexplained anemia with iron deficiency without overt bleeding," Dan. Med. J., 2015.
17. B. Schöttker, M. A. Adamu, M. N. Weck, H. Müller, and H. Brenner, "Helicobacter pylori infection, chronic atrophic gastritis and major cardiovascular events: A population-based cohort study," Atherosclerosis, 2012.
18. E. Miceli et al., "Common Features of Patients With Autoimmune Atrophic Gastritis," Clin. Gastroenterol. Hepatol., 2012.
19. A. Tenca et al., "Gastro-esophageal reflux and antisecretory drugs use among patients with chronic autoimmune atrophic gastritis: A study with pH-impedance monitoring," Neurogastroenterol. Motil., 2016.
20. S. H. Chung et al., "Association of the extent of atrophic gastritis with specific dyspeptic symptoms," J. Neurogastroenterol. Motil., 2015.
21. E. Rusak, A. Chobot, A. Krzywicka, and J. Wenzlau, "Anti-parietal cell antibodies - Diagnostic significance," Advances in Medical Sciences. 2016.

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Review

From Sidney to OLGA: an overview of atrophic gastritis

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Summary. Chronic gastritis is a long-lasting disease that can lead to a loss of appropriate gastric glands. Gastritis, as term, apply to an inflammation of the stomach, histologically proven, sometimes with structural mucosal changes. Worldwide Helicobacter pylori's infection play a pivotal role as the main etiological effector of chronic active gastritis. H. p. is a bacterium with a selective tropism for the gastric mucosa, able to survive in a hostile environment for colonization of organisms other than itself, able to develop strategies for survival and for avoidance of the defence mechanisms, causing inflammatory changes, that vary from asymptomatic mild gastritis to more severe injury such as peptic ulcer as well as premalignant lesions and malignant tumours. The pattern and distribution of gastritis strongly correlate with these sequelae and chronic atrophic gastritis with intestinal metaplasia is now assessed as a precancerous lesion with definite risk of evolution towards intraepithelial lesions of both low and high grade, as expected in the model of the Correa's cascade. In fact, the leading complication of chronic gastritis remains its close correlation with gastric cancer being biologically linked to H. pylori infection, nowadays known as a class I carcinogen. Gastric carcinogenesis is due to environmental factors, as well as to bacterial strain, host responses and gastric mucosal microbiome dysbiosis. Since, individual patients show different gastric cancer risk, it is mandatory to identify patients at risk of developing gastric cancer to offer a targeted search for lesions with a more rapid development of neoplasm liable, in an early phase, to a less destructive treatment. OLGA staging system is the most reliable and powerful system that allow the recognition of patient with a higher risk of developing gastric cancer. (www.actabiomedica.it)

Key words: chronic atrophic gastritis, OLGA, Sidney system, OLGIM

Introduction

Although fully recognized in 1984 (1), Helicobacter pylori (H. p.) a spiral shaped, microaerophilic, Gram-negative bacterium probably present in humans for millenia (2), has developed a selective tropism for the gastric mucosa, causing inflammatory changes, that vary from asymptomatic mild gastritis to peptic ulcer, as well as premalignant lesions and malignant tumours, including gastric lymphoma and epithelial gastric neoplasia. H. p. is responsible for a long-standing infection with a slow course, one of the most common chronic infection in humans at the present time (2).

Worldwide, the epidemiology of H. pylori infection, which affects approximately 50% of the world's population, overlaps that of gastritis (3)

A gastritis is an inflammation of the gastric mucosa, histologically proven (4), even when patients have no symptoms and irrespective of complications as stated in the Kyoto consensus report (5), H. pylori being the most frequent causative agent which ultimately interfere with acid and pepsin secretion,

disrupting a unique acid environment that requires functional gastric surface mucus barrier, bicarbonate buffering and epithelial integrity for its functions, making it vulnerable to gastric secretions. In most cases the HP infection is not clinically manifested. Different characteristics of virulence of the infecting strain, such as initial bacterial load, production of toxins (cagA and vacA strains are associated with ulcers and gastric cancer), adhesins, host response such as type and expression of HLA gastric epithelium response to IgA, IgM and IgG immunoglobulin, release of prostaglandins and leukotrienes, mass of the parietal cells and acid secretion, duodenogastric reflux, vascularization of the gastric mucosa and the presence of environmental cofactors such as age at time of infection, dietary factors (salt excess and nitrates, vitamins C and E deficiency), nonsteroidal anti-inflammatory drugs may explain the variability of clinical presentation. For this reason, the diagnostic approach to gastric inflammatory pathology (gastritis) has evolved over time moving on the simple presence of inflammation histologically (biopsies) proved to a pathology that must be approached in a multimodal way where laboratory tests, endoscopy and histology converge to provide a diagnosis not only of specific disease but also providing a picture of the risk of evolution in more serious pathologies.

It is the same informative concept that made it possible to step from the descriptive model of the Sydney System, proposed in 1991 revisited in 1994, known to us as Houston update Sydney System (6), to the current OLGA classification system (7).

The grading systems: The updated Sydney System and OLGA system (Operative Link for Gastritis Assessment system)

The updated Sydney System (6) has been and even now is a widespread used system of reporting that has provided guidelines for pathologists taking into account, in a systematic way, each relevant pathologic feature, such as density of H. pylori, intensity of neutrophilic and mononuclear inflammation, atrophy of the antrum and corpus, and presence/absence of intestinal metaplasia.

In the Sydney System has been recommended that at least five biopsy specimens should be evaluated. This statement has been reassessed in the Kyoto Consensus Report (5) Statement 13 that affirm with a strong grade of recommendation and high level of evidence (Consensus level: 92.1%): accurate histological assessment of gastritis requires biopsy sampling of both antrum and corpus, needing the specimens to be put into separate vials and grouped for each site or lesion or as Italian pathologist do, identified on a squared paper.

The major reason for taking multiple biopsy specimens throughout the gastric mucosa is to assure the correct diagnosis. Most of gastric disease occurs in a disorderly fashion, with an irregular topographic distribution. Therefore, multiple specimens are also necessary to determine disease distribution within the mucosa. The information obtained are useful for the diagnosis, to clarify the etiology and are also important in the differential diagnosis of gastric diseases that may have similar histological features. Multiple specimens from: a) antrum (2) from the lesser and the greater curvature of the antrum, both within 2 to 3 cm from the pylorus; b) antral-body transitional zone (1) from the incisura angularis; and c) corpus (2) from the lesser curvature of the corpus about 4 cm proximal to the angulus and from the middle portion of the greater curvature of the corpus, approximately 8 cm from the cardia should be properly identified and should be submitted in separate containers to the pathology laboratory

In addition, biopsies from any macroscopically lesion should be taken (ulcer, erosion, or depressed area detected etc.). This sampling mode provides the best cost/benefit ratio in terms of diagnostic yield for identifying patients with premalignant lesions and provides a better overview of the severity and distribution of these lesions and the histopathological grading of individual abnormalities—in particular, inflammation, gland loss and metaplasia (5).

Corpus biopsies are particularly valuable for yielding positive results after treatment, especially where proton pump inhibitors have been used. Under these circumstances, organisms may become rare or disappear from the antrum but remain in the oxyntic mucosa, which may also develop cystic dilatations with

hypertrophy of the parietal cells (6). The sample from incisura angularis should be taken into account, given that in such a place can be consistently found metaplastic and dysplastic lesions. It should generally be treated as an additional antral specimen and its scores averaged with the antral ones. OLGA staging system (7) has adopted these indications too.

Sampling orientation is critical for optimal histologic evaluation: fragments shall be deposited with the uneven, rough surface, as such adhers on paper blotting and then into the fixative. This allows proper orientation of the biopsy.

The gastritis characterization is possible whereas each biopsy include the muscularis mucosae, being completely represented the full thickness of the mucosa. Assessments of the degree of atrophy are reliable where the sample should cover at least 15-20 pits. In the Sidney system, in antrum and corpus, the presence of H. p., neutrophilic and mononuclear cells, loss of proper glands of the antrum and corpus, and intestinal metaplasia are recorded and then a numeric or descriptive value are assigned: 0 for absent, 1 for mild, 2 for moderate, and 3 for marked (or severe). This is a basic level represented by a set of elementary lesions (Polymorphonuclear neutrophil activity, Chronic inflammation, Glandular atrophy, Intestinal metaplasia, Other Histological Features (Nongraded Variables) such as Surface epithelial damage, mucous depletion, and erosions, Lymphoid follicles, Foveolar hyperplasia, Pseudopyloric metaplasia, Pancreatic or acinar metaplasia, Endocrine cell hyperplasia), that characterize the morphological pictures allowing to distinguish the topographic types of H. pylori induced chronic gastritis, metaplastic or not, from other subtypes of gastritis that recognize different etiologic agents. But it is only the combination and topographical distribution of the different elementary lesions that returns the overview of gastritis in the individual patient.

Given the considerable variation of intensity within the same biopsy sample in such cases, the observer should attempt to average the different areas and score the specimen accordingly (6). This evaluation attempt led to a variable reproducibility among pathologists.

The degree of inflammation in the antrum and corpus allows to determine whether the inflammation is similar in intensity (i.e., pangastritis) or more severe in either the antrum (antrum-predominant gastritis) or the corpus (corpus-predominant gastritis). Most cases show diffuse chronic inflammation, but a small proportion will show a two-grade difference between the antrum and corpus or vice versa. These cases should be distinguished as antral predominant or corpus predominant, respectively Gastritis staging, combined with H pylori status, provided clinically relevant information on the overall status of the gastric mucosa with implications for prognosis, therapy and management The last step in the Sydney classification is to decide whether focal atrophy or diffuse atrophy is present (metaplastic or nonmetaplastic). With regard to this last topic, the interobserver agreement among pathologists had revisited the spectrum of gastric atrophy and intestinal metaplasia (IM) (Atrophy Club 2000) and finally gastrointestinal pathologists were able to obtain a higher level of interobserver consistency (8).

But the real keystone was the introduction of the OLGA system, born in Parma (7) when a restricted international group of experts in the gastroenterological field, pathologists and gastroenterologists of both sides of the ocean had a meeting to release a grading system that turn the simplicity, the reproducibility and, above all, the predictability of the lesions in its main strategies.

Currently, the degree of atrophy and metaplasia can be assessed according to the OLGA (the Operative Link for Gastritis Assessment) system that considers gastric atrophy as the lesion that indicates disease progression.

This system report gastritis in terms of stage organizing the histological phenotypes of gastritis along a scale of progressively increasing gastric cancer risk, from the lowest (OLGA stage 0) to the highest (OLGA stage IV). This staging framework is borrowed from the oncology vocabulary and it applies to gastritis a histology reporting format successfully adopted for chronic hepatitis too.

Gastritis is staged by combining the extent of atrophy (scored histologically) with its topographical location (resulting from the mapping protocol) (10).

As the Sydney System, OLGA system can be applied only when a full set of biopsy specimens is avail-

able. Recently the importance of this classification system has been strongly reiterated by the panel of experts gathered in Kyoto (8) with two important statements: statement 14A that establish that gastric cancer risk correlates with the severity and extent of atrophic gastritis with a strong grade of recommendation and high level of evidence (Consensus level: 94.7%) and statement 14B that claims that histological staging systems such as OLGA and OLGIM are useful for risk stratification, with a strong grade of recommendation but with low evidence level (Consensus level: 97.3%). The long course inflammation triggered by H.p. infection can exert a multistep pathway of precancerous lesions, in particular, atrophic gastritis, intestinal metaplasia and finally intraepithelial neoplasia. It is a common finding for an expert gastroenteropathologist, the association between presence of premalignant gastric lesions and presence of gastric cancer in a complete set of gastric biopsies and even more in surgical samples, showing that the risk to develop gastric cancer in a patient with premalignant lesions is nevertheless small, and that's why it is necessary the use of risk stratification methods. Gastric biopsy(ies) sampling can and must be used to provide the most important information for risk classification. Both OLGA staging system and its following modification OLGIM (Operative Link on Gastric Intestinal Metaplasia) staging system grades patients with gastritis into stages with a progressive risk of developing gastric cancer as the OLGA or OLGIM stage grows. The difference between the two systems is the evaluation of only intestinal metaplasia in the OLGIM system, improving in that way the interobserver reproducibility.

In the OLGA system the assessment of gastric atrophy is also extended to morphological findings that include every loss of appropriate glands with every following glandular substitution and, therefore, not only intestinal metaplasia, OLGA system result more adherent to real life, made of different facets of the pathology, even in the same patient. Long follow-up studies based had shown, with the proof of evidence, that OLGA systems showed a higher gastric cancer risk in patients in stage III or IV (10). As a logical effect, upper gastrointestinal endoscopic follow-up should be offered to patients that fall down in these subcategories.

Metaplasia

Metaplasia is the phenotypic replacement of one somatic, differentiated cell type with another differentiated somatic cell type in the tissue that is not normally present in that tissue, typically triggered by environmental stimuli which may act in concert with effects of H.p. infection and inflammation. A hallmark of metaplasia is a change in cellular identity and this process can be regulated by transcription factor that initiate and/or maintain cellular identity perhaps in concert with epigenetic reprogramming. Universally speaking, metaplasia is a precursor to low grade dysplasia which can culminate in high grade dysplasia and carcinoma. Improved clinical screening for and surveillance of metaplasia might lead to better prevention or early detection of dysplasia and cancer (8). High salt intake, low vegetables and fruit intake, low vitamin C intake, Helicobacter pylori infection, autoimmune gastritis can determine transition to columnar (gastric) cell towards intestinal cell type as transition in cell lineage. Intestinal metaplasia is a phenotypic change due to the replacement of gastric mucinous epithelial cells with goblet cells, enterocytes and colonocytes and it is easily detected in histopathologic findings, based on the markedly different cellular organization. It is a common feature in atrophic chronic H. pylori induced gastritis and increases in prevalence with disease duration. Intestinal metaplasia is considered to be an advanced stage of atrophy because the metaplastic glands replace the original glands and chronologically appear after the gastric glands are lost. This morphological aspect defines chronic atrophic gastritis as loss of appropriate glands. By adding the adjective appropriate (i.e. native to the specific area) to the original definition, metaplasia is incorporated in the definition of atrophy (9).

Different subtypes of intestinal metaplasia have been classified, on the basis of morphology and enzyme histochemistry into small intestinal and colonic types or complete and incomplete forms and using mucin histochemistry into three main types according to its morphology and glycoprotein content.

