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Infectious proctitis: what every gastroenterologist needs to know

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Abstract

The incidence of sexually transmitted infections (STI) is rising, especially in high-risk groups, namely people living with human immunodeficiency virus (HIV), men who have sex with men, and people with multiple sexual partners. Additionally, the growing availability and use of pre-exposure prophylaxis to prevent HIV infection appears to be associated with an increased risk of infection by venereal agents. The correct recognition of these infections is crucial, not only for individual patients, but also in terms of public health. Furthermore, a diligent diagnostic assessment is key for an efficient therapeutic approach. Infectious proctitis (IP) predominantly occurs in individuals with a history of receptive anal exposure, being a frequent cause for referral to a gastroenterology specialist. The most frequently identified agents are *Neisseria gonorrhoeae*, *Chlamydia trachomatis,* Herpes simplex virus, and *Treponema pallidum.* This paper aims to provide a practice-oriented and up-to-date review regarding the diagnostic and therapeutic approaches to patients with suspected IP. The authors reviewed the most important issues in terms of clinical history, physical examination, and specific diagnostic and therapeutic methods. It is also highlighted the most important topics regarding vaccination, screening for other STIs and differential diagnosis with inflammatory bowel disease. Identification of high-risk groups, screening of potential STIs, and notification of diagnosed anorectal diseases are extremely important and essential to prevent transmission and other complications.

Keywords Infectious proctitis, sexually transmitted infections, pre-exposure prophylaxis, inflammatory bowel disease

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Introduction

In recent years, there has been an increasing trend in the incidence of sexually transmitted infections (STIs), particularly those caused by *Chlamydia trachomatis (C. trachomatis), Neisseria gonorrhoeae (N. gonorrhoeae),* and *Treponema pallidum (T. pallidum)* [1]. The incidence of these infections is particularly high in certain groups with risk factors, namely people living with human immunodeficiency virus (HIV), men who have sex with men (MSM), and people with multiple sexual partners [1]. Additionally, the growing availability and use of pharmacologic mechanisms to prevent HIV infection (pre-exposure prophylaxis), appear to be associated with an increased risk of infection by venereal agents, most notably *C. trachomatis* and *N. gonorrhoeae*. This heightened risk may be due to more frequent risky sexual practices in this population [2,3].

Proctitis, defined as inflammation of the rectum, is a frequent cause for referral to a Gastroenterology specialist. In general, the etiology of proctitis is divided into 2 groups: infectious (IP) and inflammatory, the latter intricately associated with inflammatory bowel disease (IBD). IP predominantly occurs in individuals with a history of receptive anal exposures (oral-anal, genital-anal, digital-anal) [4]. Of all plausible agents of IP, venereal agents are the most frequently isolated [5]. The identification of microorganisms by molecular biology techniques, particularly polymerase chain reaction (PCR), has marked a significant improvement in the investigation and diagnosis of patients with suspected IP [4]. In the MSM population, the most frequently

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identified agents of IP are *N. gonorrhoeae* (30%), *C. trachomatis* (19%), Herpes simplex virus (HSV) (16%), and *T. pallidum* (2%) [5]. Co-infection by 2 or more agents is not rare, being described in 10% of MSM with IP [5].

The growing incidence of this entity translates into more frequent contact between gastroenterologists and these patients. A diligent diagnostic assessment is key for an efficient therapeutic approach. The combination of clinical history, physical examination and specific diagnostic methods, including endoscopy with tissue sampling, is essential to provide an accurate differential diagnosis in relation to other etiologies of proctitis, particularly ulcerative proctitis [6]. This paper aims to provide a practice-oriented and up-to-date review regarding diagnostic and therapeutic approaches to patients with suspected IP.

Diagnosis

Symptoms and clinical history

The approach to patients who present with a suspicion of IP should begin with a comprehensive clinical history, including pathological personal and family histories, particularly respecting colorectal disease, and current medications. The interview should be conducted in an environment that favors patient engagement and compliance with detail lifestyle habits, namely, sexual behaviors, previous STIs, history of sexual trauma, or drug abuse. The interview should also include a judicious and systematic assessment of systemic and anorectal symptoms and signs suggestive of IP (Table 1).

