Infections in patients with inflammatory bowel disease

Ann. Ital. Chir., 2020 91, 6: 627-632
pii: S0003469X20033783

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BACKGROUND/AIM: *Inflammatory bowel diseases (IBD) are a group of conditions characterized by chronic inflammation of all or part of the digestive tract and primarily includes Ulcerative Colitis (UC) and Crohn's Disease (CD). This review has as target to summarize the complicated correlation between IBD and infections, which can affect patients' quality of life and increase substantially morbidity and mortality rates.*
RESULTS: *Scientific evidence in recent years shows a growing recognition of the phenomenon although the association between these two aspects is not definitively clear. Despite the fact that our understanding of this linkage is still incomplete, it is easily deducible that infections can start whether it be the onset or the relapse of IBD. In addition to this, the course of the disease predisposes the patient to numerous infections caused by the drugs used to treat IBD and this also raises the risk of infection complications.*
CONCLUSIONS: *Clinical trials have demonstrated that the combined use of immunomodulating agents may increase the risk of new infections. The infections might be intensified by an insufficient vaccination of adults with IBD. Physicians have to be aware of these risks and try to attenuate and treat them properly.*

KEY WORDS: Infections, Inflammatory bowel disease, Risk factors

Introduction

A considerable number of observational studies and case reports have underlined the predisposition of patients with IBD to develop severe infections caused by opportunistic and ordinary microbial pathogens [1]. The European Crohn's and Colitis Organization (ECCO) affirms that all patients with IBD on immunomodulators, corticosteroids and biological agents have to be considered immunocompromised and therefore at high risk for opportunistic infections [2].

Today, the challenge for a physician is not only to manage IBD, but also to prevent and treat common and uncommon infections [3].
In this ongoing process, prevention becomes the first and most important step. Prevention of opportunistic infections is based on recognition of risk factors for infection, the use of primary or secondary chemoprophylaxis, careful monitoring before and during the use of immunomodulating therapy [4].

Epidemiology

In a six-year period (1998 – 2003) Toruner et al. [5] identified 100 consecutive IBD patients who developed an opportunistic infection. This suggests that infections are not so common, but the age is an important and significant risk factor for infections in patients with IBD. A wide range of opportunistic infections arise, caused by

Pervenuto in Redazione Giugno 2020. Accettato per la pubblicazione Luglio 2020
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fungal, viral, and bacterial pathogens. The age, as significant risk factor for opportunistic infections, is confirmed by the fact that patients older than 65 years treated with TNF inhibitors show a higher rate of severe infections and mortality if compared to younger patients and to other patients of the same age who did not receive the same kind of treatment. The effects of anti-TNF agents in patients over 65 with IBD should be more carefully examined, because these patients have higher risk of mortality than other patients due to hospitalization [6]. The anatomical localization and extension of Crohn's disease (CD) and of Ulcerative Colitis (UC) are correlated to the risk of infection. Patients with Crohn's ileitis demonstrate a lower risk for infection (OR, 0.4; 95% CI, 0.2–1.0), compared to Crohn's colitis. This therefore suggests that a localization of the disease in the colon is associated with a higher risk infection. As regards UC, location of disease does not correlate significantly to the odds for infection (OR, 1.5; 95% CI, 0.7–3.2) [5].

Risk Factors

Viral, bacterial, parasitic and fungal infections have all been associated with the use of immunomodulator therapy in IBD. Despite different mechanisms of action, any of those drugs can lead to any type of infection. No strict correlation between aspecific immunomodulator drug and a certain type of infection has been observed.[5] According to the ECCO guidelines (2014) we can define two categories of risk: those that are linked to the patient (age, comorbidity and malnutrition) and those that are not linked to the patient (immunomodulator therapy, exposure to pathogens, or geographic clustering) [7].
Patients with combinations of immunomodulators and/or malnutrition are at high risk for opportunistic infections. Furthermore, comorbidities should be considered while age seems to be an independent risk factor. Among all the risk factors, medical therapy is certainly the most significant [7].

