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Review Article

What Could be Happening if an Inflammatory Bowel Disease Patient is Not Improving? Some Insights about Inflammatory Bowel Disease in Patients who Suffer from it

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Abstract

In general in chronic diarrhea the correct analysis of clinical clues, general laboratory, ileocolonoscopy with biopsies and radiological study, are sufficient in most cases with margins of error of less than 5%. In patients already diagnosed with inflammatory bowel disease (IBD), it is important to be attentive and not attribute any digestive symptom that appears to a reactivation of the disease. These patients in endoscopic remission may have symptoms of irritable bowel syndrome (bloating, flatulence, changes in bowel habit) and other causes of infectious origin, which may lead to the error of intensifying anti-inflammatory therapy or escalation to other immunosuppressants or to biological ones, with the risks that implies. Patients with IBD can also suffer intestinal infections, appendicitis, diverticulitis, just like any other patient. The diagnosis of the cause of the lack of improvement or relapse of the symptoms of these patients is wide, having to review the medications that they receive (need for dose increase, change or combination of therapy, adherence to treatment) and concomitant infections, common or not in our environment.

Keywords: *Inflammatory Bowel Disease; Co-Infecting Infection; Relapse*

Introduction

A good clinician evaluating in Inflammatory Bowel Disease (IBD) patient is very important. Who does not perform a thorough physical exam, or does not gather a detailed history, undoubtedly increases the risks for diagnostic errors. Taking a complete history lessens the hazards significantly. It is vital to ask about the following data: recent trips, use of antibiotics or nonsteroidal anti-inflammatory drugs, episodes of recurrent diarrhea, sexual activity, extraintestinal symptoms (joints, skin, ophthalmic, among others), history of fistulas or perianal abscesses and family history of IBD.

The clinical key to a systemic approach of these patients includes several tests, such as serology for celiac disease and levels of thyroid hormones, as well as ruling out parasitic and clostridium infection. Ileocolonoscopy with biopsies and radiological studies must be done also. This approach usually reduces the risk of diagnostic error [1].

Sometimes, when the patient presents an endoscopic remission may have symptoms of irritable bowel syndrome (bloating, flatulence, changes in bowel habits) or other nonspecific symptoms, we need to think in overlap syndrome, in order to avoid erroneously to increase anti-inflammatory agents or switching to other immunosuppressant, with the inherent risks. The similarity of some IBD symptoms to the

ones Inflammatory Bowel Syndrome (IBS) can be a risk for misdiagnosing these entities. The detection of inflammatory markers in feces, such as calprotectin, is useful for the differential diagnosis. This protein is present in the IBD patient's stools and absent in the stools of the IBS patient. The use of symptomatic therapy is the measure suggested to a situation like this [2]. Patients with IBD can also suffer from intestinal infections, appendicitis, diverticulitis, etc. just like any other person. Also, it is necessary to think sometimes in side effects of any medications [3].

Some mistakes to avoid during the evaluation of the IBD patient

Ulcerative colitis (UC) and Crohn Disease (CD) have complex and heterogeneous clinical courses. Both pathologies can evolve towards innumerable complications from the initial picture if the professional does not make an early diagnosis. A mistake that should be avoided is to start treatment before a confirmed diagnosis. The clinician must rule out any other possible disease through a careful consideration of the "look alike" pathology, to avoid mistakes.

Possible mistakes while practicing ileocolonoscopic procedures

An exhaustive ileocolonoscopy with samples for biopsy studies of healthy and affected segments is the fundamental tool for a diagnosis. Partial ileocolonoscopies or studies limited to colonoscopy only, are not enough to rule out the presence of IBD, or to make the diagnosis of ileitis [4]. The gastroenterology clinic should use the expertise of its procedures to reach the ileum as a parameter of their dexterity. In reference to the clinical reports of these procedures, it is recommendable that the GI specialist makes a detailed description of the pathological findings, by means of internationally accepted terminology, followed by an appropriate diagnosis based on the reported findings (Figure 1).

