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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

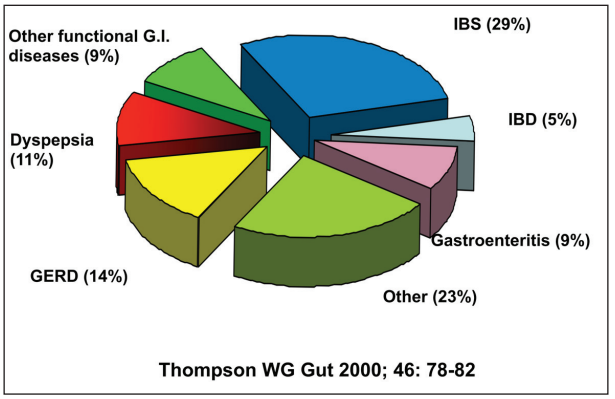

Figure 1.

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

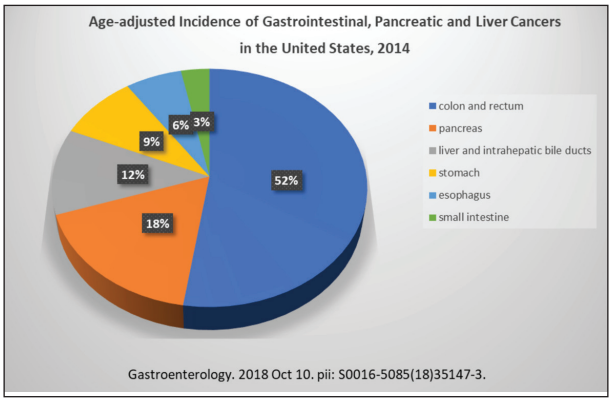

Figure 2.

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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