

## Alimentary Tract

# Overview on the management of diverticular disease by Italian General Practitioners



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## ABSTRACT

**Background:** Although very common in Western countries, poor epidemiological data on diverticular disease (DD) is available from the family practice.

**Aims:** To evaluate the behavior of Italian General Practitioners (GPs) on approaching DD.

**Methods:** Health Search Database was analyzed retrospectively.

**Results:** On a population of 975,523 individuals, 33,597 patients had a registered diagnosis of DD (“life-time” prevalence = 3.4%, M = 3.2%, F = 3.7%; higher values are found in females over-65 years old; low rates of complications: diverticulitis = 0.3%, bleeding = 0.002%). As risk factors, NSAIDs and ASA were taken by 14.8% and 26.5% respectively, opioids by 7.5%, corticosteroids by 5.2%; as protective factors, 30.4% were under statins and 17.7% under calcium-antagonists. Approximately 13% of patients were referred to specialists. Colonoscopy and abdominal CT were prescribed to 48.5% and to 13% of already diagnosed patients. Among DD sufferers, 27% experienced hospitalization, but only 3.4% of cases were for a DD-linked problem. Treatment included rifaximin (61%), mesalazine (14.7%), probiotics (12.4%), ciprofloxacin (7.6%).

**Conclusion:** DD has a large impact in general practice with a higher prevalence in the elderly. GPs are required to pay particular attention to risk factors both for disease development and for its complications in order to reduce the costs deriving from diagnostic procedures, referral and hospitalization.

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## 1. Introduction

Diverticular disease (DD) includes all the morphological features and clinical manifestations associated with the presence of diverticula in the colon. The recent Italian Consensus Conference on colon diverticulosis and DD [1] agreed on the following classification: (i) diverticulosis indicates the presence of occasionally evidenced diverticula of the colon in an asymptomatic subject; (ii) symptomatic uncomplicated diverticular disease (SUDD) is defined by recurrent abdominal symptoms (pain, bloating) and resembles the irritable bowel syndrome in the absence of clinical signs of diverticulitis; (iii) acute diverticulitis is an episode of severe and prolonged abdominal pain in the left lower region of the abdomen with alteration of fecal output, fever and leukocytosis; manifestations are limited to a single or repeated episodes; few cases may complicate with abscess, perforation or peritonitis; (iv) segmental colitis associated with diverticula (SCAD), a peculiar inflammation

of the sigmoid mucosa between diverticula never involving the ostium, is observed in a small subgroup of patients representing a possible complication or an independent form. This clinical classification, however, is not used in the general practice, being DD registered in the computerized medical record by the association with the ICD-9-CM (International Classification of Diseases) codes.

In Western countries DD is very common with the overall prevalence in the general population ranging 5–40%. DD increases with age [2] by reaching 50% of people at the age of 50 and even 70% at the age of 70 [3]. The main site of diverticula formation is the distal colon in over 90% of cases of European, American and Australian populations [4], while it is the right colon in 70–74% of African and Asiatic people [5].

Despite colonic diverticula are very common, only a small proportion of patients become symptomatic. It has been observed that up to 20% of people with diverticulosis develop diverticulitis during the life course [3], although a recent prospective study found that the cumulative probability of acute diverticulitis is only 4% of patients with incidental diverticulosis revealed by colonoscopy [6]. Following a first episode of acute diverticulitis, the risk of recurrence is 20% after 5 years with complications mainly occurring during the first episode [7]. Indeed, epidemiology of DD and diverti-

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culitis has been rapidly changing over the last few years. In fact, the incidence of diverticulitis has increased in the period 2000–2007 by 50% compared to the years before and it is involving also young people [8].

Moreover, in the last 10–20 years, an increase in hospital admissions for diverticulitis has been registered especially in surgical departments [1]. In US, DD ranks in the 6th position among gastrointestinal disorders requiring outpatient visits, while diverticulitis without hemorrhage and diverticulosis with hemorrhage represent the 3rd and 14th principal hospital discharge diagnosis, respectively, pointing to DD as the 5th most costly gastrointestinal disorder [9]. In Italy, by extending the data reported in the Marche region to the whole country, it has been calculated that the direct costs of all patients with acute episodes of diverticulitis is estimated as high as € 63.5 million/year, mainly due to hospitalization, with the costs of medications and consultations being less than 5%.

