Chapter 3

Inflammation as a Potential Therapeutic Target in IBS

Alexandra Chira, Romeo Ioan Chira and
Dan Lucian Dumitrascu

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/66193

Abstract

The pathogenesis of irritable bowel syndrome (IBS) has been intensively researched, and despite a long journey for unraveling all the structures and the pathways involved, it still remains partially obscure. Inflammation was the first to be hypothesized as a potential pathway for the pathogenesis of IBS. It remains a keystone in the complex machinery of the pathogenesis that is currently considered multifactorial. Elucidating the pathogenesis of IBS is crucial for a targeted therapy of the disease. In this chapter, we review information regarding gut inflammation in IBS, underlining some of the newest data or the cornerstones. Additionally, our aim was also to review treatment currently available and future perspectives regarding anti-inflammatory treatments for IBS. Newer techniques allow detection and research of mediators involved in inflammation, as well as their potential role to be targeted by pharmacological agents. Recent data supports not only further research of the newer agents that are currently being developed but also some of the available ones that do not have sufficient evidence. Emerging therapies that target inflammation are under evaluation, in trials. A multidrug or a multidisciplinary approach needs to be considered in some cases that fail to respond to current treatment.

Keywords: anti-inflammatory, inflammation, irritable bowel syndrome, IBS treatment, postinfectious

1. Introduction

Despite the intensive research on irritable bowel syndrome (IBS) is being conducted, the pathogenesis still remains partially obscure. Since the description of this syndrome, many researchers have questioned the cause of IBS, which is currently being considered as

multifactorial [1–3] with increasing evidence that support the concept [4, 5], since there are multiple mechanisms that could trigger the clinical complaints.

Not just one structure or system is involved in the occurrence of IBS, and there is a complex network already described and currently referred to as brain-gut axis [6–9] with multiple directions and ways to communicate or interrelate between these structures and paths [10] that are reflected also in the heterogeneity of the subtypes of IBS.

Although IBS is a functional gastrointestinal disorder [11] with no structural or biochemical abnormalities, there is some evidence suggesting that in some subtypes of IBS, inflammation might play a key role in generating a low-grade inflammatory response and a spectrum of symptoms that sometimes overlap with those of inflammatory bowel diseases in remission [12, 13], leading to difficulties in establishing the diagnosis in clinical practice.

In this chapter, we will review literature data concerning inflammation and its relation to IBS underlining some of the newest data or the key ones. Our aim was also to review treatment currently available and future perspectives regarding anti-inflammatory treatments for IBS.

2. Inflammation in IBS

Inflammation, defined as the answer of the immune system to various triggers, was first described by Celsus [14], who has assigned to it the four signs: *dolor* (pain), *rubor* (redness), *tumor* (swelling), *calor* (heat), and to which Rudolf Virchow [15] added *functio laesa* (functional impairment). All the characteristics that define inflammation are induced by a complex set of mediators [16]. In addition, the triggers that could initiate inflammatory responses are numerous and diverse [17]. The inflammatory responses may be acute or chronic [16, 17].

Inflammation was one of the first hypothesised causes of IBS [18]. Intestinal inflammation was proposed as a potential mechanism involved in the pathogenesis of IBS since 1960s, when Hiatt et al. [18] described mast cells in the muscularis externa of the terminal colon and cecum. Discovered by Paul Ehrlich, mast cells are the precursors of CD34+ hematopoietic stem cells [19]. Due to the diversity of functions of mast cells, they have been a cornerstone in the study of multiple conditions, being intensively researched in the last decades. Mast cells have multiple functions [20], some of them involving the gut: neuroimmune interactions, epithelial secretion and permeability, and visceral sensation [20, 21]. In addition, it can express receptors for several cytokines that are involved in immunity [19] or release key mediators [22]. Numerous studies assessed the presence and/or the role of mast cells in IBS [23–25]. There are also rigorous papers that reviewed studies investigating mast cells and/or the mast cell mediators in IBS [26].

Other types of mediators, such as immunoglobulin (Ig) E and atopia, have been investigated in IBS and linked to mast cells [27, 28]. Degranulation of mast cells and, subsequently, the release of mast cell mediators can also be induced by IgE [28]. There are few data regarding IgE levels in IBS. Vara et al. [29] showed higher levels of IgE in IBS compared with healthy controls.

Besides mast cells, there are data indicating that inflammatory cells are present in colonic mucosa in IBS patients [23]. They showed on colonic biopsies multiple types of cells such as neutrophils and T lymphocytes besides mast cells, all of which may support the role of the immune system in the ethiopathogenesis of IBS [23, 30]. If most of the studies examined mucosa of the rectum [31, 32], there are few studies that assessed also the deeper layers of the enteral wall [33]. There is a complex local response when triggers are detected [16, 34].

The balance of pro-inflammatory and anti-inflammatory responses and the mediators that are involved in the complex interactions have also been the subject of many studies. There is evidence of sustained inflammation in IBS supported by numerous studies that have detected low anti-inflammatory cytokines in IBS patients [35] or others that found high levels of those pro-inflammatory ones or a misbalance of the pro- and anti-inflammatory cytokine proportion [36, 37]. The complex dialogue between the structures involved in maintaining the homeostasis includes interrelation of nervous, immune, and endocrine systems [30, 34], where a pivotal piece is the brain that governs the humoral and neurological systems [34, 38, 39], in a complex network with multidirectional communicating systems [10]. Not only the anatomical integrity but also the functional status of all the systems is of major importance [40].

Psychological factors can participate in this mechanism, maintaining a state of low inflammation [41]. Inflammation in the gut might be responsible also for hyperalgesia [42] present in some patients with IBS contributing to the maintenance of the complaints.