In type I which corresponds to complete, normal appearing small intestinal epithelium containing goblet cells producing sialomucins are interspersed among

absorptive enterocytes with eosinophilic cytoplasm (expressing the complete set of digestive enzymes such as sucrase and trehalase) and a 'brush border' given by large numbers of apical microvilli. Paneth cells may also been observed. The change does not appear to be abrupt but is progressive instead, as seen in the changing pattern of mucus secretion. The normal mucins of the stomach, MUC5AC at the surface and MUC6 in deeper glands, are pH neutral, and stained magenta with the periodic acid Schiff reagent. In intestinal metaplasia, acid mucins are observed with Alcian blue staining at pH 2.5, mostly sialic MUC2, and may be seen in the cytoplasm together with neutral mucins. Other metaplastic cells express only sialic acid mucins. (12). As the metaplastic changes advance and cover larger areas of the mucosa, new phenotypes are observed in some areas. In type II, a disorderly mixture of sialomucin-containing goblet cells are scattered among gastric-type cells containing either neutral mucin or sialomucins; type III, is characterized by tortuous and branched crypts lined by tall columnar cells containing abundant sulfomucins with smaller numbers of goblet cells containing either sialomucins or sulfomucins. (6). Both type II and type III are classified as incomplete or colonic type metaplasia because it resembles the large bowel phenotype in morphology and mucin expression, and also 'incomplete' because the set of digestive enzymes disappear partially or completely. Further, some patients may also re-express gastric (neutral) mucins. Incomplete metaplastic cells, like the normal colon epithelial cells, do not display a brush border and their mucin droplets are multiple and of variable size and shape. Gastric biopsy specimens with intestinal metaplasia frequently contain foci of both complete and incomplete metaplasia (mixed metaplasia). (12) Consistent data are available to demonstrate that the extent of gastric mucosa intestinalization parallels the histochemical demonstration of type II–III intestinal metaplasia (colonic-type metaplasia) (3) that have been shown to be associated with an increased risk of gastric cancer. However, from a practical point of view, the definition of the precise type of metaplasia in any single individual is limited by the fact that in extensive sampling are always present, though to differing degrees, both types of complete or incomplete metaplasia. The degree of incomplete intestinal metaplasia parallels the extent of intestinal metaplasia in general. Thus, there is a positive correlation between both the degree of incomplete intestinal metaplasia, and the degree of intestinal metaplasia in general, and the risk of progression to carcinoma. In addition to the type of metaplasia, the extension of atrophic/metaplastic changes is another determinant of gastric cancer risk. The presence and extent of intestinal metaplasia can also be easily evaluated with the use of specific mucin histochemical stains, such as Alcian blue/periodic acid–Schiff stain at pH 2.5. In routine histology, subtyping IM by applying specific histochemical stains is not recommended and have been largely replaced by immunohistochemical stains that identify proteins associated with particular mucin-encoding genes. Although more than 20 such mucin (MUC) genes have been identified, in practice, only a few (MUC1, MUC2, MUC5AC, and MUC6) are used routinely, and even those are used mainly in research settings. Because H. pylori does not normally adhere to intestinal-type epithelium, and because the organism usually disappears in mucosa with extensive intestinal metaplasia and atrophy, one theory is that intestinal metaplasia represents a host defense against H. pylori infection. Furthermore, changes in the composition of the gastric mucus in intestinalized epithelium may provide an additional source of defense against H. pylori, or alternatively, it may represent a type of physiologic adaptation to altered bacterial flora. The clonal nature of glands with intestinal metaplasia is debated. A recent study has suggested that gastric intestinal metaplasia is the result of a mutation and the metaplastic glands spread in the mucosa by crypt fission. In addition, there is also evidence in support of the clonal origin of gastric dysplasia from metaplasia. (12). Although intestinal metaplasia causes changes in stem and progenitor cells, it is not clear whether native gastric stem cells are the initial source of the changes and metaplasia results from their reprogramming into an intestinal type or if differentiated gastric cells first acquire intestinal properties and then stem cell properties. The stomach epithelium of mice converts readily into the intestinal type on transgenic expression of CDX2, a transcription factor that regulates intestinal development and differentiation. This observation indicates that intestinalization of gastric stem cells might be the initiating event in intestinal metaplasia (13).

Recently another type of metaplasia, the spasmolytic polypeptide-expressing metaplasia (SPEM) has been described. The gastric epithelium harbours chief cells at the base, underneath acid-producing parietal cells, progenitor cells (or stem cells) and then surface cells. H.p. infection can result in parietal cell loss. Moreover the inflammatory cells recruited by the presence of H.p. can produce cytokines stimulating INF-γ or TNF-α production that ultimately can produce, via TFF-2 (trefoil factor-2 or spasmolytic polypeptide), the appearing of SPEM. Alcian Blue staining is strongly positive in the abundant cytoplasmatic mucin of SPEM cell as well as MUC-6 immunostaining. However, more specific markers of SPEM are CD44 and Sox9. Histologically, SPEM of the Helicobacter infection models can be divided into two subtypes: mucous metaplasia and pseudopyloric metaplasia, morphologically distinct (14). SPEM has assumed a new role in the metaplasia- carcinoma sequence, since it might be a precursor to intestinal metaplasia, via foveolar hyperplasia and spasmolytic polypeptide-expressing metaplasia (SPEM) that, in turn it can give rise directly to gastric adenocarcinoma of intestinal type or indirectly, via a postulated trasformation in intestinal metaplasia. Both SPEM and IM are precursors to dysplasia and later adenocarcinoma.

Conclusion

For years, "gastritis" has been considered as a simple, though common and widespread inflammation of the stomach. The discovery of H.p. gave new stimulus to scientific research. In the attempt to find a shared common language that was understandable both for endoscopists, as well as for gastroenterologists and for pathologists too, but above all, useful for patients, the classification of Sidney and its subsequent revision took place over time. The main value of this classification was the production of a set of elementary lesions that combined with each other and based on the topographical distribution allowed the framing of gastritis in gradually increasing degrees of severity, which could be simply assessed using visual analogues. On the other hand, the main demerit was that not being perfectly reproducible and above all not allowing the stratification of the risk of gastric cancer development in the different patients, thus it didn't allowed a diversified and appropriate management to the "degree of illness".

The appearance of a classification system for gastritis, such as the OLGA staging system, immediately achieved this effect. Over time it has proved its validity also and especially when long follow-up periods have been considered. It is currently an accurate system for identifying a population with a greater risk of development of gastric carcinoma.

Recent data put gastric cancer among the top ten neoplasm and although the incidence of this type of cancer shows decreasing tendency, it is a frequent neoplasia, placed at sixth place, although with different frequencies in different geographical areas with a greater or lesser risk, and above all with an unfortunately, high incidence of mortality (source Globocan 2018).

Till from 1933, William Mayo stated that gastric cancer never arises in a healthy stomach (15) and now more than ever this affirmation become valid in the light of the results obtained with the application of a staging system for gastritis such as OLGA or OLGIM.

In fact, it must be noted that it is not so important the system used, OLGA rather than OLGIM or vice versa, but even better at least one of the two systems must be used and the pathologist must be confidant with the chosen system.

References

1. Marshall BJ, Warren JR., 1984. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet 1(8390):1311-5.
2. Correa P. 1997 Helicobacter pylori as a pathogen and carcinogen., as a human pathogen, J Physiol Pharmacol. 48 Suppl 4:19-24.
3. Rugge M, Pennelli G, Pilozzi E, Fassan M, Ingravallo G, Russo VM, Di Mario F. Gastritis: the histology report. Dig Liver Dis.;43 Suppl 4:S373-84.
4. M. Rugge et al. Digestive and Liver Disease 43S (2011) S373–S384
5. Kyoto global consensus report on Helicobacter pylori gastritis Sugano K, et al. Gut 2015;64:1–15.
6. Dixon M.F., Genta R.M., Yardley J.H., Correa P. and the Participants international workshop on the histopatology of gastritis, 1996. Classification and grading of gastritis. The

Updated Sidney System. Am. J. Surg. Pathol. 20(10): 1161-1181.
7. Gastritis staging in clinical practice: the OLGA staging system Rugge M., Meggio A., Pennelli G.M., Piscioli F., Giacomelli L., De Petris G., Graham D.Y. Gut 2007, 56; 631-636
8. Metaplasia: tissue injury adaptation and a precursor to the dysplasia-cancer sequence. Giroux V. and Rustgi A.K. Nat. Rev. Cancer 2017 Sep 1
9. Gastric Mucosal Atrophy: Interobserver consistency using new criteria and grading. Rugge M., Correa P., Dixon F., Fiocca R., Hattori T., Lechago J., Leandro G., Price A.B., Sipponen P., Solcia E., Wtanabe H., Genta R.M. Aliment Pharmacol Ther 16, 1249–1259
10. Gastritis OLGA staging and gastric cancer risk: a twelve-year clinico-pathological follow-up study. Rugge M., De Boni M., Pennelli G.M., De Bona M., Giacomelli L., Fassan M., Basso D., Plebani M., Graham D.Y. Aliment Pharmacol Ther 2010 May;31(10):1104-
11. Staging and grading of chronic gastritis Massimo Rugge MD, Robert M. Genta MD* Human Pathology 2005 36, 228– 233
12. Correa P., and M Blanca Piazuelo M.B. The gastric precancerous cascade. J Dig Dis.; 2012; 13(1): 2–9
13. Mills J. C., Ramesh A. S. Gastric Epithelial Stem Cells Gastroenterology. 2011 Feb;140(2):412-24
14. Kinoshita H, Hayakawa Y, Koike K. Metaplasia in the Stomach-Precursor of Gastric Cancer? Int J Mol Sci. 2017 Sep 27;18(10)
15. Bockus's Gastroenterology, 2rd Ed.,1963, pag. 748

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Review

Autoimmune diseases in autoimmune atrophic gastritis

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Summary. Autoimmune diseases, characterized by an alteration of the immune system which results in a loss of tolerance to self antigens often coexist in the same patient. Autoimmune atrophic gastritis, characterized by the development of antibodies agains parietal cells and against intrinsic factor, leads to mucosal destruction that affects primarily the corpus and fundus of the stomach. Autoimmune atrophic gastritis is frequently found in association with thyroid disease, including Hashimoto's thyroiditis, and with type 1 diabetes mellitus, Other autoimmune conditions that have been described in association with autoimmune atrophic gastritis are Addison's disease, chronic spontaneous urticaria, myasthenia gravis, vitiligo, and perioral cutaneous autoimmune conditions, especially erosive oral lichen planus. Interestingly, however, celiac disease, another frequent autoimmune condition, seems to play a protective role for autoimmune atrophic gastritis. The elevated prevalence of autoimmune disease clustering should prompt the clinicial to exclude concomitant autoimmune conditions upon diagnosis of any autoimmune disease. (www.actabiomedica.it)

Key words: autoimmune atrophic gastritis, Hashimoto's thyroiditis, diabetes mellitus, celiac disease

Autoimmune diseases, characterized by dysregulation of the immune system which results in a loss of tolerance to self-antigens, tend to cluster, often coexisting in the same patient. While the exact etiology of the majority of these diseases is unclear, a complex combination of host and environmental factors seem to play a pivotal role. Moreover, sequential or simultaneous development of two or more autoimmune disorders, causing deficiencies in the function of several endocrine organs, is termed autoimmune polyglandular syndrome (1).

Autoimmune atrophic gastritis (AAG) is a chronic disease that affects the corpus-fundus of the stomach, and is characterized by the development two types of auto-antibodies: anti-parietal cells antibodies and anti-intrinsic factor antibodies. A strong association between autoimmune atrophic gastritis and other autoimmune disorders has been well documented. The hypergastrinemia that ensues as a consequence of gastric cell destruction and hypochlorhydria increase the risk of adenocarcinoma and neuroendocrine tumors; an early diagnosis and an appropriate follow-up are therefore warranted. AG is usually diagnosed using a combination of APCA positivity and histological criteria. However, the latter is an invasive and costly method, and lacks an evaluation of gastric function.

The unraveling of the pathophysiology leading to autoimmune atrophic gastritis is somewhat challenging due to the following reasons: 1) the prevalence of autoimmune atrophic gastritis is relatively low, possibly due at least in part to underdiagnosis, 2) in many cases there is a concurrent *Helicobacter pylori*-induced gastritis, and 3) early stages of disease lack clinical manifestations. Alike other autoimmune disorders, autoimmune atrophic gastritis more commonly affects females than males, with a 3:1 ratio.

Although mechanisms of disease development are yet to be established, disease evolution appears to fol-

low through a sequence that commences with infiltration of the oxyntic mucosa by lymphocytes and plasma cells. At this initial stage, endoscopic appearance of islets is due to the uneven destruction of parietal cells with preserved islands of relatively normal oxyntic mucosa. Subsequently, loss of oxyntic mucosa as well as disruption of maturation of parietal cells (2) lead to hypochlorydria. Thereafter, loss of negative feedback from parietal cells induces G-cell hyperplasia and increased gastric secretion in the antrum, which, in turn, leads to parietal cell pseudohypertrophy and proliferation of enterochromaffin-like (ECL) cells. Progression of ECL cell hyperplasia to neoplastic subtype can ultimately result in carcinoid tumor formation. Metaplasia develops primarily within corpus and fundus, leading to "oxyntic antralization", with appearance of mucus-secreting cells which phenotypically resemble antral mucous cells in oxyntic regions of the stomach (3).

Aside from the fact that most cases of micro- as well as macrocytic anemia are treated with iron, folic acid and vitamin B12 without a complete workup that excludes the presence of autoimmune atrophic gastritis, anemia might be attributed to concomitant autoimmune disorders. Thus, if unsuspected and not specifically sought for, autoimmune atrophic gastritis easily goes undiagnosed.