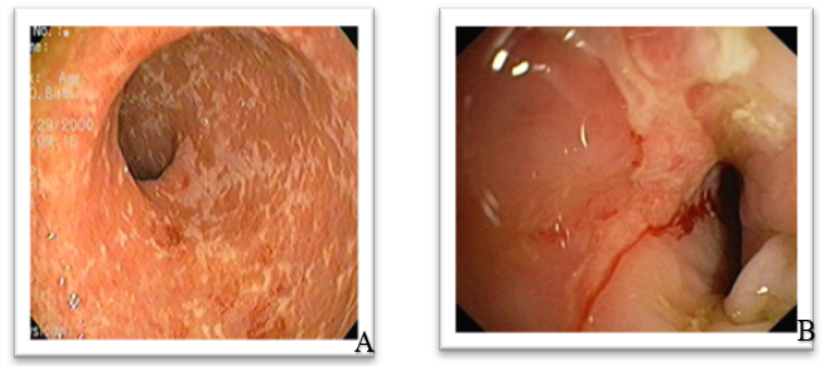

Figure 1: *A) 22 y/o male, with loss of vascular pattern, with mucosa diffusely affected with erythema, edema and circumferential erosions in rectum and simoids. According to the endoscopic classification corresponds to Ulcerative colitis, May 2. B) 27 year old female with deep ulcerated lesions and stenosis in colon. According to the Montreal Classification Crohn's Disease A2-B2-L2.*

When ileocolonoscopy does not identify the lesion because it is in another segment of the small intestine, enteroscopy is indicated. The clinician must be aware of the limitations of using the endoscopic capsule, as it precludes taking samples for biopsies. The author suggests reserving this technic as a second choice, as it is well known that there is as much as 10% of the general population -even asymptomatic subjects- who would have small bowel erosions [5].

About the study of images

This resource must be used thoughtfully, as it is unnecessary in many occasions. It must be done when there is a suspicion for CD of the small intestine, stenosis (Figure 2), or fistulas; as well as possible complications (perforations, toxic megacolon and abscesses). The physician must remember that repeated radiographic procedures give accumulative radiations to the patients. It is worth to keep in mind this caveat, especially when a young patient has IBD, because this population will be subjected to many radiological procedures during their lives. This fact makes magnetic resonance (MR), enterography or MR enteroclysis the first option to study the small intestine and the pelvic and perianal CD [6].

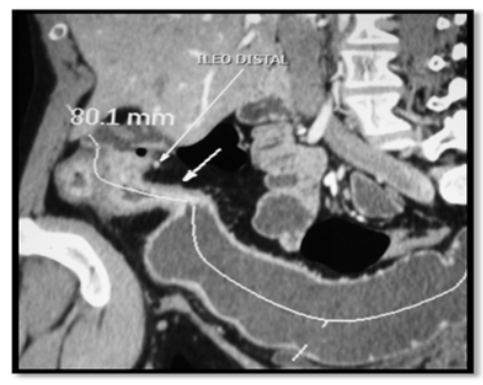

Figure 2: *Enterotomography of a 29 y/o male with Crohn Disease and secondary stenosis of the terminal ileus, who presents distal ileum stenosis of the ileocecal valve, and cecal inflammatory changes. Images of pseudo-polyps and sign of comb at the intestinal loops. (Vasa Recta ingurgitations).*

Regarding treatment

- Are we prescribing sub-therapeutic doses?
- Are we prescribing overdoses?
- Are we not giving any treatment at all?

5-Amimosalycilates. (5-ASA)

Clinicians have prescribed different doses and forms of Sulfapyiridine and Mesalazine for many years, undoubtedly using sub-therapeutic doses in many occasions. It is possible that many patients have received those medications when they did not need them. These drugs are useful to maintain control of mild or moderate UC and of very low or dubious efficacy in the treatment of CD. Favorable results depend also on using correct therapeutic doses; with a dose of no less than 4 gr/d during the flare up and 2 gr/d for maintenance. Preferably the entire dose once daily [7]. Similar results may be obtained with other compounds such as thiopurines or methotrexate, or with biological agents. These therapeutic options for UC enhance the possibility of reserving the use of steroids for controlling acute crisis of ulcerative colitis.

It has been demonstrated that the pharmacological treatment for distal colitis with topic Mesalazine (suppositories, enemas or foams) is more effective than oral therapy. Besides, if the clinical result is partial, there is always the possibility of adding oral therapy. For a good medical-patient relationship it is recommended to inform about other options, as the ones described above. Topical therapy for example, has few side effects and can be used three times a week [8].

Corticosteroids

Secondary Cushing Syndrome is a frequent side effect in those patients who take steroid doses throughout long periods of time or take them intermittently. It is an undesirable and easy to avoid side effect, as there are many other effective options nowadays. Those options include: high doses of 5-ASA molecules, thiopurines, methotrexate and biological therapies to mention some of them [9]. When the GI practitioner decides to use corticosteroids, some caveats deserve special consideration. Administer whole doses from the start of therapy and up to the end. Example: Prednisone, 1 mg/kg body weight per day by mouth. Taper off the dosage every 5 days after 4 weeks, according to patient's response and stop in 8 to 12 weeks later.