Table 1 The most common signs and symptoms of infectious proctitis

Signs and symptoms
Mild acute proctitis (and chronic proctitis)
Mucous discharge
Constipation
Incomplete defecation
Moderate-to-severe acute proctitis
Proctalgia
Mucopurulent discharge
Bloody discharge
Rectal urgency
Tenesmus
Sensation of rectal fullness
Incomplete defecation
Abdominal pain
Fever

Adapted from de Vries et al [7]

Physical examination

A broad physical examination should be performed to exclude the presence of systemic signs of severity, including fever, tachycardia, hypotension, and dehydration. The focus of the physical examination should be on the perianal and genital regions, including a careful inspection of the skin and mucosa. In patients with IP, external inspection is typically normal. Nevertheless, rectal purulent discharge could be observed, as well as perianal and genital ulcers in primary syphilis, and vesicles in herpetic lesions.

The abdominal exam is generally normal. However, tenderness in the left lower quadrants could be observed. Additionally, palpation of the inguinal region may reveal the presence of painful adenopathy, most frequently after infection by *C. trachomatis* serovars associated with *Lymphogranuloma venereum* (LGV).

Evaluation

The following diagnostic tests should be considered: laboratory studies, anal Pap test, anoscopy, and imaging studies.

Laboratory studies

An anal swab for *N. gonorrhoeae*, *C. trachomatis* and HSV should be performed (Fig. 1A). Exclusion of other potential STIs, namely HIV, hepatitis B and C, as well as blood serology for syphilis must also be performed.

Anal Pap test

The anal Pap test technique consists of blind insertion of a Dacron swab (Fig. 1B) into the anal canal (2-4 cm) and vigorous rotation through 360°. The sample is fixed in a specific container with methanol-based fixative (Fig. 1B), and is interpreted using the Bethesda System terminology (atypical squamous cells of undetermined significance, low- and high-grade squamous intraepithelial lesion).

Anoscopy

The proctological examination must include anoscopy (without bowel preparation) with recourse to an anoscope and a light source (Fig. 1C). After digital rectal examination with the aid of a lubricant, anoscopic examination should be performed to identify lesions, such as internal hemorrhoids, fissures, warts, abscesses or tumors, that are included in the differential diagnosis of IP.

Imaging studies

IP sigmoidoscopy may reveal an inflamed rectal mucosa with erythema, erosions, ulcers or vesicles (Fig. 2). Most endoscopic findings are non-specific and rectal biopsies should be performed mainly if a *C. trachomatis* test is positive, to rule out LGV using a PCR test. If there is suspicion of IBD, colonoscopy should be performed. Radiologic imaging is

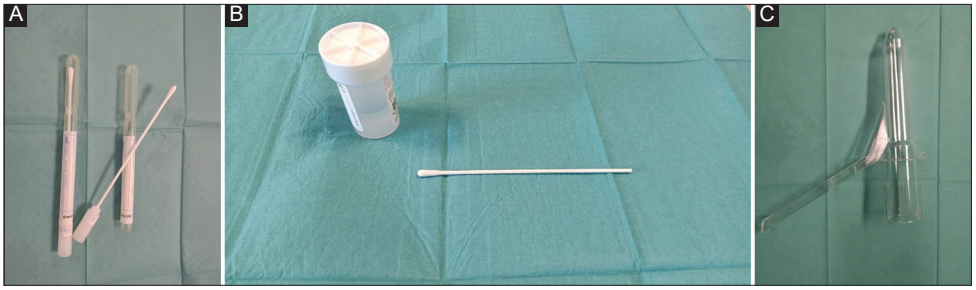

Figure 1 Anal swab for *Neisseria gonorrhoeae, Chlamydia trachomatis* and Herpes simplex virus (A), Dacron swab and a methanol-based fixative container (B) and disposable anoscope system with obturator (C)

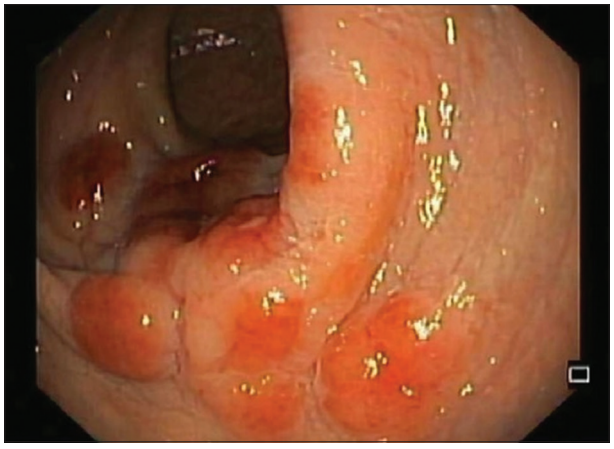

Figure 2 Endoscopic findings of the rectum of a patient with IP positive for 3 different agents: *Neisseria gonorrhoeae, Chlamydia trachomatis*, and T*reponema pallidum*. Hyperemic nodularities with "pseudotumoral" aspect were observed in the distal rectum

usually not necessary for the evaluation of anorectal symptoms, except if perianal abscess or anal cancer are suspected.