2.1. Postinfectious IBS

Postinfectious IBS (PI-IBS) is a more recently coined type of IBS, initially identified as post-dysenteric IBS (PD-IBS) [43]. PI-IBS is defined as a subset of IBS in which the onset of IBS symptoms develops after an infectious episode and was first described by Chaudhary and Truelove [43]. This entity was confirmed by other studies [44]. The incidence of PI-IBS varies between 4 and 32% [45–47]. More frequently, PI-IBS was described and studied after an enteral infection [44, 48]. Pathogens already recognized to be involved in enteral infections are the following:

- bacteria: *Campylobacter jejuni* [31], *Salmonella enterica* [45], *Shigella* [49], *Escherichia coli* [50–52], *Clostridium difficile* [53]
- viruses: *Norovirus* [50, 54]
- parasites: *Giardia lamblia* [50, 55], *Blastocystis* spp. [56], *Dientamoeba fragilis* [57]

This subset of IBS patients offers a strong support emphasizing the importance of inflammation as one of the main paths to IBS. Enteral pathogens may induce pathological changes [31]. Spiller et al. [31] reported an imbalance of the enteroendocrine cells and of T lymphocytes, these two being assessed by histopathological examination of the rectal biopsies of the PI-IBS when compared with controls. There can be at least three scenarios: a prolonged normal inflammatory response, an augmented pathological inflammatory response in these patients, or there is a certain group of patients with particular characteristics that have a higher susceptibility [44, 58–60]. Anyway, there is not yet a firm conclusion.

2.2. Barrier function

The gut barrier function is important in modulating the gut inflammation [26, 61]. The barrier has multiple roles and its integrity is essential for a normal functionality of the digestive system [61]. An impaired barrier could facilitate the passage of inflammatory triggers that might induce changes in the gut. An increased permeability of the barrier might expose various structures to antigen contact [31].

2.3. Cholinergic system

There is another important piece in the complex domino of Inflammation – the so-called "cholinergic anti-inflammatory pathway" [34, 62, 63]. We did not intend to review the data regarding this system as there are multiple reviews [34] that have already analyzed the evidence, but to find the studies that support the interrelation with inflammation in IBS. Dinan et al. [64] investigated several cytokines, such as interleukin (IL): IL-6, IL-8, IL-10, and the growth hormone in the two arms of the study. They found that only IL-6 and the growth hormone in the group of IBS patients were overproduced when compared with controls after the administration of pyridostigmine that might suggest the implication of the cholinergic system [64].

2.4. Low-grade inflammation

More and more data sustain the hypotheses of a low-grade inflammation in IBS [65–67]. The fine line between normal to a pathological inflammatory response is still difficult to set. There is a low-grade inflammation of the gut that has been already acknowledged and literature data supports the putative role of the low-grade inflammation in IBS [65–68]. Several articles addressed this issue, some authors investigated tissue samples [23], while others assessed blood or stool samples [69–72] in order to detect and determine the inflammation status in IBS patients.

There are already numerous studies that assessed erythrocyte sedimentation rate, C-reactive protein (CRP) from blood sample, fecal calprotectin, and/or lactoferin in order to detect their presence in IBS and/or to calculate their predictive values [71–73]. Valuable information was provided by a meta-analysis, although that assessed their cut-off values in order to exclude inflammatory bowel diseases [74].

There are limited data regarding the presence of high-sensibility CRP [69] in IBS, but results indicate that when compared with healthy subjects, levels of high sensibility CRP are statistically significantly higher in IBS patients ($P < 0.001$) [69]. So literature data supports the presence of low-grade inflammation in IBS since the levels of high-sensibility CRP, though were still within the normal range, were higher in IBS than in controls [69].

A similar situation is for calprotectin, which is used mainly for differential diagnosis of inflammatory bowel diseases [73], but there are also studies that showed increased levels of calprotectin in IBS patients when comparing the values of those of healthy controls [72].

In the search to quantify the levels of inflammation, many authors proposed various biomarkers, and others proposed multiple biomarkers such as a panel or a set of markers [75, 76].

2.5. Genes and inflammation in IBS

Genetic factors have also been suspected as being involved in the inflammation in IBS.

Regarding genes and polymorphism, there are several studies that have assessed gene polymorphism, of which IL-10 and α tumor necrosis factor are some of the ones that are being intensively investigated [77–79].

As for the other studies that addressed IBS, their findings are inconsistent since some of the studies that assessed IL-10 genotypes in IBS patients versus controls showed high-producer genotype for IL-10 had a lower frequency statistically significant in IBS than in controls (P = 0.003) [79], and other studies did not find statistically significant difference of IL-10 polymorphism in IBS patients [78]. Schmulson et al. [78] assessed two polymorphisms: IL-10 (-1082G/A) and α tumor necrosis factor (-308G/A) in IBS patients and compared them with controls. There were no statistically significant differences between IBS and controls regarding either of the two polymorphisms.

There are also other studies besides these that assessed single nucleotide polymorphisms and more complex studies such as genome-wide association studies [80].

2.6. New hypotheses

There is a growing interest in applying the latest techniques used in molecular biology also for the study of IBS, such as the study of microRNA—miRNAs [81], small interfering RNA—siRNAs [82] or new approaches such as meta-omics [83].

Recently, new directions have been proposed in the study of the etiopathogenesis of IBS [81, 84]. The role of stem cells has been already intensively researched [85, 86], even in inflammatory bowel diseases [87], but these potent cells have raised interest about their role or potential use in IBS.

Very recent data advances the hypotheses that intestinal stem cells might be involved in the inflammatory paths discussed in IBS [84, 88]. Due to their properties, stem cells not only are able to respond to pathogens but also may modulate the spectrum of answers by their secretory functions [84, 89]. These stem cells might also represent therapeutic targets [84], but future studies to identify a specific target, either structural or functional, of the stem cells are mandatory.

The scientific community is eager to develop and improve current technologies, both for identifying new therapeutic targets and also for new treatment.

3. Anti-inflammatory treatment

Treatment of IBS still represents a challenge for clinicians. Due to the marked heterogeneity of the IBS subtypes, we will address anti-inflammatory agents used or those with potential use in IBS. Considering the multifactorial etiology, there are authors who propose a treatment determined by the main pathological path that led to IBS [4]. Literature data are limited concerning pharmacological anti-inflammatory classes studied in IBS as well as for the number of the members of these pharmacological classes that were investigated. Since we cannot still establish the main cause that led to IBS, an etiopathogenetic treatment is not possible, and some are currently being developed; a main aim in the treatment of IBS still is to alleviate the symptoms [1]. Though there are few studies that assessed anti-inflammatory classes or members of these classes in IBS, there is an intensive research activity into unraveling new targets and new treatments [90]. There are ongoing trials [91] and research programs and networks [92] that bring valuable information for a deeper understanding of IBS.