Since general practitioners (GPs) are actively involved in campaigns for the prevention of chronic illnesses, the knowledge of risk and protective factors [7,26] for the development of DD and its complications is deemed to be of great interest.

This article retrospectively investigates the demographic characteristics and the management of patients with DD, extracted from the Health Search database (HSD) of the Italian GPs.

## 2. Materials and methods

### 2.1. Data source

The HSD is a general practice research database containing data from computer-based patient records and covers a total of 1.5 million individuals. HSD was established in 1998 by the Italian College of General Practitioners and Primary Care [10]. The database contains all the data concerning demographic features, lifestyle, clinical records (diagnoses, patient referrals, hospital admissions and discharges, clinical investigations' results and date of death) and prescription data (drug name, prescription date, number of days' supply) for the drugs which are reimbursed by the National Health System (NHS) and for those not reimbursed but requiring prescription. All prescription data is coded by the ATC classification system, while the ICD-9-CM is used for all medical records.

HSD also serves important Italian government and administrative reports (i.e. ISTAT, National Institute of Statistics, OsMed, Italian drug prescription monitoring; AIFA, Italian drug agency). All the information is anonymously transferred to the center for storage and analysis.

The GPs included in the study had to meet 'up-to-standard' quality criteria for epidemiological studies, in particular: levels of coding, prevalence of well-known diseases, and mortality rates. Furthermore, only GPs who provided data for at least one year were included in the analysis [11]. HSD is a valid data source for scientific research and it is aligned with the European Union guidelines on the use of medical data for research. For these reasons, HSD has been used as data source in many studies and publications [12,13]. On December 31, 2016, the results of over 975,523 patients, assisted by 800 Italian GPs homogeneously distributed across the country using the best accuracy for data registration, were recorded.

### 2.2. Outcome definition

To identify patients diagnosed with DD, HSD [14] was searched by the ICD-9 classification system coding for colon-sigma diverticulosis (562.1), diverticulosis of the colon, diverticulosis of the large intestine (562.10), diverticulosis with diverticulitis (562.11), diverticulosis of the colon with bleeding (562.12), diverticulitis of the colon with bleeding (562.13). Patients diagnosed with DD were characterized whether prescribed with imaging, such as colonoscopy, abdominal ultrasonography, abdominal CT; hospitalization and type of ward; and/or treatment with fibers, probiotics, rifaximin, mesalazine, antimicrobials, aspirin (ASA), non-steroidal anti-inflammatory drugs (NSAIDs), opioids, corticosteroids, calcium-channel blockers, statins, warfarin and new oral anticoagulants. The search was performed on the active population (alive and currently registered in HSD) by December 31, 2016.

### 2.3. Data analyses

Data is reported as descriptive statistics, in which proportions were calculated for categorical variables. The lifetime prevalence of DD was calculated by considering the number of patients diagnosed with DD (numerator) on the overall active population registered