The fact that patients with autoimmune atrophic gastritis are more prone to developing other concomitant autoimmune diseases began to be a consistent observation upon initial recognition and description of cases of autoimmune atrophic gastritis. In a series of 34 patients with pernicious anemia, in whom parietal cell antibodies (PCA) were detected in 97% of patients, and intrinsic factor blocking antibody (IFBA) was found in 52%, 32 patients had concomitant autoimmune or immunologic diseases (4). Autoimmune thyroid disease is frequent in patients with autoimmune atrophic gastritis, and in turn, patients with autoimmune thyroid disease are also frequently affected by autoimmune atrophic gastritis. Other autoimmune conditions that have been described in association with autoimmune atrophic gastritis include Addison's disease (5), chronic spontaneous urticaria (6), type 1 diabetes mellitus (7), myasthenia gravis (8), vitiligo (9) (10), and perioral cutaneous autoimmune conditions (especially erosive oral lichen planus). In a small case series reporting on 8 patients with marked pangastric atrophy, associated systemic autoimmune and/or connective tissue diseases included inflammatory bowel disease, systemic lupus erythematosus, and autoimmune hemolytic anemia (11).

It has long been recognized that AAG, as well as other autoimmune disorders, tend to cluster in families, which could reinforce the genetic component of disease. Using mouse models, it has been possible to discover AAG susceptibility genes (Gasa 1, 2, 3, and 4) on chromosomes 4 and 6 and H2 region, three of which are located on the same locus as non-obese diabetic mouse diabetes mellitus susceptibility genes (12, 13) The prevalence of AAG is increased 3- to 5-fold in patients with type 1 diabetes mellitus (14), reportedly reaching 5% to 10% and 2.6% to 4%, for autoimmune atrophic gastritis and for pernicious anemia, respectively (7). In a study conducted at Washington University Diabetes Center analyzing over 1200 patients with type 1 Diabetes Mellitus, incidence and prevalence of concomitant autoimmune disorders increased with age, and female gender strongly predicted the development of concomitant autoimmune disorders. Aside from thyroid disease and collagen vascular diseases, pernicious anemia was one of the most frequent autoimmune comorbidities in patients with type 1 diabetes (15).

Approximately 10-40% of patients with Hashimoto's thyroiditis, the most frequent thyroid disease, have associated gastric disorders. Similarly, Hashimoto's thyroiditis is present in nearly 40% of patients with AAG. In a recently published study analyzing 320 patients with autoimmune atrophic gastritis, an associated autoimmune disorder was present in 53.4%; the most common concurrent disease was autoimmune thyroiditis, found in 116 (36.2%) patients. Interestingly, authors found that serum levels of gastrin, chromogranin A, as well as the presence of ECL hyperplasia, correlated significantly with the coexistence of an autoimmune disease (16).

In a study analyzing (17) 115 patients with Hashimoto's thyroiditis, enterochromafin-like cells were found in 11.3%; nevertheless, normal levels of gastrin and chromogranin were found in a fraction of these patients. Conversely, elevated gastrin levels with concomitant low vitamin B12 levels constituted the

most specific combined parameters associated with a 96.1% specificity for the presence of enterochromafin-like cells. Thus, the authors conclude that elevated gastrin levels have a high diagnostic accuracy for enterochromafin-like cell hyperplasia identification in patients with Hashimoto's thyroiditis, and that the concomitance of low levels of Vitamin B12 are highly specific for the former. The authors acknowledge, however, that gastrin levels may be normal in the presence of enterochromafin-like cell hyperplasia, which is why monitoring is needed in time, and further examinations may be required.

The association between chronic AAG and autoimmune thyroid disease, first described in the early 1960s, was initially termed "thyrogastric syndrome". In recent times, this association has been encompassed in polyglandular autoimmune syndrome type IIIb, in which autoimmune thyroiditis is the principal disease (18).

Anti-thyroid antibody titers are a frequent finding in patients with pernicious anemia, and an important group of this subset of patients will go on to develop overt autoimmune thyroid disease. Anti-thyroid autoimmunity was found in 44% of patients with pernicious anemia in a study by Chan and coworkers (19); interestingly, thyroid disease was more frequent in females. Atrophic gastritis has been reported in 35% of patients with autoimmune thyroid disease, with the presence of pernicious anemia in 16% of patients, in a study by Centanni and collaborators (24), while the prevalence was similar (40%) in a later study by Lahner and coworkers (25). In a study exploring the association between pernicious anemia and type 1 diabetes coexisting with autoimmune thyroid disease, Perros and collaborators found that 6.3% of patients were affected by the three conditions at the same time, the risk being particularly elevated in women (8.5%) (26).

Vitamin B12 deficiency is frequent in autoimmune thyroid disease, primarily represented by patients with hypothyroidism and Graves disease, with studies reporting rates as high as 28%-55% (20, 21). Importantly, symptoms of vitamin B12 deficiency may be poorly expressed and/or attributed to the underlying thyroid disease. The presence of neurophyschiatric disturbances including lethargy, weakness, motor alterations, memory loss and paresthesis, especially if persistent after adequate L-thyroxine replacement, warrant determination of levels of Vitamin B12. Paresthesis, dysphagia and numbness are more frequently reported in hypothyroid patients with vitamin B12 deficiency with respect to patients with normal vitamin levels (22).

It is advisable to screen for Vitamin B12 deficiency (with or without chronic atrophic gastritis) upon initial diagnosis of an autoimmune disorder, and levels should be assessed periodically every 3 to 5 years, independently from the stability of the primary autoimmune disease (23). Low levels of Vitamin B12 should prompt determination of serum gastrin levels; however, although performing upper endoscopy to exclude chronic atrophic gastritis as an examination following elevated levels of Vitamin B12 and gastrin is debatable, determination of the complete Gastropanel test (including pepsinogen I and II, as well as Gastrin and anti-H. pylori antibodies) is certainly useful to identify patients in whom endoscopic evaluation is warranted.

For reasons that must still be clarified, no patient with celiac disease, another frequent autoimmune disorder, has been reported to be affected by autoimmune atrophic gastritis. In a study analyzing a cohort of 107 patients with polyglandular syndrome type 3, Hashimoto's thyroiditis coexisted with only celiac disease, and no patient with celiac disease was affected by another non-thyroid autoimmune disorder (27).

Conclusion

In practical terms, it is advisable to screen for concomitant autoimmune disease in all patients with chronic AAG. Conversely, a high-degree of suspicion must be maintained to look out for atrophic gastritis in patients with other autoimmune diseases. Although the gold-standard remains histological demonstration of atrophy of the gastric corpus and fundus, together with determination of positivity for anti-parietal cell antibodies, the elevated sensitivity and specificity of serologic assessment of gastric function (Gastropanel) render this non-invasive test an important tool for the clinician to aid in the identification of patients who should undergo endoscopic evaluation.

References

1. A. Rojas-Villarraga, J. Amaya-Amaya, A. Rodriguez-Rodriguez, R. D. Mantilla, and J. M. Anaya, "Introducing polyautoimmunity: Secondary autoimmune diseases no longer exist," Autoimmune Diseases. 2012.
2. L. M. Judd, P. A. Gleeson, B. H. Toh, and I. R. van Driel, "AAG results in disruption of gastric epithelial cell development.," Am. J. Physiol., vol. 277, no. 1 Pt 1, pp. G209-18, Jul. 1999.
3. A. Minalyan, J. N. Benhammou, A. Artashesyan, M. S. Lewis, and J. R. Pisegna, "Autoimmune atrophic gastritis: current perspectives.," Clin. Exp. Gastroenterol., vol. 10, pp. 19–27, 2017.
4. J. W. Hughes et al., "High-risk gastric pathology and prevalent autoimmune diseases in patients with pernicious anemia," Endocr. Pract., vol. 23, no. 11, pp. 1297–1303, Nov. 2017.
5. P. M. J. Zelissen, E. J. E. G. Bast, and R. J. M. Croughs, "Associated Autoimmunity in Addison's Disease," J. Autoimmun., vol. 8, no. 1, pp. 121–130, Feb. 1995.
6. P. Kolkhir, E. Borzova, C. Grattan, R. Asero, D. Pogorelov, and M. Maurer, "Autoimmune comorbidity in chronic spontaneous urticaria: A systematic review," Autoimmun. Rev., vol. 16, no. 12, pp. 1196–1208, Dec. 2017.
7. G. J. Kahaly and M. P. Hansen, "Type 1 diabetes associated autoimmunity," Autoimmun. Rev., vol. 15, no. 7, pp. 644–648, Jul. 2016.
8. K.-H. Chang, R.-K. Lyu, L.-S. Ro, Y.-R. Wu, and C.-M. Chen, "Coexistence of Pernicious Anemia and Myasthenia Gravis—A Rare Combination of Autoimmune Diseases in Taiwan," J. Formos. Med. Assoc., vol. 105, no. 11, pp. 946–949, Nov. 2006.
9. P. Amerio et al., "Vitiligo associated with other autoimmune diseases: polyglandular autoimmune syndrome types 3B + C and 4," Clin. Exp. Dermatol., vol. 31, no. 5, pp. 746–749, Sep. 2006.
10. A. M. Dahir and S. F. Thomsen, "Comorbidities in vitiligo: comprehensive review," Int. J. Dermatol., vol. 57, no. 10, pp. 1157–1164, Oct. 2018.
11. D. Jevremovic, M. Torbenson, J. A. Murray, L. J. Burgart, and S. C. Abraham, "Atrophic autoimmune pangastritis: A distinctive form of antral and fundic gastritis associated with systemic autoimmune disease.," Am. J. Surg. Pathol., vol. 30, no. 11, pp. 1412–9, Nov. 2006.
12. P. A. Silveira et al., "Identification of the Gasa3 and Gasa4 AAG susceptibility genes using congenic mice and partitioned, segregative and interaction analyses," Immunogenetics, vol. 53, no. 9, pp. 741–750, Dec. 2001.
13. A. G. Baxter, M. A. Jordan, P. A. Silveira, W. E. Wilson, and I. R. Van Driel, "Genetic Control of Susceptibility to AAG," Int. Rev. Immunol., vol. 24, no. 1–2, pp. 55–62, Jan. 2005.
14. C. E. M. De Block, I. H. De Leeuw, and L. F. Van Gaal, "AAG in Type 1 Diabetes: A Clinically Oriented Review," J. Clin. Endocrinol. Metab., vol. 93, no. 2, pp. 363–371, Feb. 2008.
15. J. W. Hughes et al., "Late-Onset T1DM and Older Age Predict Risk of Additional Autoimmune Disease," Diabetes Care, p. dc181157, Oct. 2018.
16. D. Kalkan and I. Soykan, "Polyautoimmunity in AAG," Eur. J. Intern. Med., 2016.
17. A. Nicolaou, D. Thomas, K. I. Alexandraki, S. Sougioultzis, A. V. Tsolakis, and G. Kaltsas, "Predictive value of gastrin levels for the diagnosis of gastric enterochromaffin-like cell hyperplasia in patients with hashimoto's thyroiditis," Neuroendocrinology, 2014.
18. M. Cellini et al., "Hashimoto's thyroiditis and AAG," Frontiers in Endocrinology. 2017.
19. J. C. W. Chan et al., "Pattern of thyroid autoimmunity in Chinese patients with pernicious anemia," Am. J. Med. Sci., 2009.
20. C. Das, P. K. Sahana, N. Sengupta, D. Giri, M. Roy, and P. Mukhopadhyay, "Etiology of anemia in primary hypothyroid subjects in a tertiary care center in Eastern India.," Indian J. Endocrinol. Metab., 2012.
21. Y. P. Wang, H. P. Lin, H. M. Chen, Y. S. Kuo, M. J. Lang, and A. Sun, "Hemoglobin, iron, and vitamin B12 deficiencies and high blood homocysteine levels in patients with anti-thyroid autoantibodies," J. Formos. Med. Assoc., 2014.
22. A. Jabbar et al., "Vitamin B12deficiency common in primary hypothyroidism," J. Pak. Med. Assoc., 2008.
23. R. Ness-Abramof et al., "Prevalence and evaluation of B12 deficiency in patients with autoimmune thyroid disease," Am. J. Med. Sci., 2006.
24. M. Centanni et al., "Atrophic body gastritis in patients with autoimmune thyroid disease: An underdiagnosed association," Arch. Intern. Med., 1999.
25. E. Lahner et al., "Occurrence and Risk Factors for Autoimmune Thyroid Disease in Patients with Atrophic Body Gastritis," Am. J. Med., 2008.
26. P. Perros, R. K. Singh, C. A. Ludlam, and B. M. Frier, "Prevalence of pernicious anaemia in patients with type 1 diabetes mellitus and autoimmune thyroid disease," Diabet. Med., 2000.
27. R. Vita et al., "Serum Thyroid Hormone Antibodies Are Frequent in Patients with Polyglandular Autoimmune Syndrome Type 3, Particularly in Those Who Require Thyroxine Treatment.," Front. Endocrinol. (Lausanne)., vol. 8, p. 212, 2017.

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Review

Advanced gastric cancer: the value of systemic and intraperitoneal chemotherapy

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Summary. Several possibilities in treating advanced gastric cancer exist. Radical surgery associated with chemotherapy represents the cornerstone. Which one is more effective among neoadjuvant, adjuvant or perioperative chemotherapy is still a matter of debate. Several innovative results showed the necessity to keep increasingly into consideration the intraperitoneal administration of chemotherapies. Moreover, classical drugs and their ways of administration should be combined with the new ones to improve results. Lastly the prevention of recurrence should be considered: one possibility is to administer intraperitoneal chemotherapy earlier in the therapeutic algorithm. (www.actabiomedica.it)

Key words: advanced gastric cancer, chemotherapy, hipec, intraperitoneal, surgery, carcinosis, metastasis

Introduction

Several possibilities exist in treating advanced gastric cancer (AGC). Radical surgery associated with chemotherapy (CT) represents the cornerstone. Several innovative results showed the necessity to keep increasingly into consideration the intraperitoneal administration of chemotherapies (IPC). Moreover, and their ways of administration should be combined with the new ones to improve results. Lastly the prevention of recurrence should be considered: one possibility is to administer intraperitoneal chemotherapy earlier in the therapeutic algorithm.

The CT can be administered through different ways and at different time points. The present review aims to give a comprehensive overview of the different possibilities in treating AC.

Neo-adjuvant chemotherapy

The primary aim of neo-adjuvant chemotherapy (NACT) is to reduce the tumoral extension to potentially increase the effects of a radical surgery and to reduce the biological potential of tumor cells with particular attention to subclinical micrometastases. One possible disadvantage of NACT could be to delay the surgical intervention.