If the patient does not respond to this approach after 7 - 10 days of treatment, consider resistance to corticoids and hospital admission to give intravenous hydrocortisone, 100 mg every 8 hours [10]. The author does not recommend using corticosteroids for prolonged maintenance periods, as they become ineffective and multiply the risks of side effects. This warning is valid also when oral Budesonide is used to treat ileal or ileo-colonic CD. The dose of this drug -when used for the pathology mentioned above is: 9 mg/day by mouth. And, a taper off period of 3 - 6 months. Neither of these drugs should be used for maintenance treatment [11].

Immunomodulators

Thiopurines (TP), Azathioprine (AZA), 6-Mercaptopurine (6-MP) and Methotrexate (MTX). The main mistake regarding the use of TP is the prescription of sub-therapeutic doses. This error is often preceded by a prolonged use of corticosteroids, that has been prescribed repeatedly, or as crisis controlling "magic drugs". Cortico-dependence and cortico-resistance are, undoubtedly, indications for the need of immunomodulators! This must be done early on because these compounds have a prolonged latency period.

Safety concerns

The effective doses are: a) 6-MP 1.5 mg/kg/day. b) AZA 2.5 mg/kg/day. As immunomodulators can have a suppressant side effect on the bone marrow, it is necessary to monitor its function throughout the time when the patients receive these drugs. The effectiveness of these drugs may vary and some patients require incremented doses. A white blood count (WBC) can help the practitioner make decisions about increasing the amount of medication or not. The dose of TPs for example, can be augmented until the WBC gets to a leucopenia of 3000 to 4000, accompanied by a significant increase of the mean corpuscular volume (MCV). There is also the possibility of measuring TP metabolites, as well as thiopurine methyltransferase (TMT) activity, to take care of medication-safety concerns. However, nothing replaces a hemogram every 3 months or less, if the dose has been modified. It is important also, to continue administering the immunomodulators during pregnancy, as the risk of reactivation of the disease surpasses by far the risks related to the continuation of treatment.

MTX is an excellent alternative when the therapeutic response is weak, the patient does not tolerate TPs, or for the elderly patients. The prescription of MTX, that is recommended for women throughout the fertility years, is absolutely banned during pregnancy [14].

Biological therapy

Anti-Tumor Necrosis Factors (Anti-TNFs), Human Tumor Necrosis Factor Alfa (Anti-TN-α): Infliximab, adalimumab, certolizumab and golimumab. Anti-integrin antibodies (Natalizumab, vedolizumab).

This therapeutic approach has been the greatest development for the treatment of IBD in the last 20 years. It is possible that many clinicians do not have the information yet to use this resource. It can be mention two more factors that could be prevailing the use of these drugs: high cost and health systems dysfunctionality.

A note of caution should be mentioned regarding the prescription of Anti-TNF-α in patients who have an intra-abdominal fistula or a stricture which may be secondary to CD: It well known that the treatment of this pathology needs to be treated by IBD multidisciplinary team, were the coloproctologies have a relevant job.

The GI specialist must start therapy of every patient who suffers CD taking into account prognostic factors and escalate complexity as needed. It also a serious mistake to delay escalating when needed. e.g. when the patient becomes cortico-resistant, or when the clinical course of the CD worsens [15-17]. Again, a multidisciplinary team must be structured for the care of these patients; this would contribute to better results when treating the CD population.