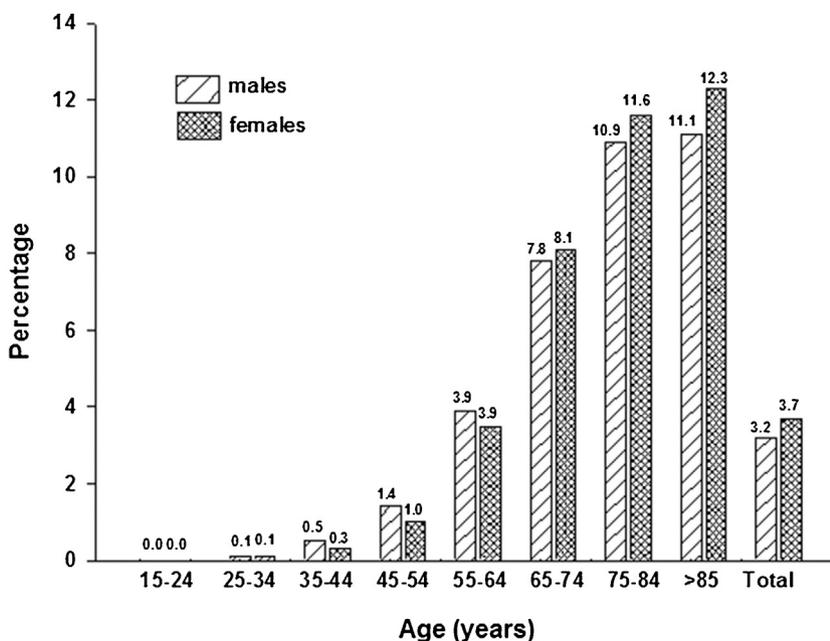


Fig. 1. "Lifetime" prevalence (%) of diverticular disease: analysis by gender and age.

**Table 1**

International code of disease (ICD-9) related to diverticular disease and distribution of patients by absolute number and by percentage of the total patients with diverticular disease.

	ICD-9	Number	%
Colon-sigma diverticulosis	562.1	23838	2.44
Diverticulosis of the colon, diverticulosis of the large intestine	562.10	7956	0.82
Diverticulosis of the colon, diverticulosis with diverticulitis	562.11	3216	0.23
Diverticulosis of the colon with bleeding	562.12	0	0
Diverticulitis of the colon with bleeding	562.13	23	0.002
Total		33597	3.44

**Table 2**

Incidence of diverticular disease as a registered problem in the whole population of Health Search Database, divided by gender and year of registration.

Year	Males		Females		Total	
	N	×1000	N	×1000	N	×1000
2006	1156	2,37	1481	2,69	2637	2,54
2007	1174	2,34	1473	2,61	2647	2,48
2008	1319	2,59	1634	2,85	2953	2,73
2009	1280	2,49	1655	2,87	2935	2,69
2010	1278	2,45	1594	2,74	2872	2,60
2011	1331	2,54	1627	2,78	2958	2,67
2012	1280	2,43	1677	2,86	2957	2,65
2013	1379	2,62	1560	2,68	2939	2,65
2014	1408	2,68	1530	2,65	2938	2,66
2015	1327	2,54	1399	2,46	2726	2,50
2016	1280	2,49	1451	2,62	2731	2,56

**Table 3**

Patients with diverticular disease in the whole population of Health Search Database distributed by gender and age at the time of first registration.

Age range	Males		Females		Total	
	N	%	N	%	N	%
≤50	2008	13,2	1397	7,6	3400	10,1
50–59	3312	21,8	3343	18,2	6652	19,8
60–69	5149	33,9	6085	33,1	11234	33,4
70–79	3690	24,3	5523	30,0	9218	27,4
≥80	1036	6,8	2053	11,2	3093	9,2
Total	15195	100,0	18402	100,0	33597	100,0

in HSD by December 31, 2016 (denominator). Each analysis was stratified by age and sex.

### 3. Results

From HSD, 33,597 patients with diagnosis of DD were identified showing a lifetime prevalence of 3.4% (3.2% in men, 3.7% in women) (Fig. 1, Table 1). The prevalence increased by age with a slightly higher level for females aged over-65 years. The incidence of DD as a registered problem in the whole population of HSD, divided according to sex and year of registration, is reported in Table 2. As shown, the incidence did not differ significantly by the year of registration. By contrast, patients with DD in the whole population of HSD distributed according to sex and age at the time of first registration, showed that people aged 60–80 years old represented the age range with a higher prevalence of diagnosis (Table 3).

In the whole population of DD patients, the prevalence of the main complications was 0.33% (diverticulitis) and 0.002% (bleeding). Among risk factors for the development of DD and its complications (Table 4), overweight (BMI 25–29 kg/m<sup>2</sup>) and obesity (BMI ≥ 30 kg/m<sup>2</sup>) were present in 19.4% and 13.6% of patients with DD, respectively, in which the weight parameter was registered (82%). Smoking habit had been recorded in 52.7% of DD

**Table 4**

Risk and protective factors in the development of diverticular disease and its complications [7,22,26] as indicated in Health Search Database.