4. Aminosalicylic acid agents

Since the discovery of 5-aminosalicylic acid agents (5-ASA) by Svartz [93] and afterward with their active properties being described by Azad et al. [94], these agents were intensively researched as well as used in clinical practice [95]. The 5-ASA derivates have been used in several inflammatory conditions such as the inflammatory bowel disorders [95]. There are already consistent data regarding the efficacy of 5-ASA in ulcerative colitis [95] as well as regarding their safety. The rationale for prescribing 5-ASA agents in IBS is represented by their anti-inflammatory properties and is the result of several mechanisms [96].

Article	Type of article	Conclusions
Min et al. [97]	Letter	In selected subgroups of IBS might be efficient
Törnblom et al. [98]	Commentaries	In selected subgroups of IBS might be efficient
Lazaraki et al. [99]	Review	Inconclusive regarding the use of mesalasine in IBS
Camilleri et al. [100]	Review	Inconclusive, though some studies show a positive effect on pain, results were not replicated by others
Xue et al. [101]	Letter	Inconclusive—analyzed impact of mesalazine on gut microbiota
Hanevik et al. [102]	Letter + pilot CT	Inefficient
Farup et al. [103]	Letter	Inconclusive – authors underline that Andrews et al. [108] did not analyze drop out patients in their study

Table 1. Articles reviewing the use of 5-ASA in IBS.

Though there are few original studies, there are also reviews that analyze the use of 5-ASA in IBS (**Table 1**). Literature data indicate that in certain group of patients such as those with

http://dx.doi.org/10.5772/66193

PI-IBS, especially the IBS with diarrhoea (IBS-D) subtype could benefit, at least for a certain period of the anti-inflammatory effects of this class (see **Tables 1** and **2**). Regarding the length of treatment, dosing, and schemes of treatment, there are few data in the literature, and there is no study to assess all of this. Future studies are required in order to configure an a priori set of features regarding what type of IBS patient is likely to respond to 5-ASA treatment, as well as the regimen and dosing.

Article	**Type of article, type of IBS**	**Dose and time of treatment**	**Conclusions**
Barbara et al. [104]	Placebo-controlled trial (CT), multicentre IBS	800 mg tid, 12 weeks	Mesalazine treatment was not statistically significant or more efficient than placebo (P = 0.870). In certain groups of patients, it might be useful.
Lam et al. [105]	CT, IBS-D	2 g/day—2 weeks, if tolerated 2 g bid—11 weeks	In certain groups of selected IBS-D patients, it might be efficient, although there is no clear evidence of it being useful.
Bafutto et al. [106]	Pilot study, IBS-D	Various dosing—in the fourth groups	May be useful in certain groups of patients.
Tuteja et al. [107]	CT, PI-IBS	1.6 g bid, 12 weeks	No statistically significant improvement of symptoms ($P \geq 0.11$) nor QOL ($P \geq 0.16$).
Andrews et al. [108]	Pilot study, IBS-D	1.5 g bid, 4 weeks	Significant improvement of pain.
Bafutto et al. [109]	CT, IBS-D	800 mg tid, 30 days	Significant improvement of total symptom score, inclusive of pain. ($P < 0.0001$)
Dorofeyev et al. [110]	CT, IBS, all subtypes	500 mg qid, 28 days	Statistical improvement of abdominal pain ($P < 0.01$) as well as some histopathological aspects.
Hanevik et al. [102]	Letter + pilot CT	800 mg bid, 6 weeks	Inefficient.
Corinaldesi et al. [111]	CT, IBS	800 mg tid, 8 weeks	Mesalazine significantly improved only general well-being ($P = 0.038$), having no significant statistic effect regarding bloating ($P = 0.177$), abdominal pain ($P = 0.084$), or bowel habits.
Preobrazhenskii [112]*	Study	4–6 g daily, not shown	Efficient.

*Articles in other languages (Russian) or full text could not be retrieved.

Table 2. Studies assessing 5-ASA agents in IBS.

4.1. Acetylsalicylic acid

Regarding the use of acetylsalicylic acid, we have identified just one study that assessed it in relation to IBS, but the purpose of the study was to determine if certain anti-inflammatory drugs could induce constipation [113]. In fact, the study assessed that the use of some anti-inflammatory drugs among acetylsalicylic acid was related to constipation. [113].

4.2. Mast cell stabilizers

Mast cell stabilizers (cromoglycate and ketotifen) have been tested in IBS, but there are very few literature data concerning this class of drugs. Also, the criteria used for diagnosing IBS were different; therefore, there is no uniformity when comparing these studies. Subsequent studies are mandatory in order to have the answer: which IBS patients are suited to a mast cell stabilizer treatment and what is the dosing, or what is a suitable regimen.

4.3. Ketotifen

Klooker et al. [114] investigated ketotifen, suggesting that it can reduce visceral hypersensitivity and improve the quality of life. Though there is just one study to investigate ketotifen in IBS patients, there has already been questions about its safety [115]. For certain other studies, to assess this class for IBS treatment is mandatory in order to grade the levels of evidence. Although there is just one study with positive results, we also consider encouraging these results [33], and we strongly feel that there are more therapeutic options that have not yet been explored.

4.4. Cromoglycate

Regarding cromoglycate, there are several studies that assessed it in IBS patients. Literature data suggest that they could have a beneficial role in certain groups of patients, especially in those who have also food allergies or intolerances (see **Table 3**). There are methodological issues concerning these studies; so in order to reduce some of the biases, rigorous parallel studies are needed.

Article	Conclusion
Leri et al. [116]	Efficient (in conjunction with dietary exclusions in IBS patients with food intolerance)
Stefanini et al. [117]	Efficient (in IBS patients with food intolerance)
Grazioli et al. [118]	Efficient (in pediatric IBS patients with food intolerance)
Stefanini et al. [119]	Efficient (in IBS patients with food intolerance)
Lunardi et al. [120]	Efficient (in IBS patients with food intolerance)
Paganelli et al. [121]	Inconclusive
Antico et al. [122]*	—
Stefanini et al. [123]	Efficient
Tomecki et al.* [124]	Inefficient

*Article in other languages than English (Polish, Italian) also could not be retrieved.

Table 3. Articles that assessed cromoglycate in IBS.

4.5. Montelukast

There is just one report of the use of montelukast in IBS stating a positive effect [125]. Considering the pathways that are involved in the pathogenesis of IBS, it seems reasonable that the authors proposed and used it. The wonder is that there are so few data regarding it, though there are data regarding IBS and allergies [29]. Montelukast might be an option for the patients who have IBS and allergic conditions, but there is a lack of studies to address this issue. Rigorous trials with such drugs are needed in order to conclude about their use in IBS.