The EORTC 40954 trial (1) showed an increased rate of R0 resections in NACT group, more frequent postoperative morbidity and positive hazard ratio in favor to NACT with regards to survival although not significantly. Few randomized studies were closed prematurely with no favorable results. The FAMTX trial (2, 3) gave no survival differences related to NACT. However, several evidences exist about the value of this

kind of CT. A recent meta-analysis including 15 randomized controlled trials (RCTs) and involving 2001 patients showed that the NACT does not give any adverse effect during the perioperative period. In fact, it does not increase the risk of complications nor the post-operative mortality rate. Furthermore, the effect on early gastric cancer (EGC) and AGC was positive in term both of survival and recurrence rate (4).

Perioperative chemotherapy

Perioperative chemotherapy consists in combining CT before surgery and post-operative CT with interval surgery. The concept at the base of this combined approach is to obtain the advantages of neoadjuvant schemes in reducing tumor size and facilitating radical surgery associated to the advantages offered by post-operative drug administration. In Europe, this approach is diffused, and several trials have been published.

The MAGIC trial enrolled gastric or distal esophagus adenocarcinoma (5). Preoperative CT improved R0 resection rate; almost half of the patients who received preoperative treatment completed the postoperative CT. Perioperative CT reduced the risk of relapse and improved median overall survival.

The ACCORD07 RCT enrolled patients with gastro and gastro-esophageal junction cancer (6). Perioperative CT resulted in higher rates of R0 resection, in reduction of the risk of relapse and of the risk of death.

A Cochrane single patient data meta-analysis on the perioperative CT in resectable gastric adenocarcinoma (7) included 14 RCTs. The cumulative analysis showed an increase in overall survival (OS), R0 resection and longer disease-free survival (DFS) with no differences in term of mortality and morbidity. Advantages of the perioperative scheme were more pronounced in gastro-esophageal junction cancers. When radiotherapy was added, a better OS was obtained. The best effect was found in younger patients, whereas no survival benefit was demonstrated for elderly patients.

Another British study (8) demonstrated a considerable gain in DFS in neoadjuvant and adjuvant treatment in comparison with those who didn't receive postoperative CT. OS was not significantly different.

A recent meta-analysis of RCT, involving 1240 patients comparing prognosis and safety between perioperative CT and adjuvant chemotherapy (ACT), showed an improved survival for patients treated with perioperative CT. In addition, combination CT resulted in better survival compared to monotherapy in the NACT regimens (9).

Adjuvant chemotherapy

ACT is the most applied scheme throughout the world. Many colleagues from surgical and oncological department prefer to face cancer primarily with the surgical intervention, as surgery is universally considered the main curative option in gastric cancer.

The single patient data meta-analysis by the GASTRIC group (10) analyzed 17 RCTs (3838 patients). Results showed as ACT improved 5-years survival with similar DFS. No differences were found regarding the several fluoropyrimidine based drug regimens applied (i.e. mono-, poly-chemotherapy). Further studies, the ACTSGC study (11) and the CLASSIC study (12), (13), confirmed the results.

A recent RCT did not find a significant survival benefit to be associated with ACT with fluoropyrimidines in patients with stage IB-IIIA gastric cancer. However, patients with stage II disease and those receiving uracil-tegafur treatment in the adjuvant group showed significantly better prognosis than those in the surgery-alone group (14).

S-1 is an orally active combination of tegafur, a prodrug that is converted by cells to fluorouracil, gimeracil, which inhibits dihydropyrimidine dehydrogenase, and oteracil, which inhibits the phosphorylation of fluorouracil in the gastrointestinal tract, thereby reducing the toxic gastrointestinal effects of fluorouracil (15). In Japan ACT using S-1 has become a standard treatment in patients treated by curative gastrectomy for stage II or stage III gastric cancer on the basis of results from a randomized phase III study comparing surgery plus adjuvant S-1 with surgery alone (ACTSGC trial) (16, 17).

New agents

Tumor biology and the cellular and molecular mechanisms of malignant proliferation have been studied deeply, leading to the comprehension of part of their

pathways. This permitted to develop targeted therapies against specific mechanisms. Target therapies permitted to decrease toxicity of traditional chemotherapy agents and improve survival. In gastric cancer HER-2/neu (ERBB2) has demonstrated to be the principal molecular target where monoclonal antibodies have showed their efficacy. HER2 is over-expressed in 10-40% of gastric cancer. Data from a few meta-analyses defined the prognostic role of HER2 over-expression in gastric cancer. However contrasting results have been published (18-22) depending from the diagnostic technique. Trastuzumab (Herceptin®, Genentech) demonstrated its efficacy against HER2. The ToGA trial (23) reported a reduced relative risk of death by the addiction to the traditional CT scheme of the monoclonal antibody. This result was even more evident in the HER2-enriched population, with 3+ or 2+ immunohistochemistry and FISH-positive. Several countries routinely use this drug as standard treatment in AGC.

Lapatinib is another tyrosinkynase inhibitor against Epithelial Grow Factor Receptor (EGFR), usually applied in the treatment of breast cancer. The phase II trials that tested it for AGC showed no increase in OS (24, 25).

EGFR over-expression in gastric cancer is happens in 30-50% of cases (25, 26) and tests of new drugs against this agent have been done only in metastatic or inoperable cancers. Cetuximab (Erbitux®) and Panitumumab (Vectibix, Amgen) usage brought discordant results but it seems to slightly improve the progression free survival in AGC (26, 27). Several trials are needed to estimate the real benefit and the eventual translation in operable gastric cancer in perioperative settings. Other molecules have demonstrated their ineffectiveness in gastric cancer (Gefitinib (Iressa®, AstraZeneca Pharmaceuticals) and Erlotinib (Tarceva®, Roche-Genetech) (26).

The role of angiogenesis in tumoral growth and survival and metastatic diffusion are well known pathogenetic factors. For this reason vascular endothelial growth factor (VEGF) and its receptors (VEGFR-1 and VEGFR-2) are main molecular targets of some novel drugs. Bevacizumab, a monoclonal antibody against VEGF, was at the beginning applied in colorectal, lung, ovarian, and renal cell cancers. Two randomized phase III trial, the AVAGAST and the AVATAR trials studied its application in advanced gastric cancer (28, 29). Bevacizumab insertion in treatment algorithm of AGC showed no difference in overall survival but improved progression free survival and overall response rate.

Intra-peritoneal chemotherapy

Gastric cancer cells diffuse mainly through lymphatic flow and via cell seeding after serosa invasion. The 53-60% of patients affected by AGC present peritoneal carcinosis (PC) (stage III-IV), and the 40% hepatic metastases (30) (31). Moreover, the main cause of death is PC, despite R0 resections associated to systemic CT and/or radiotherapy (30, 32-34).

A meta-analysis (32) evaluated the effect of intraperitoneal chemotherapy (IPC) associated to cytoreductive surgery (CRS) compared with surgery alone, in patients with AGC with or without peritoneal, nodal and distant metastasis. This analysis of 20 RCTs (2145 patients) reported an increase in morbidity rate in the IPC group, but also an improvement in OS, in overall recurrence rate, in hematogenous metastasis rate and in peritoneal recurrence rate in the IPC group. No statistically significant difference in lymph nodal recurrence rate was found.

Another meta-analysis (33) reported the effects of IPC and R0 resections on patients with AGC without PC compared with surgery alone. 16 RCTs (1906 pts.) were included. An increase in survival rate at 1, 2, 3, 5, 9 years and a significant reduction in recurrence rate after 2, 3, 5 years were reported in IPC group. No increase in anastomotic leakage, ileus, bowel perforation, myelosuppression, gastrointestinal reaction and hepatic failure were associated to IPC, only an increased the incidence of abdominal pain.

Lastly, another meta-analysis (35) reported an increased OS in IPC group particularly compared to surgery alone in patients with serosal invasion with no macroscopic spread of disease.

From these data results the feasibility of prophylactic IPC associated to neoadjuvant chemotherapy in order to increase the DFS and OS in patients with AGC without PC.

IPC was considered also in a neoadjuvant setting. In 2012 Yonemura et al. (36) (37) proposed a new

therapeutic approach called "bidirectional chemotherapy" which consisted in a neoadjuvant intraperitoneal and systemic chemotherapy (NIPS) that can act on PC from the inside of peritoneum and from the subperitoneal blood vessels. He proposed a drug regimen with oral S-1, i.v. taxotere and cisplatinum and intraperitoneal cisplatinum and docetaxel with good result in terms of CC-0 achievement during surgery, DFS and OS.

The role of intra-peritoneal cytology

The finding of free intraperitoneal tumor cells (FITC) has a fundamental importance in defining the prognosis of patients with AGC (38-40). Positive cytology is described in 11 to 27% of patients with gastric cancer (41).

When gastric serosa is involved, PC could be considered practically unavoidable (32). In case of free peritoneal tumor cells in abdominal cavity the natural evolution in PC occur in 80% of cases, with a distant survival near to 0% (42). PC was considered the more important prognostic factor (more than T or N) for advanced disease, early recurrence, and decreased disease-specific survival following curative resection in patients with AGC (38). In the AJCC-NCCN TNM classification, the positive cytology at the staging laparoscopy is considered as M1 disease (43-45).

The main criticism of peritoneal washing cytology remains its low sensitivity (14-70% reported in the literature, but these rates are in heterogeneous cohort of patients and stage of disease) (39). To improve sensitivity, Homma et al. (40) suggested to perform the washing in multiple cavities (in the right and left subphrenic space, inside the omental bursa, and in the Douglas pouch), and not only in the Douglas pouch (41). Furthermore, with the introduction of new molecular techniques, some studies directly compared cytology by Papanicolaou staining with molecular detection by PCR. Detection methods using PCR offer considerably higher sensitivity and a marginally lower specificity (46).

A meta-analysis including 12883 patients revealed FITC to be associated with poor overall survival poor peritoneal recurrence free survival, regardless of the detection method (47).

Then FITC represents an "*in fieri*" PC, practically comparing patients with FITC to those with PC in terms of survival. A meta-analysis focusing on the effect of IPC on patients with AGC with FITC and without macroscopic PC showed that 2- and 5-years survival was increased by IPC (RR=1.62, RR=3.10). Two- and 5-years survival was further increased by IPC associated with peritoneal lavage (PL) (RR=2.33, RR=6.19). Furthermore, peritoneal recurrence was reduced by IPC (OR=0.45) and by IPC with PL (OR=0.13) (48).

Conclusions

Gastric cancer is an aggressive disease with a high risk of peritoneal dissemination even at early stages. The surgical therapy of gastric cancer should be based on radical surgery aiming to eradicate all the macroscopic disease and perform adequate lymphadenectomy. As the peritoneal dissemination of gastric cancer is the main cause of long-term failure of the treatment, a peritoneal fluid cytology should always be done. However, the uncertainty of its results suggests preventing peritoneal dissemination and subsequent carcinosis with an early use of the intraperitoneal CT. Moreover, the use of perioperative and bidirectional CT should be considered. AGC with invasion of serosa and/or positive cytology at stadiation laparoscopy should be treated in experienced centers in order to introduce the use of "prophylactic IPC" even in absence of macroscopic peritoneal dissemination associated to perioperative CT regimen.

References

1. Schuhmacher C, Gretschel S, Lordick F, et al. Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European Organisation for Research and Treatment of Cancer randomized trial 40954. J Clin Oncol 2010; 28: 5210-8.
2. Songun I, Keizer HJ, Hermans J, Klementschitsch P, de Vries JE, Wils JA, van der Bijl J, van Krieken JH, van de Velde CJ. Chemotherapy for operable gastric cancer: results of the Dutch randomised FAMTX trial. The Dutch Gastric Cancer Group (DGCG). Eur J Cancer 1999; 35: 558-62.
3. Hartgrink HH, van de Velde CJ, Putter H, Songun I, Tesselaar ME, Kranenbarg EK, de Vries JE, Wils JA, van der Bijl J, van Krieken JH and Group., Cooperating Investigators of