	Prevalence in DD patients (%)
Risk factors	
Obesity (BMI > 30 kg/m <sup>2</sup> )	13.6
Overweight (BMI 25–29 kg/m <sup>2</sup> )	19.4
Smoking	17.2
Non-steroid anti-inflammatory drugs	14.8
Low dose aspirin	26.5
Opioids analgesic	7.5
Corticosteroids	5.2
Warfarin	7.6
Novel oral anticoagulants	2.5
Protective factors	
Physical activity:	
- Absent	48.0
- Mild-moderate	42.7
Statins	30.4
Calcium-antagonists	17.7

**Table 5**

Patients with at least one drug prescription related to diverticular disease.

Drug class	ATC	%
Anti-diarrhea; anti-inflammatory; antimicrobial	A07	65.4
Rifaximin	A07AA11	60.9
Mesalazine	A07EC02	14.7
Probiotics	A07-4AA2F	12.4
Ciprofloxacin	J01MA02	7.6
Metronidazole	P01AB01	2.7
Amoxicillin + clavulanate	J01CR02	1.8
Sulfametoxazole + trimetoprim	J01EE01	0.8
Fibers	A06AC	0.3

Results are expressed as percentage.

patients with 17.2% of them resulting smokers. Data on physical activity had been registered in 40.7% of DD patients, of them: 48% reported no activity, 42.7% declared mild activity. NSAIDs and ASA (>2 packs/year) were taken by 14.8% and 26.5% of patients respectively, with about 40% of patients over 75 years old taking ASA. Opioid analgesics and corticosteroids (>2 packs/year) were prescribed to 7.5% and to 5.2% of patients with DD, respectively. Finally, 7.6% of DD patients were under warfarin and 2.46% of them under new oral anticoagulants. Concerning protective factors, 30.4% of patients were under statins and 17.7% under calcium-channel blockers.

A total of 27% of patients with DD had experienced hospitalization after the diagnosis and, in particular, 62% of them refer to a surgical department, 28.6% to internal medicine, 5% to gastroenterology and 3.3% to a geriatric ward, but only 3.4% of patients with DD had hospitalization linked to this problem, mainly in surgical departments.

A high number of patients known to carry a DD underwent further investigations after the first diagnosis of DD. In particular, colonoscopy was prescribed to 48.5% of patients, abdominal ultrasonography was performed in less than 1% of them, while 13% of patients performed an abdominal CT in relation to DD.

The list of medications prescribed (at least one pack) in relation to DD is reported in Table 5. As indicated, antidiarrheal, anti-inflammatory and antimicrobial drug classes were prescribed in over 65% of DD patients and approximately 61% of them received rifaximin, 14.7% mesalazine, 12.4% probiotics, and only 0.28% pharmaceutical preparations containing fibers. About antibiotics, ciprofloxacin was prescribed in 7.6% of patients, metronidazole in 2.7%, amoxicillin/clavulanate in 1.8% and sulfametoxazole/thimetoprim in 0.8 of them.

Finally, 18% of patients registered with DD had no investigations and no treatment related to the DD problem.

#### 4. Discussion

DD is becoming a leading chronic condition in terms of costs and burden for the health service. The management of DD greatly rely on GPs who have to approach patients also in terms of diet, lifestyle and prevention of complications [15].

The prevalence of the DD detected in the HSD is 3.4% and expresses the proportion of patients for whom a diagnostic and/or therapeutic intervention related to the DD problem is carried out from the time they are taken in care by GPs. Our data is in line with the epidemiology of the disease in the general population confirming that it is a major prerogative of over-65 years old people [16]. However, although the prevalence of diverticulosis is extremely common in the general population, our data is in line with the literature suggesting that the incidence of diverticulitis is much less than previously believed, and occurrence does not necessarily increase with age. Moreover, data points to a higher prevalence of DD among females aged 65 or more compared to males, and the extension of endoscopic findings of diverticula to subjects younger than 40.