4.6. Corticosteroids

Some authors even proposed corticosteroids as anti-inflammatory agents in IBS [126]. A short course-3 weeks, 30 mg prednisolone/day was administered to PI-IBS patients and compared with placebo. There was no statistically significant difference between the number of enterochromaffin cells between patients treated with prednisolone and those that received placebo ($P = 0.5$). Though for the reduction of the number of T lymphocytes in the lamina propria. Dunlop et al. [126] found a statistically significant difference that favors prednisolone, there was no improvement regarding several symptoms of IBS.

Due to their known side effects, one study investigated the impact of using oral steroids, showing that they do not have a higher risk for inducing IBS symptoms in adults under 40 years [127].

We conducted a search on PubMed search motor between 1–21st July 2016 using multiple strategies as seen in **Table 4**. There is just one study that assessed the corticoid therapy in IBS, though there are several authors who consider corticosteroids as a reasonable treatment option in certain subgroups of IBS patients (**Table 4**).

Strategy	Results	Appropriate	Inappropriate
"Corticosteroids, irritable bowel syndrome"	91	2 [127, 128]	89
"Corticosteroids, IBS"	64	1 [128]	63
"Prednisone, irritable bowel syndrome"	5	0	5
"Prednisolone, irritable bowel syndrome"	12	1 [126]	11
"Prednisolone, IBS"	5	1 [127]	4
"Budesonide, irritable bowel syndrome"	10	1 [128]	9

Table 4. Results retrieved by several search strategies on PubMed search motor.

4.7. Imunglobulin E antibody (Omalizumab)

There is just one study that addresses this issue [28], which presents a case of a patient that had concurrently IBS and asthma. The patient received an IgE antibody with a major improvement of IBS symptoms. These results suggest that in certain subgroups of patients with concurrent diseases as IBS and atopic status, or extra-intestinal symptoms, IgE antibodies might be useful.

5. Conclusions

Inflammation remains an important pathway involved in the pathogenesis of IBS. Despite the high interest in the field of functional gastrointestinal disorders, till now, researchers have not entirely discovered all the pieces of the complex puzzle that is the etiopathogenesis of IBS, or all of the components of the pathways that finally lead to IBS.

Newer techniques allow detection and promote research of mediators that are involved in inflammation, even in low amounts. Also, the new technologies are able to identify new structures, as well as their potential role to be targeted by pharmacotherapeutic agents.

Results suggest that there are potential pharmacological classes, alongside with potential therapeutic targets that deserve to be reassessed for IBS.

Recent data supports further research of the pathways and structures involved, as well as assessment of not only the newer agents that are currently being developed but also of some of the available ones that do not have sufficient evidence. Emerging therapies that target inflammation are under evaluation, in trials. A multidrug or a multidisciplinary approach needs to be considered in cases that fail to respond to current treatment or to a single therapy, heading toward the current trend, of a personalized medicine.

Abbreviations

5-Aminosalicylic acid agents: 5-ASA

Bis in die: bid

C reactive protein: CRP

Irritable bowel syndrome: IBS

IBS with diarrhoea: IBS-D

Immunoglobulin: Ig

Interleukin: IL

Quarter in die: qid

Quality of life: QOL

Placebo-controlled trial: CT

Postinfectious IBS: PI-IBS

Postdysenteric IBS: PD-IBS

Ter in die: tid

http://dx.doi.org/10.5772/66193

Author details

Alexandra Chira[1], Romeo Ioan Chira[2] and Dan Lucian Dumitrascu[1*]

*Address all correspondence to: ddumitrascu@umfcluj.ro

1 - 2nd Medical Clinic, Department of Internal Medicine, "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca, Romania

2 - 1st Medical Clinic, Department of Internal Medicine, Div. Gastroenterology, "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca, Romania

References

[1] Drossman DA, Camilleri M, Mayer EA, Whitehead WE. AGA technical review on irritable bowel syndrome. Gastroenterology. 2002;123(6):2108–31.

[2] Bellini M, Gambaccini D, Stasi C, Urbano MT, Marchi S, Usai-Satta P. Irritable bowel syndrome: a disease still searching for pathogenesis, diagnosis and therapy. World J Gastroenterol. 2014;20(27):8807–20.

[3] Barbara G, De Giorgio R, Stanghellini V, Cremon C, Corinaldesi R. A role for inflammation in irritable bowel syndrome? Gut. 2002;51 Suppl 1:i41–4.

[4] Malagelada JR, Malagelada C. Mechanism-oriented therapy of irritable bowel syndrome. Adv Ther. 2016;33(6):877–93.

[5] Chumpitazi BP, Shulman RJ. Underlying molecular and cellular mechanisms in childhood irritable bowel syndrome. Mol Cell Pediatr. 2016;3(1):11.

[6] Mayer EA. Gut feelings: the emerging biology of gut-brain communication. Nat Rev Neurosci. 2011;12(8):453–66.

[7] Jones MP, Dilley JB, Drossman D, Crowell MD. Brain-gut connections in functional GI disorders: anatomic and physiologic relationships. Neurogastroenterol Motil. 2006;18(2):91–103.

[8] James W. What is an emotion? Mind. 1884;9:188–205.

[9] Fichna J, Storr MA. Brain-gut interactions in IBS. Front Pharmacol. 2012;3:127.

[10] Koloski NA, Jones M, Talley NJ. Evidence that independent gut-to-brain and brain-to-gut pathways operate in the irritable bowel syndrome and functional dyspepsia: a 1-year population-based prospective study. Aliment Pharmacol Ther. 2016;44(6):592–600.

[11] Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology. 2006;130(5):1480–91.

[12] Grover M, Herfarth H, Drossman DA. The functional-organic dichotomy: postinfectious irritable bowel syndrome and inflammatory bowel disease-irritable bowel syndrome. Clin Gastroenterol Hepatol. 2009;7(1):48–53.

[13] Berrill JW, Green JT, Hood K, Campbell AK. Symptoms of irritable bowel syndrome in patients with inflammatory bowel disease: examining the role of sub-clinical inflammation and the impact on clinical assessment of disease activity. Aliment Pharmacol Ther. 2013;38(1):44–51.

[14] Celsus AC. De Medicina, praef. iii. 4.

[15] Rather LJ. Disturbance of function (functio laesa): the legendary fifth cardinal sign of inflammation, added by Galen to the four cardinal signs of Celsus. Bull N Y Acad Med 1971;47:303–322.