Some other considerations about treatment

- **Resistance to Anti-TNF-α treatment** There is an important number of patients with IBD who do not respond to treatment with these drugs. There is still no consensus about the definition of Primary lack of response to Anti-TNFs. Some authors define Primary failure as the incomplete remission of the clinical picture, while other authors refer to Primary failure as the absence of improvement after starting treatment [19]. There are different ways to evaluate treatment results. Those include: Clinical symptoms, analytic parameters (PCR, Calprotectin) and endoscopic findings. Besides, different researchers make their evaluations at different times after initiation of treatment; i.e. after the administration of a second dose, after two weeks of treatment, etc. The incidence of primary lack of response to primary treatment varies in most studies (10 - 40%), due to the variability in the timing when the treatment failure is acknowledged. The ratios reported vary if the parameter is no response at all (10 - 40%) or if it is the absence of total remission (50 - 80%). One more disparity to mention: The percentages reported from population studies are higher than the ones reported from clinical studies [20].
- The information about what causes primary failure treatment of IBD patients with Anti-TNFs is limited. One hypothesis is that patients with IBD can have an undiagnosed intercurrence. Sometimes they are treated for the primary clinical picture when the symptoms are expressing a different disease. Such is the case of the IBD patient with Short Bowel Syndrome. Some other patients, who present malabsorption of bile salts, may lead the clinician to mistakenly attribute the symptoms to an activation of the IBD and prescribe an Anti-TNF when the problem is due to a different cause.
- Drugs pharmacodynamics and pharmacokinetics are other aspects to keep in mind. TNFs are a relevant therapeutic resource for most IBD patients, but there are some patients whose etiopathogenetic mechanism for developing IBD predispose them to resistance to Anti-TNFs [20].
- The tendency nowadays, when the lack of response to treatment arises, is to try with another Anti-TNF. But a metanalysis recently published by Gisbert and Col. reveled that this strategy induces remission in only 30% of the patients. Such remission is even lower when the responders are compared with the group of patients exposed to a secondary try with Anti-TNFs, after primary lack of response (45%) or intolerance (61%). Thus, once the clinician concludes that the lack of response to treatment with Anti-TNF is pharmacological in origin, the next intent must be to try with a molecule of a different class (e.g., Vedolizumab or Ustekinumab).

Lack of response to treatment to an Anti-TNF

Anti-TNF treatment loses its effect in 40% of the IBD patients who respond initially to thee drugs. Gisbert and Panes [21] published a metanalysis about the lack of response rate. They also focused on the rate of recovery of response after increasing the dose in patients who were receiving Infliximab. The authors reviewed 16 studies, which included 2236 IBD patients. 37% of these patients lacked the response to Anti-TNFs after 1 year. A different metanalysis, this one published by Billiob [22] that included 39 studies about the lack of response to Adalimubad, a human monoclonal antibody, revealed a loss of response of 18 - 20% per year.

Some factors are associated with the loss of response to treatment with Anti-TNFs (Table 1). They include smoking, family history of IBD, extra-intestinal expression, inaccurate dosage and lack of response to previous treatment with Anti-TNFs [23]. The GI specialist must be aware that the replacement of an Anti-TNF for another one reduces the future treatment options, a difficult clinical problem per see [24]. The author suggests using biological therapy as a valid alternative; such as Vedolizumab or Ustekizumab.

Loss of response to treatment with Anti-TNF
(Up to 40% of initial responders to Anti-TNFs eventually stop responding)
Risk factors to lose the therapeutic effect of an Anti-TNF
• Positive IBD family history
• Smoking
• Extra-intestinal symptoms
• Frequent discontinuation of treatment
• Inadequate Anti-TNF dosage
• Previous lack of response to another Anti-TNF

Table 1: *Source [21].*

Infections

A limited number of microorganisms can cause prolonged diarrhea. So, it is necessary to study the acute diarrhea episodes since most of them cease spontaneously. Conversely, it is necessary to rule out the presence of *Clostridium difficile* (*C. difficile*), *Cytomegalovirus, Yersinia, Giardiasis, Cryptosporidium* and *Entamoeba histolytica*, if the diarrhea does not cease after a few days of treatment. It is important to think of the differential diagnosis with infectious processes as factors interfering with better control of the basic clinical picture.

Amebiasis

It is an important agent to be considered when the patient lives in an area where amebiasis is an endemic agent. Its symptoms can simulate IBD, mainly ulcerative colitis (UC). Amebiasis can coexist also with IBD and hinder the patient's progress when they receive Anti-TNF drugs. There is also a potential for deterioration if there is spreading of the parasite, a complication which can lead to fatal outcome.

The detection of discrete colonic ulcers intermingled with healthy mucous membrane, should conduct the endoscopist to ruling out amebiasis. On the other hand, mucous membrane alterations surrounding the ulcers suggest UC. The distinctive architectonic alterations of the mucosa affected by amebiasis include necrotic material mixed with mucin, proteinaceous exudates, ulcers with blood clot lining and significant epithelial changes. These changes include shortening of the surrounding areas of the ulcers, that in some cases reach the deep mucosa. Therefore, those patients who live in endemic amebiasis regions and have light architectonic mucous alterations (which may reach the deep mucosa) and do not have any other characteristic changes of IBD, should be thoroughly studied, to rule out the presence of amebic trophozoites. This is particularly important if ulcers are detected. Amebic trophozoites are usually present within the necrotic material, the mucin and the ulcer of the blood coat lining (Figure 3) [25].