Although familial predisposition and genetic factors have been estimated to account for 50% susceptibility [17], it is important to consider both the risk and the protective factors for the development of the disease and its complications. In fact, the incidence of diverticulitis appears to be reduced by physical activity [18], while obesity seems to be associated with an increased risk of diverticulitis and bleeding [19]. Smoking may favor the onset of complications [20]. A BMI exceeding 25 was detected in about 1/3 of patients, smoking in 17% and physical activity was absent or mild in 91% of patients. GPs should be advised about the importance of these factors for both lifestyle indications to patients with DD and as management indicator to insert as a tool in electronic audit programs.

Among drugs, ASA and NSAIDs are known to potentially increase the risk of diverticulitis and bleeding [21], while corticosteroids and opioids increase the risk of perforation which is by contrast reduced by statins and calcium channel blockers [22]. Diverticular bleeding is the most common cause of low gastrointestinal hemorrhage with a high mortality rate in frail older people [23]. Beside ASA and NSAIDs, oral anticoagulants are also a major risk factor for diverticular bleeding at a comparable extent between Non-Vitamin K Antagonist Oral Anticoagulants (OACs) and conventional anticoagulation as reported in a systematic review and meta-analysis [24]. Our investigation provides evidence that ASA, NSAIDs and oral anticoagulants are largely prescribed in patients with DD. Since these medications could potentially favor bleeding and other complications, GPs should be advised of this risk, also by applying specific alerts on the medical records, as it is currently recommended in patients with peptic disease.

According to a statement from the Italian consensus, “endoscopic follow-up should be reserved only to those patients with persistent alarm symptoms in order to exclude both cancer and inflammatory bowel disease” [1]. We found a high rate of patients who performed colonoscopy (48.5%) and abdominal CT (13%) after the diagnosis of DD; this could be explained by the appearance of symptomatic manifestations of the disease or even complications.

During the last 2 decades there has been an increased rate of hospital admission for diverticulitis [25,26] likely due to the increased age of patients with a poorer prognosis especially in those with comorbidities [27]. In our survey, 27% of patients were hospitalized after the DD diagnosis, mainly in surgical (approximately 2/3) and internal medicine (approximately 1/3) departments, while a small number was admitted to gastroenterology and geriatric wards. This distribution is in line with the data found in an investigation carried out in an Italian hospital [28].

Other interesting aspects concern the treatment choices, the main purposes of which are the reduction of symptoms and the

prevention of diverticulitis. Scientific societies of different countries have proposed standard approaches for the treatment of DD; however, recommendations are not homogeneous. Besides medical therapy, general mainstreams regard both diets and changes in lifestyle. In fact, the use of a vegetarian diet and/or a fiber rich diet has been associated not only to a lower risk of disease development but also with a reduced risk of hospitalization or death by DD [29]. The use of probiotics in DD is justified by the potential existence of a small intestinal bacterial overgrowth with changes in quality and biodiversity of microbiota. These changes may be responsible for mucosal barrier alteration with activation of a low grade inflammatory response and generation of symptoms and complications. On the basis of this hypothesis, probiotics may restore intestinal microbiota and change the course of the disease [30]. However, the best results on reducing the symptoms of DD occurred when probiotics were used together with anti-inflammatory drugs (mesalazine, balsalazide) [31]. In our survey the prescription of fibers is very low while probiotics were prescribed to 12.4% of patients with DD. By comparing HSD data, which reflects the current activity of 800 GPs uniformly distributed throughout the Italian regions, with those resulting from a survey carried out through an online interview to 245 Italian GPs in relation to the use of drugs in DD patients [32], significant differences emerge in particular in the prescription of probiotics. On the online survey, 59.5% of GPs indicated the use of probiotics in symptomatic patients, while 44% of them to prevent recurrence.