Medications

One retrospective cohort study asserts that preoperative use of corticosteroids, without considering AZA/6MP, increased the potential danger of postoperative infections in patients with CD and UC [8]. The use of any of the following drugs is associated with an important expansion odd for opportunistic infection: Mesalamine, Corticosteroids, AZA/6MP, Thiopurines, Methotrexate, Infliximab, Cyclophosphamide, and Tacrolimus [(5)]. Regarding anti-TNF therapy, a recent meta-analysis of all published data from 22 randomized controlled trials in IBD, demonstrated a two-fold increased risk of opportunistic infections [9]. Regarding corticosteroids, immunosuppression extension increases proportionally with dose and duration; the exact dose and duration necessary for systemic corticoids to suppress the immune system is not clear but a total daily dose equivalent of corticosteroids (Prednisolone) to ≥20 mg for ≥2 weeks is associated with an increased risk of infections [7]. Toruner et al. affirm that patients who received cumulative doses of corticosteroids superior to the median dose of 3600 mg were at greater risk for opportunistic infection (OR, 5.0; 95% CI, 2.2–11.5). Nevertheless, those who received corticosteroids at doses lower than the median had smaller odds for opportunistic infection (OR, 2.5; 95% CI, 1.2–5.1) [5]. In the case of AZA/6MP alone, the prevalence of an opportunistic infection is two to three times greater than the rate related to general population, and when administered with corticosteroids, the risk was about 15-fold increased [5]. It is demonstrated that odds of severe infections are increased when TNF-inhibitors (Infliximab, Adalimumab and Certolizumab Pegol) or immunomodulators are used alone and with systemic corticosteroids. Use of TNF-α inhibitors was associated with a slightly increased odd of severe infections within the first 90 days after beginning treatment, which decreased during the prolonged follow-up [10,11].

Drugs and specific infections

Specific drugs seemed to be cause of specific infections. Corticosteroids are associated most frequently with fungal (Candida species infection), AZA/6MP most commonly with opportunistic viral infections, and immunomodulators such as Infliximab with either fungal or mycobacterial infections [5].
Corticosteroids block neutrophil extravasation and monocyte/macrophage activation, with consequences on lymphocytic activation. These features can lead to infections at mucosal surfaces such as candidiasis. AZA/6MPinhibits the activity of T lymphocytes [12,13], cells which are important in the prevention of viral infections. Anti–tumor necrosis factor-agents, for example Infliximab, are active against monocyte cells[(12)], which are essential in granulomas, for the containment of intracellular pathogens.

Differential diagnosis between different infections and ibd

Over the years, many pathogens have been associated to the development of opportunistic infections in patients with IBD. There are viral infections (herpes viruses [13,14], human papillomavirus, influenza virus, and JC virus), bacterial infections (tuberculosis) [1], Clostridium difficile infections, Pneumococcal infections, (legionellosis), fungal infections (cryptococcosis, Pneumocystis jirovecii infection, aspergillosis, and candidiasis), and parasite infections (Strongyloides stercoralis). It should be remembered that although these infections are characterized by

high morbidity and mortality, only few patients with IBD develop opportunistic infections [15-17]. The infection correlation in IBD is complicated as on one hand infection can be a trigger to start an inflammatory response but at the same time genetic susceptibility can lead to an increased exposure to luminal bacteria. First of all we need to distinguish between IBD and intestinal infections which can simulate the classic aspects of IBD (clinical and endoscopic); these intestinal infections may also have the same extraintestinal manifestations [18]. Among extraintestinal manifestations there are bronchopulmonary and pneumonia signs and symptoms [6,19].

Yersinia Enterocolitica
Yersinia *i*nfection can anticipate or superinfect CD. The differential diagnosis is made with the help of culture or serology [20,21]

Campylobacter Species
Endoscopy shows focal colitis, which may be difficult to differentiate from IBD. Stool culture allows distinguishing it from CD [22,23].