Management

Information, explanation and advice for the patient

As a first approach, all patients with IP should receive clear information about their condition, including details of transmission, complications and prevention. Screening for anorectal infections at 3- to 6-month intervals should be offered to individuals who engage in receptive anal sex, in case of multiple sexual partners and/or recent STIs [4,7].

To minimize transmission and reinfection, patients should be advised to abstain from unprotected sexual contact until the resolution of symptoms, completion of treatment and negative test results for the specific pathogen. The use of condoms, and avoidance of sharing sex toys and using swimming pools and spa centers, are other measures that should be communicated.

Partners of affected patients should be offered medical evaluation, screening for STIs and treatment. Patients should abstain from sexual activity for 7 days after they and their partners have completed treatment [8,9].

Most cases of IP are considered notifiable diseases and must be reported to the government health authorities since they represent a public health risk, particularly infections caused by *N. gonorrhoeae*, *C. trachomatis, T. pallidum,* HIV, hepatitis A virus (HAV) and monkeypox [4].

Therapy

Empiric therapy

In acute proctitis with mild symptoms, empirical treatment should be avoided, considering antibiotic resistance. However, therapy can be initiated in patients with a severe clinical presentation pending results of microbiological investigation, especially if anorectal exudate is detected on examination, or polymorphonuclear leukocytes detected on a gram-stained smear of anorectal exudate or secretions. Empiric therapy should only be considered after a proctological examination and after exclusion of other diagnoses with similar symptoms, such as anal cancer.

European guidelines suggest single-dose administration of ceftriaxone 500 mg (or 1 g if weight ≥150 kg) plus doxycycline 100 mg b.i.d. for 7 days [9]. Alternatives to ceftriaxone include cefoxitin (2 g i.m. plus probenecid 1 g orally) and cefotaxime (500 mg i.m.). An extended course of doxycycline to 21 days is recommended if clinical suspicion of LGV is strong (Fig. 3). Empirical treatment of genital herpes should also be considered in cases of painful ulcers and among patients with HIV [4,7].

Specific therapy

To avoid antibiotic resistance, patients with mild symptoms could wait for microbiology results (anal swabs and rectal biopsies). After identifying the etiologic pathogen, a specific therapy should be initiated. In fact, this is a critically important component of therapy, because it prevents the emergence of antimicrobial resistance in the community and can reduce cost and toxicity of therapy.

However, if the microbiology results fail to detect a specific pathogen, empiric therapy could be initiated if the clinical suspicion for an infectious cause (based on history and physical examination) is high. In this scenario, an alternative etiology should also be considered, such as non-infectious processes (IBD, traumatic or radiation proctitis), or an infectious disease caused by non-sexually transmitted pathogens.

Symptoms →	**Assessment** →	**Procedures** →	**Empiric therapy** for gonorrhea and chlamydia (after procedures and exclusion of other possible diagnosis)
> Receptive anal intercourse > Rectal pain > Hematochezia > Purulent or bloody discharge > Urgency > Tenesmus In the presence of: fever, weight loss, diarrhea, abdominal pain considered other differential diagnosis ↓	> HIV screening status > HBV/HCV screening status > HAV vaccination[1] > Consider HPV vaccination[2] > Case report in the National Epidemiological Surveillance System > Test recent sexual partners	> Anal swab for: • Gonorrhea • Chlamydia • HSV infection > Blood serology for syphilis[3] > Anal Pap smear[4] > Anoscopy > Sigmoidoscopy	(a) Ceftriaxone 500-1000 mg[5] i.m. (single dose) plus Doxycycline 100 mg, b.i.d. for 7 days[6] (b) Non-specific acute proctitis: Doxycycline 100 mg b.i.d. for 7 days add Ceftriaxone 1000 mg i.m. (if NG is suspected) In case of perianal ulcers or mucosa ulcers consider HSV infection[7] ↓ Acyclovir 400 mg p.o. t.i.d. for 5-10 days ↓ Assess clinical response to therapy (If patients did not respond to standard therapy as expected, consider other differential diagnosis**) ↓