The Dutch Gastric Cancer. Neo-adjuvant chemotherapy for operable gastric cancer: long term results of the Dutch randomised FAMTX trial. Eur J Surg Oncol 2004; 30: 643-9.
4. Coccolini F, Nardi M, Montori G, Ceresoli M, Celotti A, Cascinu S, Fugazzola P, Tomasoni M, Glehen O, Catena F, Yonemura Y, Ansaloni L. Neoadjuvant chemotherapy in advanced gastric and esophago-gastric cancer. Meta-analysis of randomized trials. Int J Surg 2018 Mar;51:120-127. doi: 10.1016/j.ijsu.2018.01.008. Epub 2018 Feb 20.
5. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006; 355: 11-20 .
6. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011; 29: 1715-1721.
7. Ronellenfitsch U, Schwarzbach M, Hofheinz R, Kienle P, Kieser M, Slanger TE, Jensen K and Group., GE Adenocarcinoma Meta-analysis. Perioperative chemo(radio)therapy versus primary surgery for resectable adenocarcinoma of the stomach, gastroesophageal junction, and lower esophagus. Cochrane database Syst Rev 2013 May 31; 5:CD008107.
8. Reim D, Gertler R, Novotny A, Becker K, Zum Büschenfelde C, Ebert M et al. Adenocarcinomas of the esophagogastric junction are more likely to respond to preoperative chemotherapy than distal gastric cancer. Ann Surg Oncol 2012; 19: 2108.2118.
9. Zhao JH, Gao P, Song YX, Sun JX, Chen XW, Ma B, Yang YC, Wang ZN. Which is better for gastric cancer patients, perioperative or adjuvant chemotherapy: a meta-analysis. BMC Cancer. 2016 Aug 12; 16: 631. doi: 10.1186/s12885-016-2667-5.
10. GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group, Paoletti X, Oba K, Burzykowski T, et al. Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. JAMA 2010 May 5; 303(17): 1729-37.
11. Sasako M, Sakuramoto S, Katai H, et al. Fiveyear outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol 2011; 29: 4387-4393.
12. Bang YJ, Kim YW, Yang HK, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 openlabel, randomised controlled trial. Lancet 2012; 379: 315-321.
13. Noh SH, Park SR, Yang HK, et al and investigators., CLASSIC trial. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of anopen-label, randomised phase 3 trial. Lancet Oncol 2014 Nov; 15(12): 1389-96.
14. Moon JH, Fujiwara Y, Hirao M, Imamura H, Kimura Y, Fujitani K, Fujita J, Tamura S, Takiguchi S, Yano M, Mori M, Doki Y. Randomized Controlled Trial of Adjuvant Chemotherapy with Fluoropyrimidines Versus Surgery-alone for Gastric Cancer. Anticancer Res 2017 Jun; 37(6): 3061-3067.
15. Namikawa T, Maeda H, Kitagawa H, Oba K, Tsuji A, Yoshikawa T, Kobayashi M, Hanazaki K. Treatment using oxaliplatin and S-1 adjuvant chemotherapy for pathological stage III gastric cancer: a multicenter phase II study (TOSA trial) protocol. BMC Cancer 2018 Feb 13; 18(1): 186. doi: 10.1186/s12885-018-4109-z.
16. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, Furukawa H, Nakajima T, Ohashi Y, Imamura H, Higashino M, Yamamura Y, Kurita A, Arai K, ACTS-GC Group. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 2007; 357(18): 1810-1820. doi: 10.1056/NEJMoa072252.
17. Sasako M, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, Nashimoto A, Fujii M, Nakajima T, Ohashi Y. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol 2011; 29(33): 4387-4393. doi: 10.1200/JCO.2011.36.5908.
18. Liang JW, Zhang JJ, Zhang T, Zheng ZC. Clinicopathological and prognostic significance of HER2 overexpression in gastric cancer: a meta-analysis of the literature. Tumour Biol 2014 May; 35(5): 4849-58.
19. Gu J, Zheng L, Wang Y, Zhu M, Wang Q, Li X. Prognostic significance of HER2 expression based on trastuzumab for gastric cancer (ToGA) criteria in gastric cancer: an updated meta-analysis. Tumour Biol 2014 Jun; 35(6): 5315-21.
20. Chen C, Yang JM, Hu TT, Xu TJ, Yan G, Hu SL, Wei W, Xu WP. Prognostic role of human epidermal growth factor receptor in gastric cancer: a systematic review and meta-analysis. Arch Med Res 2013 Jul; 44(5): 380-9.
21. Chua TC, Merrett ND. Clinicopathologic factors associated with HER2-positive gastric cancer and its impact on survival outcomes--a systematic review. Int J Cancer 2012 Jun 15; 130(12): 2845-56.
22. Kurokawa Y, Matsuura N, et al. Multicenter large-scale study of prognostic impact of HER2 expression in patients with resectable gastric cancer. Gastric Cancer 2014 Sep 16.
23. Bang YJ, Van Cutsem E, Feyereislova A, et al and Investigators, ToGA Trial. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010 Aug 28; 376(9742): 687-97.
24. Satoh T, Xu RH, Chung HC, et al. Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-amplified advanced gastric cancer in Asian populations: TyTAN--a randomized, phase III study. J Clin Oncol 2014 Jul 1; 32(19): 2039-49.
25. Kothari N, Almhanna K. Current status of novel agents in advanced gastroesophageal adenocarcinoma. J Gastrointest Oncol 2015 Feb; 6(1): 60-74.
26. Cappetta A, Lonardi S, Pastorelli D, Bergamo F, Lombardi G, Zagonel V. Advanced gastric cancer (GC) and cancer of the gastro-oesophageal junction (GEJ): focus on targeted therapies. Crit Rev Oncol Hematol 2012 Jan; 81(1): 38-48.
27. Lordick F, Kang YK, Chung HC, et al and Investigators., Arbeitsgemeinschaft Internistische Onkologie and EX-

PAND. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase3 trial. Lancet Oncol 2013 May; 14(6): 490-9.
28. Ohtsu A, Shah MA, Van Cutsem E, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. J Clin Oncol 2011 Oct 20; 29(30): 3968-76.
29. Shen L, Li J, Xu J, et al. Bevacizumab plus capecitabine and cisplatin in Chinese patients with inoperable locally advanced or metastatic gastric or gastroesophageal junction cancer: randomized, double-blind, phase III study (AVATAR study). Gastric Cancer 2015 Jan; 18(1): 168-76.
30. Montori G, Coccolini F, Ceresoli M, Catena F, Colaianni N, Poletti E, Ansaloni L. The treatment of peritoneal carcinomatosis in advanced gastric cancer: state of the art. Int J Surg Oncol 2014; 2014: 912418.
31. Coccolini F, Gheza F, Lotti M, Virzì S, Iusco D, Ghermandi C, Melotti R, Baiocchi G, Giulini SM, Ansaloni L, Catena F. Peritoneal carcinomatosis. World J Gastroenterol 2013 Nov 7; 19(41): 6979-94.
32. Coccolini F, Cotte E, Glehen O, Lotti M, Poiasina E, Catena F, Yonemura Y, Ansaloni L. Intraperitoneal chemotherapy in advanced gastric cancer. Meta-analysis of randomized trials. Eur J Surg Oncol 2014 Jan; 40(1): 12-26.
33. Mi DH, Li Z, Yang KH, et al. Surgery combined with intraoperative hyperthermic intraperitoneal chemotherapy (IHIC) for gastric cancer: a systematic review and meta-analysis of randomised controlled trials. Int J Hyperthermia 2013; 29(2): 156-67.
34. Sadeghi B, Arvieux C, Gilly FN et al. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. Cancer 2000 Jan 15; 88(2): 358-63.
35. Sun J, Song Y, Wang Z, Gao P, Chen X, Xu Y, Liang J, Xu H. Benefits of hyperthermic intraperitoneal chemotherapy for patients with serosal invasion in gastric cancer: a meta-analysis of the randomized controlled trials. BMC Cancer 2012 Nov 16; 12: 526.
36. Canbay E, Mizumoto A, Ichinose M, et al. Outcome data of patients with peritoneal carcinomatosis from gastric origin treated by a strategy of bidirectional chemotherapy prior to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in a single etc. Ann Surg Oncol 2014 Apr 21(4): 1147-52.
37. Yonemura Y, Elnemr A, Endou Y, et al. Effects of neoadjuvant intraperitoneal/systemic chemotherapy (bidirectional chemotherapy) for the treatment of patients with peritoneal metastasis from gastric cancer. Int J Surg Oncol 2012; 2012: 148420.
38. De Andrade JP, Mezhir JJ. The critical role of peritoneal cytology in the staging of gastric cancer: an evidence-based review. J Surg Oncol 2014 Sep; 110(3): 291-7. doi: 10.1002/jso.23632. Epub 2014 May 22. Review.
39. Ang CW, Tan LC. Peritoneal cytology in the staging process of gastric cancer: do or don't? J Gastroint Dig Syst 2013; 3: 5.
40. Homma Y, Ushida S, Yamada M, Kobayashi H, Suzuki K. Positive peritoneal washing cytology in multiple cavities can predict poor prognosis of advanced gastric cancer patients. Ann Surg Oncol 2010; 17: 455-460.
41. Kano Y, Kosugi SI, Ishikawa T, Otani T, Muneoka Y, Sato Y, Hanyu T, Hirashima K, Bamba T, Wakai T. Prognostic significance of peritoneal lavage cytology at three cavities in patients with gastric cancer. Surgery 2015 May 6.
42. Kodera Y, Yamamura Y, Shimizu Y et al. Peritoneal washing cytology: prognostic value of positive findings in patients with gastric carcinoma undergoing a potentially curative resection. J Surg Oncol 1999 Oct; 72(2): 60-4; discussion 64-5.
43. Ajani A, Bentrem D, Besh S, et al. NCCN Clinical Practice Guidelines in Oncology: Gastric Cancer 2013; Version 2.2013: www.nccn.org.
44. S, Edge. Cancer AJCo: AJCC cancer staging manual. New York: Springer; 2010.
45. Ajani JA, In H, Sano T, et al., Stomach, Amin MB E. AJCC Cancer Staging Manual, eigth ed. 2017.
46. Fujiwara Y, Okada K, Hanada H, Tamura S, Kimura Y, Fujita J, Imamura H, Kishi K, Yano M, Miki H, Okada K, Takayama O, Aoki T, Mori M, Doki Y. The clinical importance of a transcription reverse-transcription concerted (TRC) diagnosis using peritoneal lavage fluids in gastric cancer with clinical serosal invasion: a prospective, multicenter study. Surgery 2014 Mar; 155(3): 417-23.
47. Pecqueux M, Fritzmann J, Adamu M, Thorlund K, Kahlert C, Reißfelder C, Weitz J, Rahbari NN. Free intraperitoneal tumor cells and outcome in gastric cancer patients: a systematic review and meta-analysis. Oncotarget 2015 Nov 3; 6(34): 35564-78. doi: 10.18632/oncotarget.5595.
48. Coccolini F, Catena F, Glehen O, Yonemura Y, Sugarbaker PH, Piso P, Ceresoli M, Montori G, Ansaloni L. Effect of intraperitoneal chemotherapy and peritoneal lavage in positive peritoneal cytology in gastric cancer. Systematic review and meta-analysis. Eur J Surg Oncol 2016 Sep; 42(9): 1261-7. doi: 10.1016/j.ejso.2016.03.035. Epub 2016 Apr 19.
49. Bang YJ, Kim YW, Yang HK, Chung HC, Park YK, Lee KH, Lee KW, Kim YH, Noh SI, Cho JY, Mok YJ, Kim YH, Ji J, Yeh TS, Button P, Sirzén F, Noh SH, CLASSIC trial investigators. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet 2012; 379(9813): 315-321. doi: 10.1016/S0140-6736(11)61873-4.

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Review

Advanced gastric cancer: the value of surgery

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Summary. Gastric cancer is a common disease with high mortality. The definition of advanced gastric cancer is still debated. Radical surgery associated to appropriate systemic and intra-abdominal chemotherapy is the gold standard treatment. In presence of peritoneal carcinosis, reaching a complete cytoreduction is the key to achieve long-term survival. Adequate lymphadenectomy is also fundamental. Conversion therapy could be applied to selected IV stage patients. No definitive evidences exist regarding the oncological and surgical superiority of mini-invasive approaches over the classical open techniques. (www.actabiomedica.it)

Key words: advanced gastric cancer, chemotherapy, hipec, intraperitoneal, surgery, definition, metastasis, carcinosis

Introduction

Gastric cancer (GC) is the fifth cause of cancer death in the world. Some differences exist according to the geographic area. Eastern countries have a better prognosis in the treatment of these patients when compared to western. In Japan the survival for resectable GC is almost 70% (1), while in Europe and US the 5-year survival is almost 25% in advanced gastric cancer (AC) (2-6).

The TNM classification of the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) is widely used, even if with some criticisms (7-9).

However, precise definition of AC is still matter of debate. Some authors defined as AC the T3 and T4 cancers. As a counterpart, the vast majority considers advanced those tumors infiltrating beyond the submucosal layer that are not-early and not-metastatic even with N0 staging. Practically, AC could be considered the T2-T4b/N0-N3b/M0 according to the AJCC/UICC TNM classification. In addition the proposal of esophagogastric junction cancers classification to replace the Siewert one raised many concerns. Recently the new TNM 8th classification of neoplastic diseases redefined the classification of the gastric and gastroesophageal junction cancers (GEJC) and formally included the GEJC among the gastric cancers (10). A meta-analysis confirmed the same biological behavior of the GEJC and the AC. The main difference is the anatomical diffusion due to the localization, to the different anatomy of the two regions and the consequent lymphatic drainage (11).

Extension of gastric resection

Radical surgery including adequate resection and lymphadenectomy is the only curative treatment either for early stage either for advanced but non-metastatic disease. Lymphadenectomy could be considered adequate with the retrieval of at least 16 lymph nodes (12).

The recommended oncologically correct proximal margins are: at least 3 cm for T2 or higher degree tumors with "expansive growth pattern" and at least 5 cm in "infiltrative growth pattern" diseases. The concept of adequacy of surgical resection has been defined as total gastrectomy for large tumors or for tumors of the lesser curve and in general in all those situations in which resection margins cannot be respected.

Lymphadenectomy

Besides the penetration of the serosa, the principal factors strongly related with prognosis are the lymph node (LN) involvement (13) and the clearance of lymph nodes (14-16).

As a matter of fact lymphadenectomy is important in staging and in increasing the long-term survival (5, 13). Eastern and western countries use different standard to regulate the extension of the lymphadenectomy. In "standard lymphadenectomy" (D1) almost 15-18 lymph nodes (LN) must be removed to have a proper staging. In "extended lymphadenectomy" (over-D1) the number of LD to remove is 31-35 to have a better staging of the N3 (according to the TNM) and to increase survival (17-20). In D2 lymphadenectomy at least 27 LN should be retrieved for optimal results (19). In Europe, the state-of-the-art in curative-intent surgery for AC is gastrectomy, D2 lymphadenectomy and omentectomy (5, 13, 15, 21-23).

Extent of lymphadenectomies

- *D1 lymphadenectomy* includes the peri-gastric stations (from station 1 to 7) (5, 24). When facing esophageal-gastric junction tumors also the infradiaphragmatic, paraesophageal and supradiaphragmatic LN stations (19, 20, 110 and 111 LN stations) should be resected for D1 lymphadenectomy (5).
- *"D1 plus" lymphadenectomy* consists in the resection of the stations 8a, 9, and 11p too (25).
- *D2 lymphadenectomy* consists in the D1 resection associated to stations 10, 11d, and 12a (5, 25).
- *D3 lymphadenectomy* includes also the posterior (12p, 13, 14v) and para-aortic station (26).
- *Super-extender D3 lymphadenectomy* includes splenectomy or distal pancreatectomy associated to D2 lymphadenectomy.

At least 16 LN should be retrieved for accurate pathologic evaluation. Some data suggested no increase in accuracy of pN staging with an increase of LN retrieval (27).

D1 vs D2 vs D3 lymphadenectomy

In T1a tumor not suitable for endoscopic resection and for differentiated and ≤1.5 cm cT1bN0 lesions *D1 lymphadenectomy* is indicated (25). A *"D1 plus" lymphadenectomy* has been reported as an alternative of D2 in high-risk cT1N0. *D2 lymphadenectomy* is indicated for potentially curable T2–T4 tumors, as well cT1N + tumors (25). Two randomized controlled trials (RCTs) (18, 28, 29) reported a superiority of the D1 compared with D2 lymphadenectomy. However, no other studies confirmed these results (22, 23, 30). The Italian Gastric Cancer Study Group (GIRCG) showed that D2 dissection without splenectomy and pancreatic resection is feasible and safe with similar results to D1 (22). Some data from a randomized trial (18, 31) showed an increased survival rate in patients who underwent D2 vs. D1, where gastric-cancer-related death and a regional recurrence were higher in D1. Another RCT (25) comparing the difference between D1 plus and D2 showed higher LN removal in D2 lymphadenectomy, no differences in LN ratio, no significant differences in median recurrence rate.