From our data it emerges that rifaximin is the most widely used medication in DD patients with at least one prescription in 60.9% of them. Rifaximin is a poorly absorbed oral given antibiotic, commercialized for the treatment of intestinal bacterial infections. Recent preclinical and clinical data suggest that rifaximin acts not only as a direct antibacterial in the intestinal region, but also as a modulator of the intestinal microenvironment with eubiotic and cytoprotective properties, thus promoting resistance to bacterial colonization. For all these properties it has been suggested in the treatment of DD [31]. According to the Italian consensus on DD, it appears that rifaximin, together with fibers, is effective in treating the symptoms of DD, and also shows a potential efficacy in the prevention of diverticulitis, even if at a lower rate [1]. Indeed, rifaximin is effective in treating SUDD, with NNT=3 [33], as also confirmed by statement 3.6 of the Rome Consensus [34].

There is evidence that the anti-inflammatory drug mesalazine is effective in reducing the symptoms of DD but not in preventing complications [35–37]. From our data extraction, mesalazine was prescribed to about 15% of patients with DD, although its use in this condition should remain off-label. From recent evidence, mesalazine appears to be effective in treating SUDD with NNT=3 [38], as also confirmed by statement 3.8 of the Rome Consensus Conference [34]. Even rifaximin could be effective in preventing complication of SUDD, but with NNT=57 [33], as reported in the statement 3.7 of the Rome Consensus Conference [34]. On the other hand, mesalazine could be effective in the prevention of the first episode of acute diverticulitis in patients with SUDD, with NNT=8 [38], as indicated by statements 3.9 and 3.11 of the Rome Consensus Conference [34].

Pharmacological approach to treat acute diverticulitis depends on the severity of the episode. There are no specific randomized trials suggesting the best rule to follow. However, since anaerobic bacteria are predominant in the colon and are considered the potential responsible for diverticulitis especially as a polymicrobial infection, a combination regimen of antibiotics is usually recommended in this condition. From our study, it emerges that ciprofloxacin is the most widely used antibiotic, followed by metronidazole and amoxicillin/clavulanate. Finally, neither rifaximin nor mesalazine appear to be effective in preventing recurrences of acute diverticulitis as reported by statement 3.7,

3.10 and 3.12 of the Rome Consensus Conference [34], and by both the German and American guidelines [39,40].

By providing information on a large population of individuals and although showing some limitations (exclusion of pediatric population; data mostly registered at the time of the visit, although GPs represent the crucial point for health care delivery; accuracy of registration anyway guaranteed by a constant monitoring of quality indicators; lack of diet recording, supplements and drugs not needing prescription), HSD has shown to be a useful tool for research activity in general practice.

In conclusion, DD is a chronic condition at risk of exacerbations and complications and, for this reason, GPs are directly involved in its management and in particular they should pay attention to both protective and risk factors. In addition to continuing education, an aid for the clinical practice may be given by introducing specific alerts and performance indicators in computerized medical records. DD is more prevalent in the elderly; therefore, an appropriate management of these patients is important to reduce excessive and not useful investigations, hospitalizations and costs.

#### Conflict of interest

None declared.