[16] Baumann H, Gauldie J. The acute phase response. Immunol Today. 1994;15:74–80.

[17] Sell S, editor. Immunology, Immunopathology, and Immunity. 6th ed. Washington, DC: ASM Press; 2001.

[18] Hiatt RB, Katz L. Mast cells in inflammatory conditions of the gastrointestinal tract. Am J Gastroenterol. 1962;37:541–5.

[19] Shea-Donohue T, Stiltz J, Zhao A, Notari L. Mast cells. Curr Gastroenterol Rep. 2010;12(5):349–57.

[20] Zhang L, Song J, Hou X. Mast cells and irritable bowel syndrome: from the bench to the bedside. J Neurogastroenterol Motil. 2016; 22(2):181–92.

[21] Bischoff SC, Kramer S. Human mast cells, bacteria, and intestinal immunity. Immunol Rev. 2007; 217:329–37.

[22] Barbara G, Stanghellini V, De Giorgio R, Cremon C, Cottrell GS, Santini D, et al. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. Gastroenterology. 2004;126(3):693–702.

[23] Chadwick VS, Chen W, Shu D, Paulus B, Bethwaite P, Tie A, et al. Activation of the mucosal immune system in irritable bowel syndrome. Gastroenterology. 2002; 122(7): 1778–83.

[24] O'Sullivan M, Clayton N, Breslin NP, Harman I, Bountra C, McLaren A, et al. Increased mast cells in the irritable bowel syndrome. Neurogastroenterol Motil. 2000;12(5):449–57.

[25] Cremon C, Gargano L, Morselli-Labate AM, Santini D, Cogliandro RF, De Giorgio R, et al. Mucosal immune activation in irritable bowel syndrome: gender-dependence and association with digestive symptoms. Am J Gastroenterol. 2009; 104(2):392–400.

[26] Camilleri M, Lasch K, Zhou W. Irritable bowel syndrome: methods, mechanisms, and pathophysiology. The confluence of increased permeability, inflammation, and pain in

irritable bowel syndrome. Am J Physiol Gastrointest Liver Physiol. 2012; 303(7):G775–85.

[27] Coca A, Cooke R. On the classification of the phenomena of hypersensitiveness. J Immunol; 1923 8: 163–182.

[28] Pearson JS, Niven RM, Meng J, Atarodi S, Whorwell PJ. Immunoglobulin E in irritable bowel syndrome: another target for treatment? A case report and literature review. Therap Adv Gastroenterol. 2015;8(5):270–7.

[29] Vara EJ, Valeur J, Hausken T, Lied GA. Extra-intestinal symptoms in patients with irritable bowel syndrome: related to high total IgE levels and atopic sensitization? Scand J Gastroenterol. 2016;51(8):908–13.

[30] Ohman L, Simren M. Pathogenesis of IBS: role of inflammation, immunity and neuroimmune interactions. Nat Rev Gastroenterol Hepatol. 2010;7(3):163–73.

[31] Spiller RC, Jenkins D, Thornley JP, Hebden JM, Wright T, Skinner M, et al. Increased rectal mucosal enteroendocrine cells, T lymphocytes, and increased gut permeability following acute *Campylobacter enteritis* and in post-dysenteric irritable bowel syndrome. Gut. 2000;47(6):804–11.

[32] Goral V, Kucukoner M, Buyukbayram H. Mast cells count and serum cytokine levels in patients with irritable bowel syndrome. Hepatogastroenterology. 2010;57(101):751–4.

[33] O'Sullivan M. Therapeutic potential of ketotifen in irritable bowel syndrome (IBS) may involve changes in mast cells at sites beyond the rectum. Gut. 2011;60(3):423; author reply.

[34] Pavlov VA, Wang H, Czura CJ, Friedman SG, Tracey KJ. The cholinergic anti-inflammatory pathway: a missing link in neuroimmunomodulation. Mol Med. 2003;9(5-8): 125–34.

[35] Schmulson M, Pulido-London D, Rodriguez O, Morales-Rochlin N, Martinez-Garcia R, Gutierrez-Ruiz MC, et al. Lower serum IL-10 is an independent predictor of IBS among volunteers in Mexico. Am J Gastroenterol. 2012;107(5):747–53.

[36] Bashashati M, Rezaei N, Shafieyoun A, McKernan DP, Chang L, Ohman L, et al. Cytokine imbalance in irritable bowel syndrome: a systematic review and meta-analysis. Neurogastroenterol Motil. 2014;26(7):1036–48.

[37] Macsharry J, O'Mahony L, Fanning A, Bairead E, Sherlock G, Tiesman J, et al. Mucosal cytokine imbalance in irritable bowel syndrome. Scand J Gastroenterol. 2008;43(12): 1467–76.

[38] Watkins LR, Maier SF, Goehler LE. Cytokine-to-brain communication: a review and analysis of alternative mechanisms. Life Sci 57:1011–26. 1995.

[39] Elmquist JK, Scammell TE, Saper CB. Mechanisms of CNS response to systemic immune challenge: the febrile response. Trends Neurosci 20:565–9.

[40] Posserud I, Ersryd A, Simren M. Functional findings in irritable bowel syndrome. World J Gastroenterol. 2006;12(18):2830–8.

[41] Tanaka Y, Kanazawa M, Fukudo S, Drossman DA. Biopsychosocial model of irritable bowel syndrome. J Neurogastroenterol Motil. 2011;17(2):131–9.

[42] Farzaei MH, Bahramsoltani R, Abdollahi M, Rahimi R. The role of visceral hypersensitivity in irritable bowel syndrome: pharmacological targets and novel treatments. J Neurogastroenterol Motil. 2016;22(4):558–574.

[43] Chaudhary NA, Truelove SC. The irritable colon syndrome. A study of the clinical features, predisposing causes, and prognosis in 130 cases. Q J Med. 1962;31:307–22.

[44] Gwee KA, Collins SM, Read NW, Rajnakova A, Deng Y, Graham JC, et al. Increased rectal mucosal expression of interleukin 1beta in recently acquired post-infectious irritable bowel syndrome. Gut. 2003;52(4):523–6.

[45] Rodriguez LA, Ruigomez A. Increased risk of irritable bowel syndrome after bacterial gastroenteritis: cohort study. BMJ. 1999;318(7183):565–6.