Salmonella Species
Mucosal biopsies show a clinical picture of acute colitis except in the case where there is superinfection of preexisting IBD [24,25]

Escherichia coli
E coli O157:H7 infection may simulate IBD from a clinical, radiological, and endoscopical point of view. Differential diagnosis is obtained with the help of stool cultures. *E coli* is an ordinary microorganism that can be isolated from surgical specimens with CD, and more than this, *E coli* antibodies are present in a large number of patients with CD compared to controls [26].
The theory that bacteria are involved in the pathogenesis of IBD is supported by some clinical observations. Resident luminal bacteria continuously encourages the gastrointestinal mucosal and systemic immune systems to maintain the inflammatory process. However, it has been observed that even in absence of infectious episodes, increased domestic hygiene may also contribute to the patho-mechanism of CD [27].
The implication of microorganisms, like Mycobacterium Tuberculosis (risk 1.88, 95%confidence interval, 0.68 – 5.20) in the pathogenesis of IBD has been demonstrated, it is yet still imprecise if the disease can be caused by the presence of specific bacteria or if there is a total disturbance of the intestinal tract [28].

Clostridium difficile
Patients with ulcerative colitis (UC) have higher odds to contract CDI and have worse outcomes than those with Crohn's disease (CD).CDI may be difficult to distinguish from an IBD because of similar clinical presentation. Investigations for CDI is recommended at every sign or symptom [29]. IBD patients are at risk of developing C. Difficile infection and they have four times higher risk of mortality [30,31].

Helicobacter Pylori
It is now clear that IBD is more prevalent in areas with lower rates of H. Pylori infection and this aspect implies a possible protective effect of H. pylori infection against IBD. Rokkas et al in their meta-analysis affirm a statistically significant inverse relationship between H. pylori infection and IBD (both CD and UC) [32,33].

Gardnerella Vaginalis
There is an important connection between IBD and Gardnerella Vaginalis biofilm. This suggests an epithelial barrier malfunction of the genital tract and could be an important aspect to explain the high incidence of poor reproductive outcome showed in women with IBD [34].

Prevention and treatment of infections

The risk of infections in patients with IBD can also be made worse by under-use of vaccinations[34]. In the last years, guidelines and consensus papers have indicated vaccination as primary prevention of infection in these kind of patients [36]. Early immunization is generally recommended, preferably before the beginning of immunomodulating or immunosuppressing therapy. If attenuated vaccines are administered, at least 4 weeks should pass before starting an immunosuppressive therapy [30].
Attenuated vaccines are: triple viral (measles mumps rubella), Varicella, BCG, Rotavirus, yellow fever, oral typhoid fever (Ty21a), oral poliomyelitis, and herpes zoster. Inactivated vaccines are administered without any problem to immunodepressed patients but immune response may be lower in comparison to healthy population. These vaccines may be given at any time during the treatment, but administration before immunosuppression is largely better (2 weeks earlier) [37].
Considering IBD patients' risk factors, immunization is recommended against Pneumococcus, influenza, hepatitis A, hepatitis B, chickenpox, herpes zoster, and human papillomavirus; vaccination against Neisseria meningitidis serogroup C and Haemophilus influenzae type b (Hib) should also be assessed.
The five following vaccines should be considered for every patient with inflammatory bowel disease. Regarding dose and timing, please refer to appropriate sections: VZV varicella vaccine (if there is no medical history of chickenpox, shingles, or VZV vaccination and VZV serology is negative; Human papilloma virus; Influenza (trivalent inactivated vaccine) annually; Pneumococcal vaccines (PCV 13 and PPSV 23); Hepatitis B vaccine [7].
Varicella and herpes zoster attenuated vaccine, administration is recommended 4 weeks before beginning treat-

ment with immunosuppressants. One out of every three patients will develop shingles in their lifetime [38,39]. The herpes zoster vaccine reduces the risk by 51% and that of post-herpetic neuralgia by 67 % in people over 60 years of age [40].

Influenza vaccine: An effective strategy to prevent influenza can be obtained through vaccination with trivalent inactivated influenza vaccine on an annual basis [7].