#### References

- Cuomo R, Barbara G, Pace F, Annese V, Bassotti G, Binda GA, et al. Italian consensus conference for colonic diverticulosis and diverticular disease. *United European Gastroenterol J* 2014;2:413–42.
- Commane DM, Arasaradnam RP, Mills S, Mathers JC, Bradburn M. Diet, ageing and genetic factors in the pathogenesis of diverticular disease. *World J Gastroenterol* 2009;15:2479–88.
- Tursi A. Diverticulosis today: unfashionable and still underresearched. *Therap Adv Gastroenterol* 2016;9:213–28.
- Stollman NH, Raskin JB. Diverticular disease of the colon. *J Clin Gastroenterol* 1999;29:241–52.
- Chia JG, Wilde CC, Ngoi SS, Goh PM, Ong CL. Trends of diverticular disease of the large bowel in a newly developed country. *Dis Colon Rectum* 1991;34:498–501.
- Shahedi K, Fuller G, Bolus R, Cohen E, Vu M, Shah R, et al. Long-term risk of acute diverticulitis among patients with incidental diverticulosis found during colonoscopy. *Clin Gastroenterol Hepatol* 2013;11:1609–13.
- Peery AF. Recent advances in diverticular disease. *Curr Gastroenterol Rep* 2016;18:37.
- Bharucha AE, Parthasarathy G, Ditah I, Fletcher JG, Ewelukwa O, Pendlimari R, et al. Temporal trends in the incidence and natural history of diverticulitis: a population-based study. *Am J Gastroenterol* 2015;110:1589–96.
- Peery AF, Dellon ES, Lund J, Crockett SD, McGowan CE, Bulsiewicz WJ, et al. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology* 2012;143:1179–87.
- Filippi A, Vanuzzo D, Bignamini AA, Mazzaglia G, Cricelli C, Catapano AL, et al. The database of Italian general practitioners allows a reliable determination of the prevalence of myocardial infarction. *Ital Heart J* 2005;6:311–4.
- Cricelli C, Mazzaglia G, Samani F, Marchi M, Sabatini A, Nardi R, et al. Prevalence estimates for chronic diseases in Italy: exploring the differences between self-report and primary care databases. *J Public Health Med* 2003;25:254–7.
- Guglielmi V, Bellia A, Bianchini E, Medea G, Cricelli I, Sbraccia P, et al. Drug interactions in users of tablet vs. oral liquid levothyroxine formulations: a real-world evidence study in primary care. *Endocrine* 2018;59:585–92.
- Tocci G, Nati G, Cricelli C, Parretti D, Lapi F, Ferrucci A, et al. Prevalence and control of hypertension in the general practice in Italy: updated analysis of a large database. *J Hum Hypertens* 2017;31:258–62.
- Database Health Search/LPD. [www.healthsearch.it](http://www.healthsearch.it).
- Campanini A, De Conto U, Cavasin F, Bastiani F, Camarotto A, Gardini L, et al. A primary-care interventional model on the diverticular disease: searching for the optimal therapeutic schedule. *J Clin Gastroenterol* 2016;50(Suppl 1):S93–6.
- Tănase I, Păun S, Stoica B, Negoi I, Gaspar B, Beuran M. Epidemiology of the diverticular disease – a systematic review of the literature. *Chirurgia (Bucur)* 2015;110:9–14.
- Strate LL, Erichsen R, Baron JA, Mortensen J, Pedersen JK, Riis AH, et al. Heritability and familial aggregation of diverticular disease: a population-based study of twins and siblings. *Gastroenterology* 2013;144:736–42.
- Strate LL, Liu YL, Aldoori WH, Giovannucci EL. Physical activity decreases diverticular complications. *Am J Gastroenterol* 2009;104:1221–30.
- Strate LL, Linu YL, Aldoori WH, Syngal S, Giovannucci EL. Obesity increases the risks of diverticulitis and diverticular bleeding. *Gastroenterology* 2009;136:115–22.
- Humes DJ, Ludvigsson JF, Jarvholm B. Smoking and the risk of hospitalization for symptomatic diverticular disease: a population based cohort study from Sweden. *Dis Colon Rectum* 2016;59:110–4.
- Strate LL, Liu YL, Huang ES, Giovannucci EL, Chan AT. Use of aspirin or nonsteroidal anti-inflammatory drugs increases risk for diverticulitis and diverticular bleeding. *Gastroenterology* 2011;140:1427–33.
- Humes DJ, Fleming KM, Spiller RC, West J. Concurrent drug use and the risk of perforated colonic diverticular disease: a population based case-control study. *Gut* 2011;60:219–24.