[46] Thabane M, Kottachchi DT, Marshall JK. Systematic review and meta-analysis: The incidence and prognosis of post-infectious irritable bowel syndrome. Aliment Pharmacol Ther. 2007;26(4):535–44.

[47] McKendrick MW, Read NW. Irritable bowel syndrome—post salmonella infection. J Infect. 1994;29(1):1–3.

[48] Spiller R, Garsed K. Postinfectious irritable bowel syndrome. Gastroenterology. 2009;136(6):1979–88.

[49] Kim HS, Lim JH, Park H, Lee SI. Increased immunoendocrine cells in intestinal mucosa of postinfectious irritable bowel syndrome patients 3 years after acute Shigella infection—an observation in a small case control study. Yonsei Med J. 2010;51(1):45–51.

[50] Grover M. Role of gut pathogens in development of irritable bowel syndrome. Indian J Med Res. 2014;139(1):11–8.

[51] Okhuysen PC, Jiang ZD, Carlin L, Forbes C, DuPont HL. Post-diarrhea chronic intestinal symptoms and irritable bowel syndrome in North American travelers to Mexico. Am J Gastroenterol. 2004;99(9):1774–8.

[52] Andresen V, Lowe B, Broicher W, Riegel B, Fraedrich K, von Wulffen M, et al. Post-infectious irritable bowel syndrome (PI-IBS) after infection with Shiga-like toxin-producing Escherichia coli (STEC) O104:H4: a cohort study with prospective follow-up. United Eur Gastroenterol J. 2016;4(1):121–31.

[53] Wadhwa A, Al Nahhas MF, Dierkhising RA, Patel R, Kashyap P, Pardi DS, et al. High risk of post-infectious irritable bowel syndrome in patients with Clostridium difficile infection. Aliment Pharmacol Ther. 2016;44(6):576–82.

[54] Marshall JK, Thabane M, Borgaonkar MR, James C. Postinfectious irritable bowel syndrome after a food-borne outbreak of acute gastroenteritis attributed to a viral pathogen. Clin Gastroenterol Hepatol. 2007;5(4):457–60.

[55] Wensaas KA, Langeland N, Hanevik K, Morch K, Eide GE, Rortveit G. Irritable bowel syndrome and chronic fatigue 3 years after acute giardiasis: historic cohort study. Gut. 2012;61(2):214–9.

[56] Azizian M, Basati G, Abangah G, Mahmoudi MR, Mirzaei A. Contribution of Blastocystishominis subtypes and associated inflammatory factors in development of irritable bowel syndrome. Parasitol Res. 2016;115(5):2003–9.

[57] Borody TJ, Warren EF, Wettstein A, Robertson G, Recabarren P, Fontella A, et al. Eradication of Dientamoeba fragilis can resolve IBS-like symptoms. J Gastroenterol Hepatol 17(Suppl):A103. 2002.

[58] Wouters MM, Van Wanrooy S, Nguyen A, Dooley J, Aguilera-Lizarraga J, Van Brabant W, et al. Psychological comorbidity increases the risk for postinfectious IBS partly by enhanced susceptibility to develop infectious gastroenteritis. Gut. 2016;65(8):1279–88.

[59] Collins SM, Piche T, Rampal P. The putative role of inflammation in the irritable bowel syndrome. Gut. 2001;49(6):743–5.

[60] Spiller RC. Postinfectious irritable bowel syndrome. Gastroenterology. 2003;124(6): 1662–71.

[61] Martinez C, Gonzalez-Castro A, Vicario M, Santos J. Cellular and molecular basis of intestinal barrier dysfunction in the irritable bowel syndrome. Gut Liver. 2012;6(3):305–15.

[62] Tracey KJ. The inflammatory reflex. Nature 2002;420:853–9..

[63] Blalock JE. Harnessing a neural-immune circuit to control inflammation and shock. J Exp Med 2002;195:F25–8.

[64] Dinan TG, Clarke G, Quigley EM, Scott LV, Shanahan F, Cryan J, et al. Enhanced cholinergic-mediated increase in the pro-inflammatory cytokine IL-6 in irritable bowel syndrome: role of muscarinic receptors. Am J Gastroenterol. 2008;103(10):2570–6.

[65] Akiho H, Ihara E, Nakamura K. Low-grade inflammation plays a pivotal role in gastrointestinal dysfunction in irritable bowel syndrome. World J Gastrointest Pathophysiol. 2010;1(3):97–105.

[66] Lee E, Schiller LR, Fordtran JS. Quantification of colonic lamina propria cells by means of a morphometric point-counting method. Gastroenterology. 1988;94(2):409–18.

[67] Sinagra E, Pompei G, Tomasello G, Cappello F, Morreale GC, Amvrosiadis G, et al. Inflammation in irritable bowel syndrome: myth or new treatment target? World J Gastroenterol. 2016;22(7):2242–55.

[68] Barbara G, Cremon C, Carini G, Bellacosa L, Zecchi L, De Giorgio R, et al. The immune system in irritable bowel syndrome. J Neurogastroenterol Motil. 2011;17(4):349–59.

[69] Hod K, Dickman R, Sperber A, Melamed S, Dekel R, Ron Y, et al. Assessment of high-sensitivity CRP as a marker of micro-inflammation in irritable bowel syndrome. Neurogastroenterol Motil. 2011;23(12):1105–10.

[70] Hod K, Ringel-Kulka T, Martin CF, Maharshak N, Ringel Y. High-sensitive C-reactive protein as a marker for inflammation in irritable bowel syndrome. J Clin Gastroenterol. 2015.

[71] Chang MH, Chou JW, Chen SM, Tsai MC, Sun YS, Lin CC, et al. Faecal calprotectin as a novel biomarker for differentiating between inflammatory bowel disease and irritable bowel syndrome. Mol Med Rep. 2014;10(1):522–6.

[72] David LE, Surdea-Blaga T, Dumitrascu DL. Semiquantitative fecal calprotectin test in postinfectious and non-postinfectious irritable bowel syndrome: cross-sectional study. Sao Paulo Med J. 2014:0.

[73] Otten CM, Kok L, Witteman BJ, Baumgarten R, Kampman E, Moons KG, et al. Diagnostic performance of rapid tests for detection of fecal calprotectin and lactoferrin and their ability to discriminate inflammatory from irritable bowel syndrome. Clin Chem Lab Med. 2008;46(9):1275–80.