Cytomegalovirus (CMV)

This virus can play an important role during the evolution of IBD. 20 to 60% of IBD patients require Anti-TNF drugs for a long time [26]. This makes them a very susceptible group for a viral infection, especially at the digestive tract, as it is the ground of the inflammatory process, with activation of immunologic cells. These cells are the reservoir of the CMV [27]. The IBD patient may have a CMV primo-infection without enteric symptoms, may have a viral reactivation within the intestinal mucosa with symptoms of IBD crisis, or may not have any symptoms at all.

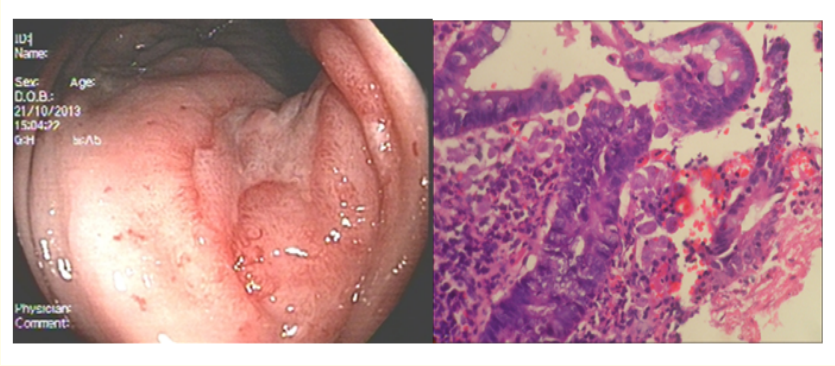

Figure 3: *Mucosa of the rectum with deep ulcers surrounded by normal mucosa with biopsy showing tissue invasion by amoebic trophozoites, staining H and E. It is proposed as a differential diagnosis Crohn's disease.*

The IBD patient who presents with a crisis accompanied by systemic symptoms usually have a very poor response to Anti-TNF. These cases have the worst prognosis [27,28]. Clinical observation, as well as pathophysiological evidence support the concept that CMV plays a role in these IBD crisis. However, studies about this topic do not allow to come to definite conclusions. Some retrospective studies based on medical records review reveal a prevalence of IBD patient with CMV infections that may vary from 0.53 to 3.4% [29]. Meanwhile, prospective-controlled studies show numbers as high as 36% for cortico-refractory patients [30-32]. There are multiple reasons to explain this variability in the findings. They include study design, type of study, diagnostic instrument utilized, sample differences, etc.

There are neither protocols, nor an appropriate test for the study of the IBD patients when the professional suspects a concurrent CMV infection. Despite of that, it is well known that such an intercurrence dramatically worsens the prognosis of an IBD patient. The author suggests that any severe crisis of these patients, that includes both no response to corticoids and more than three days of hospitalization, should be directed to rule out a concurrent CMV infection. Serology tests for CMV and endoscopic biopsies must be done.

Nowadays, the GI professional arrives at the diagnosis by means of the sum of clinical signs and symptoms, endoscopy, imagen studies, plus laboratory tests and histopathological elements. There are no pathognomonic features standards. The available tests are serology for CMV antigens and antibodies. Polymerase Change Reaction (PCR) and tissue culture. However, the specificity and sensitivity of each one of these techniques vary and there is no consensus to when the sample must be taken.

Clostridium difficile (C. difficle)

According to the Declaration 7J about the Consensus on Opportunistic Infections published in 2014 by the European Crohn Disease and Colitis Organisation, the practitioner must look for *C. difficle*, when IBD patients present with crisis. Moreover, the endoscopy image (Figure 4), the diagnosis is usually done by means of at least two criteria: Detection of toxin and, toxicogenic *C. difficle* isolation in stools, in the absence of another cause of diarrhea, or histopathological evidence of pseudomembranous colitis. Rapid detection of toxins A and B is done by immunoassay (IA) technics, such as: immuno-chromatography with immune-assay based on a final reading with spectrophotometric, or chemiluminescence technics. The main disadvantage of these resources is their lack of sensitivity, with values of 20 - 60%, when compared to the toxigenic culture. The specificity of the IA is greater than 90%.

