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Review

Infections in inflammatory bowel disease☆

Enrique Rodríguez de Santiago[a,*], Agustín Albillos Martínez[a,b], Antonio López-Sanromán[a,b]

[a] Servicio de Gastroenterología y Hepatología, Hospital Universitario Ramón y Cajal, Madrid, Spain
[b] Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Universidad de Alcalá de Henares, Alcalá de Henares, Madrid, Spain

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ABSTRACT

Patients with inflammatory bowel disease constitute a population with a special predisposition to develop bacterial, viral and fungal infections. Iatrogenic immunosuppression, frequent contact with healthcare facilities and surgical interventions are some of the risk factors that explain why these infections are one of the main causes of morbi-mortality in this disease. Some of these infections follow a subtle and paucisymptomatic evolution; their diagnosis and management may become a real challenge for the attending physician if their screening is not systematized or they are not considered in the differential diagnosis.

The objective of this review is to provide an update from a practical and concise perspective on the knowledge regarding the epidemiology, prevention, diagnosis and treatment of the most common infections.

Infecciones en la enfermedad inflamatoria intestinal

Palabras clave:
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RESUMEN

Los pacientes con enfermedad inflamatoria intestinal son una población con especial predisposición a presentar infecciones bacterianas, víricas y fúngicas. La inmunosupresión iatrogénica, el contacto frecuente con el medio hospitalario y las intervenciones quirúrgicas son algunos de los factores de riesgo que explican el que las infecciones sean una de las principales causas de morbimortalidad en esta enfermedad. Algunas de estas infecciones cursan de forma larvada y paucisintomática en muchas de las fases de su historia natural; su diagnóstico y tratamiento suponen un verdadero reto si no se sistematiza su detección o no se tienen presentes en el diagnóstico diferencial.

El objetivo de esta revisión es actualizar desde una perspectiva práctica y concisa el conocimiento sobre la epidemiología, la prevención, el diagnóstico y el tratamiento de las infecciones más comunes.

Introduction

Inflammatory bowel disease (IBD) is much more than an immunological battle between autoreactive leukocytes, intestinal microbiota and increasingly sophisticated drugs. In recent years, there have been drugs directed against targets such as *tumor necrosis factor* (TNFα), integrins, JAK kinases or interleukins 12-23. Although they have allowed to rescue patients who were refractory to conventional therapy, its mechanism of action is the same: immunosuppression. Immunosuppression, necessary in some stages of IBD, is linked in an almost unavoidable way to an increased risk of infection of primary and opportunistic pathogens. In IBD, infection cannot be labeled as anecdotal complications; a study by Ananthakrishnan et al., where a US database that records hospitalizations over 1000 sites is analyzed, found that 27.5% of IBD-related admissions were associated with an infectious process. In addition, these hospitalizations were longer and associated with increased mortality.[1]

Risk factors for infection

Malnutrition, anemia, frequent contact with the hospital environment, age > 50, moderate to severe disease and surgery[1–3]

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* Corresponding author.
E-mail address: e_rodriguez_de_santiago@hotmail.com (E. Rodríguez de Santiago).

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have been described as risk factors. *In vitro* data indicates that intestinal immunity response is defective even in the absence of immunosuppression.[4]

Immunosuppression is probably the main risk factor, although the extent of each immunosuppressant's contribution is difficult to quantify. Most studies agree that the risk is directly proportional to the number and duration of immunosuppressive used.[3] Toruner et al. estimated the net risk associated with each drug through a case–control study. Glucocorticoids are especially associated with *Candida* spp. and herpesvirus (OR 3.3; 95% CI 1.8–6.1), azathioprine (AZA) and 6-mercaptopurine (6-MP) with herpesvirus (OR 3.8; 95% CI 2–7) and anti-TNF-α with fungal infections (OR 4.4; 95% CI 1.1–17).[5]

Anti-TNFα, especially in combination with other immunosuppressants, significantly increase the risk of latent tuberculosis disease reactivation.[2,6,7]

Natalizumab, an anti-integrin drug approved in Crohn's disease (CD), has been relegated into the background due to the notification of cases of progressive multifocal leukoencephalopathy associated with JC virus and the emergence of a new biological agent: vedolizumab. This anti-integrin antibody approved for CD and ulcerative colitis (UC), acts selectively in the intestine, avoiding some of the adverse effects of natalizumab. A meta-analysis of clinical trials using intestine-specific anti-integrin antibodies (vedolizumab and etrolizumab) showed no association with an increased risk of opportunistic infections.[8]

Ustekinumab, a CD-approved antibody against interleukins 12 and 23 has also shown to have a good safety profile. In the clinical trials, the most common infections in IBD were respiratory, although these were not significantly compared to the control group.[9] In clinical practice cohorts, between 2.6 and 8.8% of treated patients develop infection; in a multicenter cohort of 116 subjects which reports the experience in our country, only three cases of infection were detected, all mild.[10,11]

Due to their design and limited duration, clinical trials are not ideal for detecting episodes of low incidence or prolonged latency; as an example, the anti-TNF-α-tuberculosis association went unnoticed in registry studies. Therefore, in order to better understand the risk of new treatments, more research with longer follow-up periods is needed.