There is global consensus in recommending influenza vaccination to people with chronic diseases, especially immunodepressed patients [41,42].

Pneumococcal vaccine: There is large consensus in recommending pneumococcal vaccination for immune compromised patients [42,43].

Hepatitis b virus vaccine: Patients who are HBsAg positive (chronic HBV infection) should receive potent antiviral agents (nucleoside/nucleotide analogues with high barrier to resistance)before, during and for at least 12 months after immunomodulator treatment has ceased. Liver dysfunction occurred in 25 to 36% of HBsAg-positive IBD patients treated with immunosuppressants [7].

Even though the prevalence of infection with hepatitis B virus in IBD patients is comparable to that of healthy population, a high risk of fulminant hepatitis B has been observed in patients who are treated with immunomodulators [44].

Human papillomavirus vaccine: Several guidelines recommend HPV vaccination for patients with IBD, particularly when under treatment with immunomodulators or immunosuppressants [45].

Meningococcus and Haemophilus influenzae type b conjugated vaccines: patients with IBD who did not receive these vaccines during childhood and who are on immunosuppressants should be immunized [45].

Health care staff and patients' relatives should receive immunization in order to reduce the risk of infection transmission to patients. A particular case is vaccination for infants with IBD mothers [5].

The Impact on Outcome

Dangerous and severe forms of pneumococcal infection [46,47], Varicella-zoster virus pneumonia [21,48], Hepatitis B virus reactivation [49,50], and shingles have all been described in IBD patients [36,51,52]. In addition, a high risk for cervical dysplasia and cancer is confirmed [52,53], particularly in women with CD, due to human Papillomavirus. Functional hyposplenism may cause a higher risk of infection by encapsulated bacteria (Streptococcus pneumoniae, Neisseria meningitides [54].

Antimicrobial chemotherapy can be used to treat opportunistic infections. In other cases when no treatment was available, no specific therapy was instituted [5]. It was demonstrated that Metronidazole might have a role in the management of acute relapse in CD [29,47]. This drug can also attenuate the symptoms of CD in the neoterminal ileum [55-58]. Ciprofloxacin in combination with Metronidazole is well tolerated and can be used in patients with active CD, especially when there is involvement of the colon [31].

Conclusions

The correlation between infections and IBD is consolidated knowledge. The use of immunosuppressive drugs such as corticosteroids, AZA/6MP, or Infliximab, particularly when used in combination and elder age are associated to greater risk of opportunistic infections. We do not know the absolute risk of infections in patients with IBD. Patients should be vaccinated before immunosuppressive therapy. Live vaccines are contraindicated in immunocompromised patients.

Riassunto

Le malattie infiammatorie intestinali (IBD) sono un gruppo di condizioni caratterizzate da infiammazione cronica di tutto o parte del tratto digestivo e comprendono principalmente la colite ulcerosa (UC) e la malattia di Crohn (CD). Questa revisione ha l'obiettivo di sintetizzare la complicata correlazione tra IBD e infezioni, che può influire sulla qualità della vita dei pazienti e aumentare sostanzialmente i tassi di morbilità e mortalità.

Le prove scientifiche degli ultimi anni mostrano un crescente riconoscimento del fenomeno, sebbene l'associazione tra questi due aspetti non sia definitivamente chiara. Nonostante il fatto che la nostra comprensione di questo legame sia ancora incompleta, è facilmente deducibile che le infezioni possano iniziare sia che si tratti dell'inizio o della ricaduta dell'IBD. Oltre a ciò, il decorso della malattia predispone il paziente a numerose infezioni causate dai farmaci usati per trattare l'IBD e questo aumenta anche il rischio di complicazioni da infezione.

In conclusione studi clinici hanno dimostrato che l'uso combinato di agenti immunomodulanti può aumentare il rischio di nuove infezioni. Le infezioni potrebbero essere intensificate da un'insufficiente vaccinazione di adulti con IBD. I medici devono essere consapevoli di questi rischi e cercare di attenuarli e trattarli correttamente.

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