D3 lymphadenectomy is supposed to provide a better local control of disease in advanced gastric tumors with mixed-diffuse histotype (32). As in upper third GC 29% of para-aortic LN are involved compared to the 7% of middle and lower third GC ($p<0.001$), the inclusion of para-aortic LN stations (16a, 16b) is important in upper third tumors, in larger tumors, or in tumor with station 7 involvement (33, 34). No benefit in survival rate is related to routine extended lymphadenectomy and removal of para-aortic LN (35, 36).

Super-extender D3 lymphadenectomy is strongly not recommended and is in the most of cases not necessary (13, 16, 37-39). Even in scenarios of higher risk for splenic hilum node involvement, i.e., with proximal and mid greater curvature primaries, spleen-preserving hilum lymphadenectomy can be performed with satis-

factory results (40). Splenectomy and pancreatectomy might be considered beneficial only in case the primary tumor or the LN metastasis involve these organs (16, 39).

The evaluation of the possible role of an extended lymphadenectomy in reducing the risk of a local recurrence has been reported in several studies (32, 34, 41-43).

Patients who underwent a D2 with para-aortic LN dissection (PAND) presented better outcome in terms of mortality and morbidity, compared to the only D2 have been reported (21). However, another study (34) reported that D2 with PAND has no improving in survival or recurrence rate in T2-subserosa, T3, T4 stages with similar perioperative mortality and an increase in morbidity for the D2 PAND group.

Wu et al. found in a RCT (41) evaluating D1 vs. D3 that morbidity rate was higher in D3 and overall survival was significantly higher and regional recurrence rate lower in D3 (35). De Manzoni reported a higher recurrence rate in D3 group in case of intestinal pattern then in mixed/diffuse pattern with a similar mortality thus emphasizing the necessity to tailor lymphadenectomy to the histology (32).

Cytoreductive surgery

In the event of local or diffuse peritoneal carcinosis (PC) the best approach combines systemic chemotherapy, radical surgery and intra-peritoneal chemotherapy (IPC). This multimodal treatment radically changed the outcomes (44-48).

Differently from ovarian cancer as well as for other diseases (49, 50) in GC with PC, cytoreductive surgery (CRS) alone is not accompanied by survival benefits. As showed by Yamamura et al. CRS alone cannot be effective in treating PC because of invisible cancer cells remain even after surgical procedure. As a counterpart, CRS plus peri-operative chemotherapy is feasible and safe with a significant increase in survival rate in GC with PC (51-54). Furthermore, a meta-analysis clearly showed a survival benefit in patients affected by advanced GC, with or without PC, treated with IPC (44). An independent favourable prognostic factor during CRS if associated to IPC is the completeness of cytoreduction (52, 55-57). A recent meta-analysis reported an increase in 1, 2, 3, and 5-years survival rate in CC-0/CC-1 cytoreduction (58) and CC-0 showed better outcomes than CC-1 with an increased survival at 1 and 3 years. The Peritoneal Cancer Index (PCI) evaluation is mandatory in selecting patients for CRS+IPC treatment. Yonemura et al. showed that it was possible to obtain a complete cytoreduction in 91% of cases in presence of a PCI≤6 but only in 42% with a PCI≥7. Moreover, the survival rate in PCI score ≤6 was significantly better than in PCI score ≥7 (45). Survival rates at different time points change significantly above and below a PCI of 12 with a progressive decrease for higher PCI scores (57, 59-61.

Surgery for IV stage gastric cancer

Chemotherapy remains the main therapeutic approach for stage IV GC and surgery is usually confined to a palliative resection or by-pass operation to relieve symptoms. However, the median survival time of this cohort of patients remains to be around 13-16 months (62). Furthermore, the REGATTA trial demonstrated that the initial removal of the primary tumor in stage IV GC could be beneficial just in case of only one affected organ other than the site of primary tumor (63).

Stage IV GC patients are heterogeneous and could be divided into four categories (62) (64):

- Category 1: absence of macroscopic PC and potentially resectable metastases
- Category 2: absence of macroscopic PC and marginally resectable metastases
- Category 3: presence of macroscopic PC without other distant metastases
- Category 4: presence of macroscopic PC and other organ metastases.

According to recent studies, patients in category 1 could be eligible for neoadjuvant chemotherapy and subsequent gastrectomy plus metastasectomy. For the other categories, much attention is being paid to conversion therapy. It is defined as a surgical treatment aiming at an R0 resection after chemotherapy for tumors that were originally unresectable for technical or oncological reasons (64). In a study on 259 patients with IV stage GC, planned resection after neoadjuvant chemotherapy was performed in 7 patients and con-

version surgery in 77. Although only 51,2% of patients underwent R0 resection, median survival time was 41.3 months, that is much longer than that reported from the first-line chemotherapy trials (62). Metastasectomy along with resection of the primary tumor might be feasible for this population, once the metastases have responded well to the chemotherapy. Some authors recommend the surgical treatment of hepatic metastases from gastric cancer to be taken into consideration after careful evaluation of each single case, as only a radical approach with curative intent is worthy (65).

Mini-invasive surgical approach

Although studies about mini-invasive surgical approach mixed AC and early gastric cancer patients exist, no dedicated studies to AC were conducted. Results however suggest the possibility to apply the mini-invasive approach to AC without PC.

Laparoscopic surgery

In early gastric cancer laparoscopic resections associated to D1 lymphadenectomy obtained better results than open technique in terms of postoperative pain, time to return to normal bowel function and resumption of oral feeding, time to recovery, length of hospital stay, cosmetic results and financial outcome (66-69). Morbidity and mortality rates in laparoscopy are not statistically different to open resections (29) (22, 70). The role of laparoscopy in D2 or higher for lymphadenectomy is still matter of debate. According to some authors, laparoscopy reduces the accuracy in dissecting lymph nodes, especially from high risk nodal stations. Wang et al. in a meta-analysis including 17 trials (2313 patients) comparing laparoscopic and open total gastrectomy (71) demonstrated a longer operative time, earlier hospital discharge, earlier passage of flatus, quicker resumption of oral intake, fewer analgesic uses, and reduced postoperative morbidity in laparoscopic approach. No difference was found in terms of hospital mortality, resected lymph nodes, proximal resection margin and 5-year overall and disease-free survival. Another meta-analysis of 15 non-randomized trails substantially confirmed the outcomes (72).

Robotic surgery

No sufficient data exist about feasibility, safety and eventual advantages of robotic gastrectomy compared to open or laparoscopic gastrectomy in early gastric cancer neither in AC. No reports exist about the use of robotic gastrectomy in patients with AC and PC.

Liao et al. published a meta-analysis of 4 studies (5780 patients) comparing robotic and open gastrectomy. Longer operation time, lower blood loss and shorter hospital stay were associated to robotic gastrectomy. Overall morbidity and number of resected lymph nodes were not different (73).

Conclusions

Therapeutic approach of AC is based on radical surgery with adequate lymphadenectomy, associated to appropriate systemic and intra-abdominal chemotherapy. In presence of PC reaching a complete removal of visible disease is even more important. In stage IV GC conversion therapy could be considered in selected patients with good response to chemotherapy. No definitive evidences exist regarding the oncological and surgical superiority of the mini-invasive approach over the classical open technique.

References

1. World Health Organization. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide. 2012.
2. Karimi P, Islami F, Anandasabapathy S, Freedman ND, Kamangar F. Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention. Cancer Epidemiol Biomarkers Prev 2014; 23: 700-713 [PMID: 24618998 DOI: 10.1158/1055-9965].
3. Bauer K, Schroeder M, Porzsolt F, Henne-Bruns D. Comparison of international guidelines on the accompanying therapy for advanced gastric cancer: reasons for the differences. J Gastric Cancer 2015 Mar; 15(1): 10-8.
4. Wang J, Sun Y, Bertagnolli MM. Comparison of Gastric Cancer Survival Between Caucasian and Asian Patients Treated in the United States: Results from the Surveillance Epidemiology and End Results (SEER) Database. Ann Surg Oncol 2015 Jan 29.
5. Japanese Gastric Cancer Association. Japanese Classification

of Gastric Carcinoma – 3nd English Edition. Gastric Cancer 2011 Jun; 14(2): 101-12.
6. Verlato G, Giacopuzzi S, Bencivenga M, Morgagni P, De Manzoni G. Problems faced by evidence-based medicine in evaluating lymphadenectomy for gastric cancer. World J Gastroenterol 2014 Sep 28; 20(36): 12883-91.
7. Washington K. 7th edition of the AJCC cancer staging manual: stomach. Ann Surg Oncol 2010; 17: 3077-3079 [PMID: 20882416 DOI: 10.1245/s10434-010-1362-z].
8. Sobin LH, Gospodarowicz MK, Wittekind C. International Union Against Cancer (UICC) TNM Classification of Malignant Tumors. 7th ed. New York: Wiley-Liss; 2010.
9. Qiu MZ, Wang ZQ, Zhang DS, Liu Q, Luo HY, Zhou ZW, Li YH, Jiang WQ, Xu RH. Comparison of 6th and 7th AJCC TNM staging classification for carcinoma of the stomach in China. Ann Surg Oncol 2011; 18: 1869-1876.
10. Ajani JA, In H, Sano T, et al.,Stomach, Amin MB E. AJCC Cancer Staging Manual, eighth ed. 2017.
11. Coccolini F, Nardi M, Montori G, Ceresoli M, Celotti A, Cascinu S, Fugazzola P, Tomasoni M, Glehen O, Catena F, Yonemura Y, Ansaloni L. Neoadjuvant chemotherapy in advanced gastric and esophago-gastric cancer. Meta-analysis of randomized trials. Int J Surg 2018 Mar; 51: 120-127. doi: 10.1016/j.ijsu.2018.01.008. Epub 2018 Feb 20. Review.
12. Seevaratnam R, Bocicariu A, Cardoso R, Yohanathan L, Dixon M, Law C, Helyer L, Coburn NG. How many lymph nodes should be assessed in patients with gastric cancer? A systematic review. Gastric Cancer 2012; 15: S70-88.
13. McCulloch P1, Niita ME, Kazi H, Gama-Rodrigues JJ. Gastrectomy with extended lymphadenectomy for primary treatment of gastric cancer. Br J Surg 2005 Jan; 92(1): 5-13.
14. Deng J, Zhang R, Pan Y, Wang B, Wu L, Jiao X, Bao T, Hao X, Liang H. Comparison of the staging of regional lymph nodes using the sixth and seventh editions of the tumor-node-metastasis (TNM) classification system for the evaluation of overall survival in gastric cancer patients. Surgery 2014 Jul: 156(1): 64-74.
15. Schwarz RE. Current status of management of malignant disease: current management of gastric cancer. J Gastrointest Surg 2015 Apr; 19(4): 782-8.
16. Jiang L, Yang KH, Chen Y, Guan QL, Zhao P, Tian JH, Wang Q. Systematic review and meta-analysis of the effectiveness and safety of extended lymphadenectomy in patients with resectable gastric cancer. Br J Surg 2014 May; 101(6): 595-604.
17. Siewert JR, Bottcher K, Roder JD et al. Prognostic relevance of systematic lymph node dissection in gastric carcinoma. Br J Surg 1993; 80: 1015-1018.
18. Bonenkamp JJ, Hermans J, Sasako M, van de Velde CJH, for the Dutch Gastric Cancer Group. Extended lymph-node dissection for gastric cancer. N Engl J Med 1999; 340(12): 908-14.
19. Wagner PK, Ramaswamy A, Rueschoff J et al. Lymph node count in the upper abdomen: anatomical basis for lymphadenectomy in gastric cancer. Br J Surg 1991; 78:825-827.
20. Bozzetti F. Principles of surgical radicality in the treatment of gastric cancer. Extended lymph-node dissection for gastric cancer. N Engl J Med 1999 Mar 25; 340(12): 908-14. Surg Oncol N Am 2001; 10:833-854.
21. Kulig J, Popiela T, Kolodziejczyk P, Sierzega M, Szczepanik A and Group., Polish Gastric Cancer Study. Standard D2 versus extended D2 (D2+) lymphadenectomy for gastric cancer: an interim safety analysis of a multicenter, randomized, clinical trial. Am J Surg 2007 Jan; 193(1): 10-5.
22. Degiuli M, Sasako M, Ponti A, Soldati T, Danese F, Calvo F. Morbidity and mortality after D2 gastrectomy for gastric cancer: results of the Italian Gastric Cancer Study Group prospective multicenter surgical study. Clin Oncol 1998 Apr; 16(4): 1490-3.
23. Degiuli M, Sasako M, Ponti A, Calvo F. Survival results of a multicentre phase II study to evaluate D2 gastrectomy for gastric cancer. Br J Cancer 2004 May 4; 90(9): 1727-32.
24. Song W, He Y, Wang S, He W, Xu J. Significance of the lymph nodes in the 7th station in rational dissection for metastasis of distal gastric cancer with different T categories. Chin J Cancer Res 2014 Aug; 26(4): 423-30.
25. Galizia G, Lieto E, De Vita F, Castellano P, Ferraraccio F, Zamboli A, Mabilia A, Auricchio A, De Sena G, De Stefano L, Cardella F, Barbarisi A, Orditura M. Modified versus standard D2 lymphadenectomy in total gastrectomy for nonjunctional gastric carcinoma with lymph nodes metastases. Srgery 2015 Feb; 157(2): 285-96.
26. Lee J, Lim do H, Kim S, et al. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. J Clin Oncol 2012; 30: 268-273.
27. De Manzoni G, Verlato G, Roviello F, Morgagni P, Di Leo A, Saragoni L, Marrelli D, Kurihara H, Pasini F. The new TNM classification of lymph node metastasis minimises stage migration problems in gastric cancer patients. Br J Cancer 2002 Jul 15; 87(2): 171-4.
28. Cuschieri A, Weeden S, Fielding J, Bancewicz J, Craven J, Joypaul V, Sydes M, Fayers P. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. Br J Cancer 1999; 79(9-10): 1522-30.
29. Cuschieri A, Fayers P, Fielding J, Craven J, Bancewicz J, Joypaul V, Cook P. Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. Lancet 1996 Apr 13; 347(9007): 995-9.
30. McCulloch P, Nita ME, Kazi H, Gama-Rodrigues J. Extended versus limited lymph nodes dissection technique for adenocarcinoma of the stomach. Cochrane Database Syst Rev. 2004 Oct 18; (4):CD001964.
31. Songun I, Putter H, Kranenbarg EM, Sasako M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol 2010; 11: 439-49.
32. De Manzoni G, Verlato G, Bencivenga M, Marrelli D, Di Leo A, Giacopuzzi S, Cipollari C, Roviello F. Impact of