- Oakland K, Guy R, Uberoi R, Hogg R, Mortensen N, Murphy MF, et al. Acute lower GI bleeding in the UK: patient characteristics, interventions and outcomes in the first nationwide audit. *Gut* 2018;67:654–62.
- Miller CS, Dorreen A, Martel M, Huynh T, Barkun AN. Risk of gastrointestinal bleeding in patients taking non-vitamin K antagonist oral anticoagulants: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2017;15:1674–83.
- Etzioni DA, Chiu VY, Cannom RR, Burchette RJ, Haigh PI, Abbas MA. Outpatient treatment of acute diverticulitis: rates and predictors of failure. *Dis Colon Rectum* 2010;53:861–5.
- Masoomi H, Buchberg BS, Magno C, Mills SD, Stamos MJ. Trends in diverticulitis management in the United States from 2002 to 2007. *Arch Surg* 2011;146:400–6.
- Jeyarajah S, Faiz O, Bottle A, Aylin P, Bjarnason I, Tekkis PP, et al. Diverticular disease hospital admissions are increasing, with poor outcomes in the elderly and emergency admissions. *Aliment Pharmacol Ther* 2009;30:1171–82.
- Aprea G, Giugliano A, Canfora A, Cardin F, Ferronetti A, Guida F, et al. Diverticular disease hospital cost impact analysis: evaluation of testings and surgical procedures in inpatient and outpatient admissions. *BMC Surg* 2012;12(Suppl. 1):S1–3.
- Crowe FL, Appleby PN, Allen NE, Key TJ. Diet and risk of diverticular disease in Oxford cohort of European Prospective Investigation into Cancer and Nutrition (EPIC): prospective study of British vegetarians and non-vegetarians. *BMJ* 2011;343:d4131.
- Narula N, Marshall JK. Role of probiotics in management of diverticular disease. *J Gastroenterol Hepatol* 2010;25:1827–30.
- Cuomo R, Barbara G, Annibale B. Rifaximin and diverticular disease: position paper of the Italian Society of Gastroenterology (SIGE). *Dig Liver Dis* 2017;49:595–603.
- De Bastiani R, Sanna G, Fracasso P, D'Urso M, Benedetto E, Tursi A. The management of patients with diverticulosis and diverticular disease in primary care: an online survey among Italian general practitioners. *J Clin Gastroenterol* 2016;50:S89–92.
- Bianchi M, Festa V, Moretti A, Ciaco A, Mangone M, Tornatore V, et al. Meta-analysis: long-term therapy with rifaximin in the management of uncomplicated diverticular disease. *Aliment Pharmacol Ther* 2011;33:902–10.
- Tursi A, Picchio M, Elisei W, Di Mario F, Scarpignato C, Brandimarte G. Management of patients with diverticulosis and diverticular disease: consensus statements from the 2nd international symposium on diverticular disease. *J Clin Gastroenterol* 2016;50(Suppl. 1):S101–7.
- Tursi A, Brandimarte G, Elisei W, Picchio M, Forti G, Pianese G, et al. Randomized clinical trial: mesalazine and/or probiotics in maintaining remission of symptomatic uncomplicated diverticular disease – a double-blind, randomized, placebo-controlled study. *Aliment Pharmacol Ther* 2013;38:741–51.
- Stollman N, Magowan S, Shanahan F, Quigley EM, DIVA Investigator Group. A randomized controlled study of mesalazine after acute diverticulitis: results of the DIVA trial. *J Clin Gastroenterol* 2013;47:621–9.
- Raskin JB, Ramm MA, Jamal MM, Márquez J, Melzer E, Schoen RE, et al. Mesalazine did not prevent recurrent diverticulitis in phase 3 controlled trials. *Gastroenterology* 2014;147:793–802.
- Picchio M, Elisei W, Brandimarte G, Di Mario F, Malfertheiner P, Scarpignato C, et al. Mesalazine for the treatment of symptomatic uncomplicated diverticular disease of the colon and for primary prevention of diverticulitis: a systematic review of randomized clinical trials. *J Clin Gastroenterol* 2016;50(Suppl. 1):S64–9.
- Kruis W, Germer CT, Leifeld L, German Society for Gastroenterology, Digestive and Metabolic Diseases, The German Society for General and Visceral Surgery. Diverticular disease: guidelines of the German society for gastroenterology, digestive and metabolic diseases and the German society for general and visceral surgery. *Digestion* 2014;90:190–207.
- Stollman N, Smalley W, Hirano I, AGA Institute Clinical Guidelines Committee. American Gastroenterological Association Institute guideline on the management of acute diverticulitis. *Gastroenterology* 2015;149:1944–9.