[74] Menees SB, Powell C, Kurlander J, Goel A, Chey WD. A meta-analysis of the utility of C-reactive protein, erythrocyte sedimentation rate, fecal calprotectin, and fecal lactoferrin to exclude inflammatory bowel disease in adults with IBS. Am J Gastroenterol. 2015;110(3):444–54.

[75] Lembo AJ, Neri B, Tolley J, Barken D, Carroll S, Pan H. Use of serum biomarkers in a diagnostic test for irritable bowel syndrome. Aliment Pharmacol Ther. 2009;29(8):834–42.

[76] Jones MP, Chey WD, Singh S, Gong H, Shringarpure R, Hoe N, et al. A biomarker panel and psychological morbidity differentiates the irritable bowel syndrome from health and provides novel pathophysiological leads. Aliment Pharmacol Ther. 2014;39(4):426–37.

[77] Olivo-Diaz A, Romero-Valdovinos M, Gudino-Ramirez A, Reyes-Gordillo J, Jimenez-Gonzalez DE, Ramirez-Miranda ME, et al. Findings related to IL-

8 and IL-10 gene polymorphisms in a Mexican patient population with irritable bowel syndrome infected with blastocystis. Parasitol Res. 2012;111(1): 487–91.

[78] Schmulson M, Pulido-London D, Rodriguez O, Morales-Rochlin N, Martinez-Garcia R, Gutierrez-Ruiz MC, et al. IL-10 and TNF-alpha polymorphisms in subjects with irritable bowel syndrome in Mexico. Rev Esp Enferm Dig. 2013;105(7):392–9.

[79] Gonsalkorale WM, Perrey C, Pravica V, Whorwell PJ, Hutchinson IV. Interleukin 10 genotypes in irritable bowel syndrome: evidence for an inflammatory component? Gut. 2003;52(1):91–3.

[80] Ek WE, Reznichenko A, Ripke S, Niesler B, Zucchelli M, Rivera NV, et al. Exploring the genetics of irritable bowel syndrome: a GWA study in the general population and replication in multinational case-control cohorts. Gut. 2015;64(11): 1774–82.

[81] Zhou Q, Souba WW, Croce CM, Verne GN. MicroRNA-29a regulates intestinal membrane permeability in patients with irritable bowel syndrome. Gut. 2010;59(6):775–84.

[82] Cenac N, Bautzova T, Le Faouder P, Veldhuis NA, Poole DP, Rolland C, et al. Quantification and potential functions of endogenous agonists of transient receptor potential channels in patients with irritable bowel syndrome. Gastroenterology. 2015;149(2):433–44 e7.

[83] Mondot S, Lepage P. The human gut microbiome and its dysfunctions through the meta-omics prism. Ann N Y Acad Sci. 2016;1372(1):9–19.

[84] Ratanasirintrawoot S, Israsena N. Stem cells in the intestine: possible roles in pathogenesis of irritable bowel syndrome. J Neurogastroenterol Motil. 2016;22(3): 367–82.

[85] Ozkul Y, Galderisi U. The impact of epigenetics on mesenchymal stem cell biology. J Cell Physiol. 2016;231(11):2393–401.

[86] Wang Q, Ding G, Xu X. Immunomodulatory functions of mesenchymal stem cells and possible mechanisms. Histol Histopathol. 2016;31(9):949–59.

[87] De Francesco F, Romano M, Zarantonello L, Ruffolo C, Neri D, Bassi N, et al. The role of adipose stem cells in inflammatory bowel disease: from biology to novel therapeutic strategies. Cancer Biol Ther. 2016;17(9):889–898.

[88] Roostaee A, Benoit YD, Boudjadi S, Beaulieu JF. Epigenetics in intestinal epithelial cell renewal. J Cell Physiol. 2016;231(11):2361–7.

[89] Owens BM. Inflammation, innate immunity, and the intestinal stromal cell niche: opportunities and challenges. Front Immunol. 2015;6:319.

[90] Corsetti M, Whorwell P. Novel pharmacological therapies for irritable bowel syndrome. Expert Rev Gastroenterol Hepatol. 2016;10(7):807–15.

[91] International Foundation for Functional Gastrointestinal Disorders, Inc. (IFFGD) [Internet]. 1998–2016. Available from: http://www.aboutibs.org/take-part-in-online-studies.html [Accessed: 2016-07-21]

[92] GENIEUR.EU [Internet]. 2012. Available from: https://genieur.eu/ [Accessed: 2016-06-12]

[93] Svartz N. Salazopyrin, a new sulfanilamide preparation: A. Therapeutic results in rheumatic polyarthritis. B. Therapeutic results in ulcerative colitis. C. Toxic manifestations in treatment with sulfanilamide preparation. Acta Med Scand 1942;11:557–590.

[94] Azad Khan AK, Piris J, Truelove SC. An experiment to determine the active therapeutic moiety of sulphasalazine. Lancet. 1977;2(8044):892-5.

[95] Bohm SK, Kruis W. Long-term efficacy and safety of once-daily mesalazine granules for the treatment of active ulcerative colitis. Clin Exp Gastroenterol. 2014;7:369–83.

[96] Desreumaux P. Understanding the mechanism of 5-ASA in treating colonic inflammation. Gastroenterol Hepatol (N Y). 2008;4(5):319–20.

[97] Min T, Ford AC. Efficacy of mesalazine in IBS. Gut. 2016;65(1):187–8.

[98] Törnblom H, Simren M. In search for a disease-modifying treatment in irritable bowel syndrome. Gut. 2016;65(1):2–3.

[99] Lazaraki G, Chatzimavroudis G, Katsinelos P. Recent advances in pharmacological treatment of irritable bowel syndrome. World J. Gastroenterol. 2014;20(27):8867–85.

[100] Camilleri M. Pharmacological agents currently in clinical trials for disorders in neurogastroenterology. J Clin Invest. 2013;123(10):4111–20.

[101] Xue L, Huang Z, Zhou X, Chen W. The possible effects of mesalazine on the intestinal microbiota. Aliment Pharmacol Ther. 2012;36(8):813–4.

[102] Hanevik K, Dizdar V, Langeland N, Eide GE, Hausken T. Tolerability and effect of mesalazine in postinfectious irritable bowel syndrome. Aliment Pharmacol Ther. 2011;34(2):259–60.

[103] Farup PG. Questions about mesalazine and the irritable bowel syndrome. Aliment Pharmacol Ther. 2011;34(8):1036–7; author reply 7–8.