Bacterial infections

Clostridium difficile

C. difficile is the leading cause of nosocomial diarrhea in our healthcare environment, with increased incidence in IBD in recent years.[12] Its prognosis and treatment have several peculiarities compared to the general population. Firstly, the percentage of asymptomatic carriers is greater; Clayton et al. found that 8.2% of IBD patients in remission had *C. difficile* in stools compared to 1% of healthy volunteers.[13] Hourigan et al. obtained similar results in a pediatric cohort.[14] Secondly, previous antibiotic therapy is less common; there are series which only report 43% of patients having this therapy.[3] Thirdly, the prevalence of pseudomembranes is lower; in a multicenter cohort only 13% had pseudomembranes and were not associated with significant clinical events, therefore, endoscopy is not recommended as a diagnostic tool.[15] Finally, the rate of recurrence, morbidity and hospitalization time exceed those of subjects without IBD.[16]

There are no clinical, radiological or laboratory data enabling an accurate differential diagnosis with an IBD flare, which, together with the above, justifies the recommendation of *screening for this infection in all patients with IBD and colonic involvement who experience a flare-up of their disease*[3] (Table 1; Fig. 1).

Mild to moderate cases can be treated with oral metronidazole 400–500 mg/8 h or oral vancomycin 125 mg/6 h for 10–14 days. Oral vancomycin 125–500 mg/4–6 h/nasogastric tube is recommended in severe and/or complicated cases and combined with metronidazole 500 IV mg/8 h[17] in enemas. Fidaxomicin has shown "non-inferiority" and fewer recurrences compared to vancomycin; however, IBD was an exclusion criterion in clinical trials and there is no data directly assessing its effectiveness in this population.[18] The largest series of microbiota transplantation was recently published in this context with promising results. Fischer et al. conducted a retrospective multicenter study in which 67 cases of recurrent/refractory disease caused by *C. difficile* were included. 79% achieved recovery, 37% experienced an improvement in their IBD and no serious adverse effects were found, although 13% showed a worsening of their CD/UC.[19]

Mycobacterium tuberculosis

The reactivation of latent disease and to a lesser extent, primoinfection, are an important source of morbidity and cost in IBD. The use of glucocorticoids, AZA/6-MP and especially anti-TNF-α (OR associated with methotrexate [MTX]/AZA 54, 95% CI 5.3–288; OR monotherapy 2.5; 95% CI 0.1–9.9),[7] malnutrition and frequent contact with the hospital make IBD patients a high-risk group. Ustekinumab and vedolizumab seem to have lower risk than anti-TNF-α, although they may also be predisposing factors.[20–22] The very physicians also contribute to increase the magnitude of this problem; in an international survey, 12% of gastroenterologists were unaware that anti-TNF-α were a risk factor for *M. tuberculosis* and 27% admitted that they carried out prophylaxis following clinical guidelines.[22] A recent Spanish study collected 50 cases of patients treated with anti-TNFα from 22 units specialized in IBD, 40% had not been treated according to the scientific societies recommendations.[6] It is also quite common to ignore recent contacts with bacilliferous agents or travel to endemic countries in the case history.

Tuberculin test and interferon gamma release assays have a limited sensitivity and specificity, preventing further screening. A chest X-ray must be added to these tests in search of signs of latent infection (apical pleural thickening, fibrous tracts or calcified nodules). *All IBD patients who are candidates for immunosuppression should undergo screening for latent tuberculosis infection.*[3,22]

Finally, the correct application of the diagnostic algorithm (Fig. 2) and prophylaxis with isoniazid do not guarantee reactivation prevention. Up to 60% of the cases in national series had been properly screened and up to 12% had received isoniazid.[6,22]

Currently, the preferred treatment for latent disease remains isoniazid for 9 months at 5 mg/kg/day.[22] There are alternatives with similar effectiveness that can improve adherence: 10–20 rifampin mg/kg/day 4 months, isoniazid 300 mg/day + rifampin 600 mg/day 3 months, isoniazid 900 mg + rifapentine 900 mg/week 3 months.[23] Anti-TNFα can be initiated 3 weeks after prophylaxis implementation. If infection is detected during anti-TNFα treatment, tuberculostatic treatment should be started and biological therapy should be discontinued, which can be restarted within 2 months.[3,22]

Streptococcus pneumoniae and other bacteria

The risk of pneumonia and invasive pneumococcal disease is increased with and without immunosuppression. The most extensive work is a Danish study with 74,156 subjects with IBD and 1,482,363 controls, which found that the risk of invasive disease tripled during the first year from diagnosis of IBD and remained subsequently above controls, both in CD (HR 1.78, 95% CI 1.34–2.36)