super-extended lymphadenectomy on relapse in advanced gastric cancer. Eur J Surg Oncol 2015 Apr; 41(4): 534-40.
33. Roviello F, Pedrazzani C, Marrelli D, Di Leo A, Caruso S, Giacopuzzi S, Corso G, de Manzoni G. Super-extended (D3) lymphadenectomy in advanced gastric cancer. Eur J Surg Oncol 2010 May; 36(5): 439-46.
34. Sasako M, Sano T, Yamamoto S, Kurokawa Y, Nashimoto A, Kurita A, et al. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. N Engl J Med 2008; 359: 453-62.
35. Wu CW, Hsiung CA, Lo SS, et al. Nodal dissection for patients with gastric cancer: a randomised controlled trial. Lancet Oncol 2006; 7: 309-15.
36. Songun I, Putter H, Kranenbarg EM, Sasako M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol 2010; 11: 439-49.
37. Schwarz RE, Karpeh MS, Brennan MF. Surgical management of gastric cancer: the Western experience. In: Daly JM, Hennessy TPJ, Reynolds JV, eds. Management of upper gastrointestinal cancer. London: W.B. Saunders; 1999: 83-106.
38. Kodera Y, Schwarz RE, Nakao A. Extended lymph node dissection in gastric carcinoma: where do we stand after the Dutch and British randomized trials? . J Am Coll Surg 2002; 195: 855-64.
39. Kuo CY, Chao Y, Li CP. Update on treatment of gastric cancer. J Chin Med Assoc. 2014 Jul;77(7):345-53.
40. RE., Schwarz. Spleen-preserving splenic hilar lymphadenectomy at the time of gastrectomy for cancer: Technical feasibility and early results. J Surg Oncol 2002; 79: 73-6.
41. Wu CW, Hsiung CA, Lo SS, Hsieh MC, Shia LT, Whang-Peng J. Randomized clinical trial of morbidity after D1 and D3 surgery for gastric cancer. Br J Surg 2004 Mar; 91(3): 283-7.
42. Wu CW, Hsiung CA, Lo SS, Hsieh MC, Chen JH, Li AF, Lui WY, Whang-Peng J. Nodal dissection for patients with gastric cancer: a randomised controlled trial. Lancet Oncol 2006 Apr; 7(4): 309-15.
43. Sano T, Sasako M, Yamamoto S, Nashimoto A, Kurita A, Hiratsuka M, Tsujinaka T, Kinoshita T, Arai K, Yamamura Y, Okajima K. Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended paraortic lymphadenectomy-Japan Clinical Oncology group Study 9501. J Clinical Oncol 2004 Jul 15; 22(14): 2767-73.
44. Coccolini F, Cotte E, Glehen O, Lotti M, Poiasina E, Catena F, Yonemura Y, Ansaloni L. Intraperitoneal chemotherapy in advanced gastric cancer. Meta-analysis of randomized trials. Eur J Surg Oncol 2014 Jan; 40(1): 12-26.
45. Yonemura Y, Elnemr A, Endou Y, et al. Multidisciplinary therapy for treatment of patients with peritoneal carcinomatosis from gastric cancer. World J Gastrointetinal Oncol 2010; 2: 85-97.
46. Montori G, Coccolini F, Ceresoli M, Catena F, Colaianni N, Poletti E, Ansaloni L. The treatment of peritoneal carcinomatosis in advanced gastric cancer: state of the art. Int J Surg Oncol 2014; 2014: 912418.
47. Rudloff U, Langan RC, Mullinax JE, et al. Impact of maximal cytoreductive surgery plus regional heated intraperitoneal chemotherapy (HIPEC) on outcome of patients with peritoneal carcinomatosis of gastric origin: results of the GYMSSA trial. J Surg Oncol 2014 Sep; 110(3): 275-84.
48. Fugazzola P, Coccolini F, Montori G, Ceresoli M, Baggi P, Costanzo A, Tomasoni M, Gregis F, Nozza S, Ansaloni L. Overall and disease-free survival in patients treated with CRS + HIPEC with cisplatin and paclitaxel for gastric cancer with peritoneal carcinomatosis. J Gastrointest Oncol 2017 Jun; 8(3): 572-582. doi: 10.21037/jgo.2017.03.11.
49. Coccolini F, Gheza F, Lotti M, Virzì S, Iusco D, Ghermandi C, Melotti R, Baiocchi G, Giulini SM, Ansaloni L, Catena F. Peritoneal carcinomatosis. World J Gastroenterol 2013 Nov 7;19(41):6979-94. World J Gastroenterol 2013 Nov 7; 19(41): 6979-94.
50. Bristow RE, Chi DS. Platinum-based neoadjuvant chemotherapy and interval surgical cytoreduction for advanced ovarian cancer: a meta-analysis. Gynecol Oncol 2006 Dec; 103(3): 1070-6. Epub 2006 Jul 27.
51. Coccolini F, Campanati L, Catena F, Ceni V, Ceresoli M, Jimenez Cruz J, Lotti M, Magnone S, Napoli J, Rossetti D, De Iaco P, Frigerio L, Pinna A, Runnebaum I, Ansaloni L. Hyperthermic intraperitoneal chemotherapy with cisplatin and paclitaxel in advanced ovarian cancer: a multicenter prospective observational study. J Gynecol Oncol 2015 Jan; 26(1): 54-61. doi: 10.3802/jgo.2015.26.1.54. Epub 2014 Nov 3.
52. Yonemura Y, Shinbo M, Hagiwara A, et al. Treatment for potentially curable gastric cancer patients with intraperitoneal free cancer cells. Gastroenterological Surg 2008; 31: 802-12. [in Japanese].
53. Yonemura Y, Bandou E, Sawa T, et al. Neoadjuvant treatment of gastric cancer with peritoneal dissemination. EJSO 2006; 32: 661-5.
54. Glehen O, Gilly FN, Arvieux C, Cotte E, Boutitie F, Mansvelt B, Bereder JM, Lorimier G, Quenet F, Elias D and Chirurgie. Association Française de. Peritoneal carcinomatosis from gastric cancer: a multi-institutional study of 159 patients treated by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. Ann Surg Oncol 2010 Sep; 17(9): 2370-7. doi: 10.1245/s10434-010-1039-7. Epub 2010 Mar 25.
55. Yonemura Y, Endou Y, Shinbo M, et al. Safety and efficacy of bidirectional chemotherapy for treatment of patients with peritoneal dissemination from gastric cancer: selection for cytoreductive surgery. J Surg Oncol 2009; 100: 311-6.
56. Yonemura Y, Kawamura T, Bandou E, et al. Treatment of peritoneal dissemination from gastric cancer by peritonectomy and chemohyperthermic peritoneal perfusion. Brit J Surg 2005; 92: 370-5.
57. Glehen O, Gilly FN, Boutitie F, Bereder JM, Quenet F, Sideris L, Mansvelt B, Lorimier G, Msika S, Elias D and Association., French Surgical. Toward curative treatment of

peritoneal carcinomatosis from nonovarian origin by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy: a multi-institutional study of 1,290 patients. Cancer 2010 Dec 15; 116(24): 5608-18. doi: 10.1002/cncr.25356. Epub 2010 Aug 24.
58. Coccolini F, Catena F, Glehen O, Yonemura Y, Sugarbaker PH, Piso P, Montori G, Ansaloni L. Complete versus incomplete cytoreduction in peritoneal carcinosis from gastric cancer, with consideration to PCI cut-off. Systematic review and meta-analysis. Eur J Surg Oncol 2015 april 14.
59. Scaringi S, Kianmanesh R, Sabate JM, Facchiano E, Jouet P, Coffin B, Parmentier G, Hay JM, Flamant Y, Msika S. Advanced gastric cancer with or without peritoneal carcinomatosis treated with hyperthermic intraperitoneal chemotherapy: a single western center experience. Eur J Surg Oncol 2008 Nov; 34(11): 1246-52. doi: 10.1016/j.ejso.2007.12.003. Epub 2008 Jan 28.
60. Yang XJ, Li Y, Yonemura Y. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy to treat gastric cancer with ascites and/or peritoneal carcinomatosis: Results from a Chinese center. J Surg Oncol 2010 May 1; 101(6): 457-64.
61. Yang XJ, Huang CQ, Suo T, Mei LJ, Yang GL, Cheng FL, Zhou YF, Xiong B, Yonemura Y, Li Y. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves survival of patients with peritoneal carcinomatosis from gastric cancer: final results of a phase III randomized clinical trial. Ann Surg Oncol 2011 Jun; 18(6): 1575-81. doi: 10.1245/s10434-011-1631-5. Epub 2011 Mar 23.
62. Yamaguchi K, Yoshida K, Tanahashi T, Takahashi T, Matsuhashi N, Tanaka Y, Tanabe K, Ohdan H. The long-term survival of stage IV gastric cancer patients with conversion therapy. Gastric cancer 2018; 21: 315-323.
63. Fujitani Kazumasa, Yang Han-Kwang, Mizusawa Junki, Kim Young-Woo, Terashima Masanori, et al. Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial. Lancet Oncol 2016; 17: 309-18.
64. Yoshida K, Yamaguchi K, Okumura N, Tanahashi T, Kodera Y. Is conversion theraphy possible in stage IV gastriccancer: the proposal of new biological categories of classification. Gastric Cancer 2016; 19: 329-338. DOI 10.1007/s10120-015-0575-z.
65. Ministrini S, Solaini L, Cipollari C, Sofia S, Marino E, D'Ignazio A, Bencivenga M, Tiberio GAM. Surgical treatment of hepatic metastases from gastric cancer. Updates in Surgery 2018; 70: 273-278. https://doi.org/10.1007/s13304-018-0536-2.
66. Kitano S, Shiraishi N, Fujii K, Yasuda K, Inomata M, Adachi Y. A randomized controlled trial comparing open vs laparoscopy-assisted distal gastrectomy for the treatment of early gastric cancer: an interim report. Surgery 2002; 131: S306-S311.
67. Lee JH, Han HS, Lee JH. A prospective randomized study comparing open vs laparoscopy-assisted distal gastrectomy in early gastric cancer: early results. Surg Endosc 2005; 19: 168-173 .
68. Kim HH, Hyung WJ, Cho GS, Kim MC, Han SU, Kim W, Ryu SW, Lee HJ, Song KY. Morbidity and mortality of laparoscopic gastrectomy versus open gastrectomy for gastric cancer: an interim report--a phase III multicenter, prospective, randomized Trial (KLASS Trial). Ann Surg 2010 Mar; 251(3): 417-20. doi: 10.1097/SLA.0b013e3181cc8f6b.
69. Yasunaga H, Horiguchi H, Kuwabara K, Matsuda S, Fushimi K, Hashimoto H, Ayanian JZ. Outcomes after laparoscopic or open distal gastrectomy for early-stage gastric cancer: a propensity-matched analysis. Ann Surg 2013; 257: 640-646 .
70. Bonenkamp JJ, Songun I, Hermans J, Sasako M, Welvaart K, Plukker JT, van Elk P, Obertop H, Gouma DJ, Taat CW. Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. Lancet 1995; 345: 745-748 .
71. Wang W, Zhang X, Shen C, Zhi X, Wang B, et al. Laparoscopic versus Open Total Gastrectomy for Gastric Cancer: An Updated Meta-Analysis. PLoS ONE 2014; 9(2): e88753.
72. Xiong JJ, Nunes QM, Huang W, Tan CL, Ke NW, Xie SM, Ran X, Zhang H, Chen YH, Liu XB. Laparoscopic vs open total gastrectomy for gastric cancer: A meta-analysis. World J Gastroenterol 2013; 19(44): 8114-8132.
73. Liao G, Chen J, Ren C, Li R, Du S, Xie G, Deng H, Yang K, Yuan Y. Robotic versus Open Gastrectomy for Gastric Cancer: A Meta-Analysis. PLoS ONE 2013; 8(12): e81946.

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Review

Risk of tumor implantation in percutaneous endoscopic gastrostomy in the upper aerodigestive tumors

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Summary. Percutaneous endoscopic gastrostomy (PEG) has become a mainstay in providing enteral access for patients with obstructive head, neck and esophageal tumors. Tumor cell implantation is a rare complication in patients with aerodigestive cancers, who have undergone PEG tube placement. The objective of this review is to determine the incidence and contributing risk factors leading to the implantation of metastases into the abdominal wall following PEG placement. A comprehensive review of the literature in PUBMED (2008-2018) was performed. The literature search revealed reports of more than 50 cases of abdominal wall metastases after PEG placement. As most of these studies were case reports, the exact rate of metastasis remains unknown. Generally pharyngoesophageal location of primary cancer (100%), squamous cell histology (98%), poorly differentiated tumor cells (92%), advanced pathological stage (97%), and large primary cancer size were identified as strong risk factors for the development of stomal metastasis. Abdominal wall metastases following PEG placement are a rare but serious complication in patients with head and neck malignancy. (www.actabiomedica.it)

Key words: percutaneous endoscopic gastrostomy, metastasis, aerodigestive tumors

Background

Patients with cancer are at high risk of malnutrition because both the disease and its treatments threaten the nutritional status. It is estimated that the deaths of 10 e 20% of patients with cancer can be attributed to malnutrition rather than to the malignancy itself (1, 2).

The prevalence of malnutrition in patients with cancer has been reported to range from about 20% to more than 70% in worldwide studies, with differences related to patient age, cancer type, and cancer stage. Patients with gastrointestinal tract, head and neck (HNC), and liver and lung cancers are at high risk for malnutrition (3-6).

It is estimated that approximately 50% of patients with HNC will require alternative means of nutrition support due to dysphagia resulting from obstructing tumors, tumor compression (arising from thyroid and tracheal cancers) within the pharyngeal region, and/or the effects of concurrent chemoradiation therapy (7). Symptoms of disease and/or treatment, such as vomiting, mucositis, xerostomia, dysphagia, and odynophagia, contribute to inadequate oral intake of nutrition and hydration, leading to weight loss, nutrition deficiencies, and dehydration. To effectively treat the patient, nutritional support is essential in stabilizing and restoring weight status, correcting nutrition deficiencies, and maintaining adequate hydration. The decision to place an enteral feeding tube prophylactically can vary based on different protocols and guidelines of treatment. If short term, temporary nutrition support is needed (defined as 4-6 weeks) a nasogastric tube (NGT) can be placed (8). PEG has superseded NGT

placement and surgical gastrostomy as the commonest method of providing long term enteral feeding (9).