[104] Barbara G, Cremon C, Annese V, Basilisco G, Bazzoli F, Bellini M, et al. Randomised controlled trial of mesalazine in IBS. Gut. 2016;65(1):82–90.

[105] Lam C, Tan W, Leighton M, Hastings M, Lingaya M, Falcone Y, et al. A mechanistic multicentre, parallel group, randomised placebo-controlled trial of mesalazine for the treatment of IBS with diarrhoea (IBS-D). Gut. 2016;65(1):91-9.

[106] Bafutto M, Almeida JR, Leite NV, Costa MB, Oliveira EC, Resende-Filho J. Treatment of diarrhea-predominant irritable bowel syndrome with mesalazine and/or *Saccharomyces boulardii*. Arq Gastroenterol. 2013;50(4):304–9.

[107] Tuteja AK, Fang JC, Al-Suqi M, Stoddard GJ, Hale DC. Double-blind placebo-controlled study of mesalamine in post-infective irritable bowel syndrome—a pilot study. Scand J Gastroenterol. 2012;47(10):1159–64.

[108] Andrews CN, Griffiths TA, Kaufman J, Vergnolle N, Surette MG, Rioux KP. Mesalazine (5-aminosalicylic acid) alters faecal bacterial profiles, but not mucosal proteolytic activity in diarrhoea-predominant irritable bowel syndrome. Aliment Pharmacol Ther. 2011;34(3):374–83.

[109] Bafutto M, Almeida JR, Leite NV, Oliveira EC, Gabriel-Neto S, Rezende-Filho J. Treatment of postinfectious irritable bowel syndrome and noninfective irritable bowel syndrome with mesalazine. Arq Gastroenterol. 2011;48(1):36–40.

[110] Dorofeyev AE, Kiriyan EA, Vasilenko IV, Rassokhina OA, Elin AF. Clinical, endoscopical and morphological efficacy of mesalazine in patients with irritable bowel syndrome. Clin Exp Gastroenterol. 2011;4:141–53.

[111] Corinaldesi R, Stanghellini V, Cremon C, Gargano L, Cogliandro RF, De Giorgio R, et al. Effect of mesalazine on mucosal immune biomarkers in irritable bowel syndrome: a randomized controlled proof-of-concept study. Aliment Pharmacol Ther. 2009;30(3):245–52.

[112] Preobrazhenskii VN. Salozinal in the treatment of the irritable bowel syndrome in young persons. Ter Arkh. 1999;71(2):37–9.

[113] Chang JY, Locke GR, Schleck CD, Zinsmeister AR, Talley NJ. Risk factors for chronic constipation and a possible role of analgesics. Neurogastroenterol Motil. 2007;19(11):905-11.

[114] Klooker TK, Braak B, Koopman KE, Welting O, Wouters MM, van der Heide S, et al. The mast cell stabiliser ketotifen decreases visceral hypersensitivity and improves intestinal symptoms in patients with irritable bowel syndrome. Gut. 2010;59(9):1213–21.

[115] Reisinger KW, de Haan JJ, Schreinemacher MH. Word of caution before implementing ketotifen for gastrointestinal transit improvement. World J. Gastroenterol. 2013;19(27):4445–6.

[116] Leri O, Tubili S, De Rosa FG, Addessi MA, Scopelliti G, Lucenti W, et al. Management of diarrhoeic type of irritable bowel syndrome with exclusion diet and disodium cromoglycate. Inflammopharmacology. 1997;5(2):153–8.

[117] Stefanini GF, Saggioro A, Alvisi V, Angelini G, Capurso L, di Lorenzo G, et al. Oral cromolyn sodium in comparison with elimination diet in

the irritable bowel syndrome, diarrheic type. Multicenter study of 428 patients. Scand J Gastroenterol. 1995;30(6):535–41.

[118] Grazioli I, Melzi G, Balsamo V, Castellucci G, Castro M, Catassi C, et al. Food intolerance and irritable bowel syndrome of childhood: clinical efficacy of oral sodium cromoglycate and elimination diet. Minerva Pediatr. 1993;45(6):253–8.

[119] Stefanini GF, Prati E, Albini MC, Piccinini G, Capelli S, Castelli E, et al. Oral disodium cromoglycate treatment on irritable bowel syndrome: an open study on 101 subjects with diarrheic type. Am J Gastroenterol. 1992;87(1):55–7.

[120] Lunardi C, Bambara LM, Biasi D, Cortina P, Peroli P, Nicolis F, et al. Double-blind cross-over trial of oral sodium cromoglycate in patients with irritable bowel syndrome due to food intolerance. Clin Exp Allergy. 1991;21(5):569–72.

[121] Paganelli R, Fagiolo U, Cancian M, Sturniolo GC, Scala E, D'Offizi GP. Intestinal permeability in irritable bowel syndrome. Effect of diet and sodium cromoglycate administration. Ann Allergy. 1990;64(4):377–80.

[122] Antico A, Soana R, Clivio L, Baioni R. Irritable colon syndrome in intolerance to food additives. Minerva Dietol Gastroenterol. 1989;35(4):219–24.

[123] Stefanini GF, Bazzocchi G, Prati E, Lanfranchi GA, Gasbarrini G. Efficacy of oral disodium cromoglycate in patients with irritable bowel syndrome and positive skin prick tests to foods. Lancet. 1986;1(8474):207–8.

[124] Tomecki R. Ineffectiveness of disodium cromoglycate in the treatment of a diarrheal form of irritable bowel syndrome. Pol Tyg Lek. 1985;40(7):181–2.

[125] Fee WH. Irritable bowel syndrome helped by montelukast. Chest. 2002;122(4):1497.

[126] Dunlop SP, Jenkins D, Neal KR, Naesdal J, Borgaonker M, Collins SM, et al. Randomized, double-blind, placebo-controlled trial of prednisolone in post-infectious irritable bowel syndrome. Aliment Pharmacol Ther. 2003;18(1):77–84.

[127] Huerta C, Garcia Rodriguez LA, Wallander MA, Johansson S. Users of oral steroids are at a reduced risk of developing irritable bowel syndrome. Pharmacoepidemiol Drug Saf. 2003;12(7):583–8.

[128] Crentsil V. Will corticosteroids and other anti-inflammatory agents be effective for diarrhea-predominant irritable bowel syndrome? Med Hypotheses. 2005;65(1):97–102.