Another optional diagnostic test is the detection of glutamate dehydrogenase (GDH). This is a protein produced abundantly by *C. difficle*. However, both its specificity and its predictive value are relatively low as it detects pathogenic and non-pathogenic strains indiscriminately.

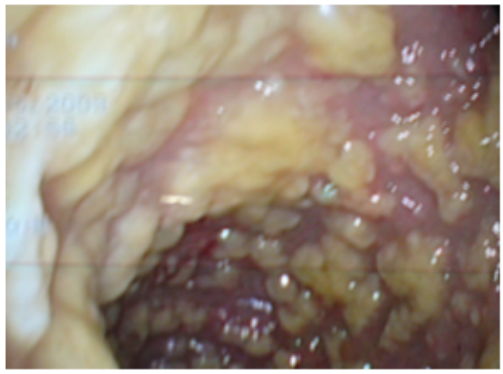

Figure 4: *Pseudomembranes in rectosigmoids due to Clostridium difficile infection in patients with recent administration of Amoxicillin-Clavulanic.*

Laboratory test manufacturers offer nowadays Immuno-Chromatography tests to detect GDH and toxins A and B simultaneously, which allows to obtain both results at once. There are Immuno-Chromatography tests also, to independently determine toxins A and B at the same time. These tests do not have a diagnostic power per se.

There is no test today to independently make the diagnosis of a *C. difficle* infection. Several diagnostic algorithms -that take advantage of the best qualities of the individual tests- have been designed to lessen that inconvenience (See figure 1).

There are fast essays (45 minutes to 3 hours), based on the amplification of *C. difficle* toxic genes. The target of these tests is mostly the gen of toxin B (*C. difficle* tB), even though some detect toxin A gen (*C. difficle* tA). There are some technics that can detect one or more genes of the binary toxin, as well as the hyper-virulent 027ribotype sensitive strains, by taking advantage of the fact that these strains have mutations of the tc *C. difficle* [34]. Those methods which basis is on *C. difficle* tA gen amplification may detect some $A^- B^+$ strains.

Finally, it is very important to insist on the discard of overlap syndrome in those patients who are in endoscopic remission and continue to present clinical symptoms of IBS according to Rome IV. Some authors state that a clinical picture of IBD patient who presents inflammatory symptoms during a remission satisfies the Roman-IV Criteria for IBS [35]. While other clinicians affirm that many IBD patient can present subtle inflammatory symptoms quite frequently [36]. A diagnostic dilemma arises: Are these true IBD symptoms?

Perhaps the scientific community is on its way to discover that the variations of the clinical picture that have been discussed here, are nothing but an ample expression of an Inflammatory Bowel Syndrome [36].

This phenomenon poses a diagnostic dilemma to the clinician, because of the uncertainty about how to treat them. Even though there is no high-level evidence yet, it seems reasonable to start the assessment of this population through the detection of calprotectin level in stool samples. The following step will be searching for other signs of activity, if the detected levels of calprotectin correspond to an active inflammatory process and, start anti-inflammatory treatment at once. Otherwise, symptomatic treatment will be the only therapeutic approach if calprotectin levels are within normal range [37]. The etiopathogenesis of this clinical picture is still unknown. But symptomatic treatment is necessary due to the high prevalence of it and the limitations that this pathology imposes on normal functioning of the patients who suffer from it.

Compliance to treatment

Moreover, it is mandatory to rule out non-compliance to treatment and to re-evaluate eating habits, psychological profile and life style, before starting treatment of a relapsing patient. A satisfactory remission, when treating one of these patients, will be more likely if a multidisciplinary team is working together. The nurse's role by means of her/his educated and comprehensive approach, together with compliance to basic norms and procedures of treatment is fundamental.

Conclusion

In conclusion, in view of the complexity and heterogeneity of the Inflammatory Bowel Disease, both Ulcerative Colitis and Crohn's Disease, once the diagnosis is made, always opening the range of the differential diagnosis to be sure that we are facing a patient with IBD and not it is another pathology, it is necessary to indicate the appropriate treatment and follow up correctly.

Once sure that there is good adherence to the treatment, it is very important to think about the need for the optimization of the treatment if necessary and in each relapse after thinking about the percentage of treatment failure, rule out the possibility of infections that can hinder the evolution of IBD. If the patient has endoscopic remission and continues to show symptoms, propose overlap with IBS.

In order to obtain the best results in the evolution of the disease, it is important to create in all IBD units the multidisciplinary team that evaluates patients in an integrated manner and that in a timely manner diagnoses and treat the complications that may occur.

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