It allows long-term tube feeding, when oral feeding is not possible, or when extra feeding is necessary (10). PEG placement involves an upper gastrointestinal endoscopy, usually under conscious sedation and with the use of local anesthesia at the gastrostomy site. Since its introduction in the 1980s, PEG has been associated with superior outcomes with respect to complication and mortality rates compared with surgical gastrostomy (11). Although PEG tube placement is common and well-tolerated, it is not completely benign. Complication of PEG tube placement include local infection, hemorrhage, tube dislodgement which can lead to peritonitis, bowel perforation, and aspiration pneumonia (12). However, specific to head and neck malignancy metastatic "seeding" of the abdominal wall following PEG placement has been documented in case reports and small retrospective analyses.

PEG insertion techniques

There are 3 methods of PEG placement: Gauderer-Ponsky pull, Sachs-Vine push, and the Russell push method, which can be placed in interventional radiology, endoscopic suite, or at the bedside (13).

The Gauderer-Ponsky pull method was first described in 1980 (14). The gastrostomy tube is placed via complete esophagogastroduodenoscopy (EGD). During EGD, the stomach is filled with air, which pushes the stomach wall up toward the abdominal wall. The light at the tip of the endoscope is turned upward, allowing the transillumination of the abdominal wall. A needle or catheter is placed through the abdominal wall into the stomach. After a small incision is made in the abdominal and gastric walls, a guidewire is passed through the needle/catheter site and is captured with a polypectomy snare. The endoscope, snare, and guidewire are pulled out through the stomach, up the esophagus, and out the mouth, and the gastrostomy tube is attached to the guidewire. The guidewire is pulled out of the abdominal wall, pulling the gastrostomy tube from the mouth, down the esophagus and stomach, and out through the abdominal incision (15). This technique requires 2 passages of the endoscope through the oral cavity and 1 passage of the PEG through the oral cavity.

The Sachs-Vine push method, which was first described in 1983, is similar to the Gauderer- Ponsky pull method, except for use of the guidewire (16). In the push method, the PEG is a long, semirigid, tapered tube with a dilator attached to the proximal end. The dilator is inserted over a guidewire and advanced into the mouth, down the esophagus, into the stomach, and out the abdominal wall through the incision site. This technique also requires 2 passes of the endoscope and passage of the PEG through the oral cavity.

The Russell push PEG, which requires only 1 pass of the endoscope, was first described in 1984. With this PEG placement method, the stomach is filled with air and a needle is placed in the stomach as in the Gauderer-Ponsky method. A 16 French peel-away introducer sheath and dilator is pushed over the guidewire into the stomach and abdominal wall. The dilator and guidewire are removed, leaving the introducer sheath in place. A 14 French balloon tip Foley catheter is placed into the introducer sheath, and the catheter balloon is inflated and pulled up against the abdominal wall, bringing the stomach wall into position with the abdominal wall (16).

The advantage of this method is the need of only one passage of the endoscope into the oral cavity and no passage of the PEG through the oral cavity. The disadvantage is that the PEG tube itself is generally smaller, such as 14 French rather than the standard PEG of 20-24 French.

The phenomenon of cancer metastasis to PEG stoma, although rare, is becoming increasingly reported. The purpose of our review is to examine the incidence and the contributing risk factors leading to metastasis to the abdominal wall following PEG placement in patients with upper aerodigestive cancer.

Methods

A comprehensive review of the literature in PUBMED database using Mesh terms "percutaneous endoscopic gastrostomy", "tumor", "metastasis", "abdominal wall" was performed. Medline, Scopus, PubMed publisher and Google Scholar were searched as well.

The research was restricted to the period of publication between 2008 and 2018. Only full text papers in English were included.

Results

During the past 2 decades, there have been increasing reports describing tumor seeding at the PEG exit site, which have caused controversy relating to the technique used in PEG insertion. The first case of spread of a cancer to a gastrostomy site was reported in 1977 by Alagaratnam and Ong (17), and the first report of a gastric and abdominal wall metastasis secondary to PEG placement specifically in a patient with head and neck squamous cell cancer was described in 1989 by Preyer (18). The literature search revealed reports of more than 50 cases of abdominal wall metastases after PEG placement. As most of these were case reports, the exact rate of metastasis remains unknown. An article by Thakore et al cites that Antler et al. reported that autopsy findings may be as high as 9% (19). However the reported frequency of stomal metastases for laryngo-esophageal cancer ranges from 0.5 to 1% (20).

Cruz et al. evaluated the incidence of abdominal wall metastases following PEG placement in 304 patients with head and neck cancer, of whom 218 had active disease and a viable tumor in the oropharynx or hypopharynx when PEG was placed. Metastases were proven in 2/218 (0,92%). However, abdominal wall metastasis was defined as macroscopic evidence of tumor masses on clinical examination or endoscopy (21).

Ellrichmann et al conducted a study of 50 patients with PEG placement (22). Brush cytology from the PEG tubing and incision site was taken immediately after PEG placement and repeated 3–6 months post procedure. Forty patients underwent the pull method, and 10 underwent direct introducer technique. In 22.5% of patients, malignant cell transfer to the abdominal incision site was demonstrated, and abdominal wall metastases were present in 9.4% after 3-6 months; however, at follow-up, none of the patients had macroscopically visible tumor masses. Of the direct introducer group, 9 patients completed the 3 to 6-month follow-up. No malignant cells were found on brush cytology.

These studies suggest that the risk of malignant cell translocation due to PEG placement seems to be underestimated.

Generally pharyngoesophageal location of primary cancer (100%), squamous cell histology (98%), poorly differentiated tumor cells (92%), advanced pathological stage (97%), and large primary cancer size were identified as strong risk factors for the development of stomal metastasis (22). Moreover, the 64% of patients diagnosed with PEG site disease either had simultaneous or subsequent locoregional or distant metastatic disease, which may be indicative of aggressive tumor biology and poor overall tumor characteristics (23).

These results suggest that in patients having these risk factors for malignant tumor cell seeding, an alternative route for PEG placement should be used to avoid direct contact of the PEG tube or secure plate with superficial tumor cells.

There have been numerous theories of the pathogenesis of tumor spread to the gastrostomy site, which include direct surgical inoculation of tumor cells at time of tube placement, tumor desquamation into the alimentary tract with seeding of the PEG site after tube placement, and hematogenous dissemination with preference of circulating tumor cells to the traumatized tissue of the PEG tube site. Both open and laparoscopic-assisted gastrostomy tube insertion do have the benefit of the utilization of separate surgical instruments and no cross-contamination with the tumor. However, open gastrostomy and laparoscopic gastrostomy tube placement were both associated with longer insertion times, increased costs, and higher rates of major complications and morbidity compared to PEG, such as respiratory failure and gastrostomy site hemorrhage (24, 25).

Pickhardt et al. have discussed the advantages of percutaneous radiologic gastrostomy placement, in which direct contact of the tube with the primary tumor is avoided (26).

In this prospective, open, randomized study on long-term PEG-related adverse events in a large cohort of patients with epithelial tumors of the upper gastrointestinal tract (27) demonstrated that the direct puncture device is associated with a higher rate of short-term PEG-related adverse events in comparison

with the traditional pull technique. None of the patients in this study developed a PEG metastasis. Case reports show that PEG insertion using this technique does not eliminate the risk of direct tumor seeding (28, 29).

Conclusions

Abdominal wall metastases following PEG placement are a rare but serious complication in patients with head and neck and esophageal malignancy. This risk is particularly high in older patients and those with higher tumor stages and the occurrence of abdominal wall metastases following PEG indicates poor prognosis. While surgical technique may play a role, factors such as tumor biology may be a significant cause in PEG site metastasis formation, which is irrespective of the technique used. A possible opinion would be to include chemotherapy or chemo-radiotherapy prior to PEG placement in patient with an intention to cure. Larger studies are necessary to confirm the best approach.

References

1. Pressoir M, Desne S, Berchery D, Rossignol G, Poiree B, Meslier M, et al. Prevalence, risk factors and clinical implications of malnutrition in French Comprehensive Cancer Centres. Br J Cancer 2010; 102(6): 966e71.
2. J. Arends, V. Baracos, H. Bertz, et al. Review ESPEN expert group recommendations for action against cancer related malnutrition. Clinical Nutrition 36 2017; 1187e1196.
3. Wie GA, Cho YA, Kim SY, Kim SM, Bae JM, Joung H. Prevalence and risk factors of malnutrition among cancer patients according to tumor location and stage in the National Cancer Center in Korea. Nutrition 2010; 26(3): 263e8.
4. Hebuterne X, Lemarie E, Michallet M, de Montreuil CB, Schneider SM, Goldwasser F. Prevalence of malnutrition and current use of nutrition support in patients with cancer. J Parenter Enteral Nutr 2014; 38(2): 196e204.
5. Dewys WD, Begg C, Lavin PT, Band PR, Bennett JM, Bertino JR, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. Am J Med 1980; 69(4): 491e7.
6. Silva FR, de Oliveira MG, Souza AS, Figueroa JN, Santos CS. Factors associated with malnutrition in hospitalized cancer patients: a cross-sectional study. Nutr J 2015; 14: 123.
7. Greaves JR. Head and neck cancer tumor seeding at the percutaneous endoscopic gastrostomy site. Nutr Clin Pract. 2018 Feb; 33(1): 73-80.
8. J. Arends, G. Bodokyb, F. Bozzetti. ESPEN Guidelines on Enteral Nutrition: Non-surgical oncology. Clinical Nutrition 2006; 25: 245-259.
9. Löser C, Aschl G, Hébuterne X, et al. ESPEN guidelines on artificial enteral nutrition-percutaneous endoscopic gastrostomy (PEG). Clin Nutr 2005; 24: 848-861.
10. Nicholson FB, Korman MG, Richardson MA. Percutaneous endoscopic gastrostomy, a review of indications, complications and outcome. J Gastroenterol Hepatol 2000; 15: 21-5.
11. Gauderer MW, Ponsky JL, Izant RJ. Gastrostomy without laparotomy: a percutaneous endoscopic technique. J Pediatr Surg 1980; 15(6): 872–875.
12. Schrag SP, Sharma R, Jaik NP, et al. Complication related to percutaneous endoscopic gastrostomy (PEG) tubes. A comprehensive clinical review. J Gastrointestin Liver Dis 2007; 16 (4): 407-418.
13. Mincheff TV. Metastatic spread to a percutaneous gastrostomy site from head and neck cancer: case report and literature review. JSLS 2005; 9: 466-471.
14. Sinapi I, Navez B, Hamoir M, et al. Seeding of the percutaneous endoscopic gastrostomy site from head and neck carcinoma: case report and review of the literature. Head Neck 2013; 35(7): E209-E212.
15. Chadha KS, Thatikonda C, Schiff M, Nava H, Sitrin MD. Outcomes of percutaneous endoscopic gastrostomy tube placement using a T- fastener gastropexy device in head and neck and esophageal cancer patients. Nutr Clin Pract 2010; 25: 658-662.
16. Vaneck VW. Ins and outs of enteral access. Part 2: long-term access-esophagostomy and gastrectomy. Nutr Clin Pract 2003; 18: 50-74.
17. Alagaratnam TT, Ong GB. Wound implantation – A surgical hazard. Br J Surg 1977; 64: 872.
18. Preyer S. Gastric metastasis of squamous cell carcinoma of the head and neck after percutaneous endoscopic gastrostomy – Report of a case. Endoscopy 21: 295, 1989.
19. Thakore JN, Mustafa M, Suryaprasad S, Agrawal S. Percutaneous endoscopic gastrostomy associated gastric metastasis. J Clin Gastroenterol 2003; 37(4) 307-311.
20. Cappell MS Risk factors and risk reduction of malignant seeding of the percutaneous endoscopic gastrostomy track from pharyngoesophageal malignancy: a review of all 44 known reported cases. Am J Gastroenterol 2007; 102(6): 1307-1311.
21. Van Dyck E, Macken EJ, Roth B, et al. Safety of pull-type and introducer percutaneous endoscopic gastrostomy tubes in oncology patients: a restrospective analysis. BMC Gastroenterol 2011; 11: 23.
22. Ellrichmann M, Sergeev P, Bethge J, et al. Prospective evaluation of malignant cell seeding after percutaneous endoscopic gastrostomy in patients with oropharyngeal/esophageal cancer. Endoscopy 2013; 45: 526-531.
23. Huang AT, Georgolios A, Espino S, et al Percutaneous endoscopic gastrostomy site metastasis from head and neck

squamous cell carcinoma: case series and literature review. J Otolaryngol Head Neck Surg 2013; 42:20.
24. Bankhead RR, Fisher CA, Rolandelli RH. Gastrostomytube placement outcomes: comparison of surgical, endoscopic,and laparoscopic methods. Nutr Clin Pract 2005; 20(6): 607-612.
25. Rustom IK, Jebreel A, Tayyab M, et al. Percutaneous endoscopic, radiological and surgical gastrostomy tubes: a comparison study in head and neck cancer patients. J Laryngol Otol 2006; 120(6): 463-466.
26. Pickhardt PJ, Rohrmann CAJr, Cossentino MJ. Stomal metastases complicating percutaneous endoscopic gastrostomy: CT findings and the argument for radiologic tube placement. AJR Am J Roentgenol 2002; 179: 735-739.
27. Teich N, Selig L, Liese S, et al. Usage characteristics and adverse event rates of the direct puncture and pull techniques for percutaneous endoscopic gastrostomy in patients with malignant tumors of the upper aerodigestive tract. Endoscopy International Open 2018; 06: E29-E35.
28. Ananth S, Amin M. Implantation of oral squamous cell carcinoma at the site of a percutaneous endoscopic gastrostomy: a case report. Br J Oral Maxillofac Surg 2002; 40: 125-130.
29. Teh JL, Wong RK, Gowans M et al. Gastric metastases of oral carcinoma resulting from percutaneous endoscopic gastrostomy placement via the introducer technique. Gastroenterol Rep (Oxf) 2013; 1: 211-13.

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