** **Differential diagnosis:** traumatic proctitis, radiation proctitis, rectal malignancy, solitary rectal ulcer syndrome, diversion colitis, ischemia and other infections such as: *Mycoplasma genitalium*, Monkeypox, Cytomegalovirus, *Campylobacter*, *Shigella*, *Salmonella*, *Giardia* and *Entamoeba histolytica*

Figure 3 Flowchart for the management of acute infectious proctitis
[1]Havrix® or Vaqta®: 2-dose series at 0 and 6-12 months
[2]Gardasil9® or Cervarix®: 2-dose vaccine schedule at 0 and 6-12 months for persons who initiate vaccination before their 15th birthday. 3-dose vaccine schedule at 0, 1-2, and 6 months for immunocompromised persons
[3]If RPR is positive: penicillin G benzathine 2.4 million
[4]If not done within past 12 months
[5]For persons weighing ≥150 kg, 1 g of Ceftriaxone should be administered.
[6]If LGV genovar positive: Doxycycline 100 mg, bid for 3 weeks
[7]Especially in cases with severe pain and among people living with HIV
(a) Workowski K, *et al*, 2021, [4] (STIs treatment guidelines, CDC)
(b) de Vries HJC, *et al*, 2021, [7] (European guideline on the management of proctitis, proctocolitis and enteritis caused by sexually transmissible pathogens)
NG, Neisseria gonorrhoeae; LGV, lymphogranuloma venereum; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HSV, Herpes simplex virus; RPR, rapid plasma regain

N. gonorrhoeae

Gonococcal infection is the second most common STI in the United States, with more than 1.5 million cases diagnosed each year [4]. The incidence of *N. gonorrhoeae* infection has been decreasing in the last decades of the 20th century [8]. Nevertheless, the rate of this infection has been increasing in the last 2 decades [8,10].

N. gonorrhoeae is a gram-negative diplococcus capable of producing symptomatic infection at several anatomic locations, including the urethra (particularly in men), cervix (women), oropharynx, and rectum. Rectal infection occurs predominantly by receptive anal intercourse, being more common in women and MSM [4,11]. Women with gonococcal cervicitis often present with concomitant rectal infection, believed to be the result of contiguous spread [8,12].

N. gonorrhoeae is considered the most common cause of sexually transmitted proctitis, accounting for 30% of all patients presenting with clinical evidence of IP [5]. Anorectal involvement is frequently associated with concomitant infection at other locations (e.g., cervix and urethra). Indeed, only 4% of women with gonococcal infection will have exclusive anorectal involvement, whereas 40-50% of MSM with gonorrhea will have isolated rectal infection [8].

Asymptomatic gonococcal infection is common, particularly in women [13]. In fact, at least half of men and 95% of women with rectal infection by *N. gonorrhoeae* are asymptomatic [8]. Symptoms of rectal infection are non-specific and most frequently include mucopurulent or

bloody discharge associated with anorectal symptoms such as tenesmus, anorectal pain or constipation [7,8,13].

Anoscopic and endoscopic findings include the presence of mucopurulent discharge over the rectal mucosa, most frequently extending no further than 10 cm from the anal verge. Mucosal lesions include loss of normal vascular pattern, mucosal edema, erythema and friability (Fig. 4). Ulceration is less common than other etiologies, namely rectal infection by *C. trachomatis* serovars associated with LGV and *T. pallidum*.

Patients with suspected rectal gonococcal infection should undergo microbiological testing [4]. Gram stains, culture, and nucleic acid amplification tests (NAATs) can be used to diagnose infection by *N. gonorrhoeae*. The identification of intracellular gram-negative diplococci within polymorphonuclear leukocytes is highly sensitive and specific for the diagnosis of gonococcal infection in symptomatic patients. Nevertheless, gram stains should not be used to rule out gonococcal infection in asymptomatic patients, given their low sensitivity in this subset of patients [4]. The introduction of NAATs has simplified the diagnostic approach to these patients. The sensitivity of these tests has been shown to be superior to that of *N. gonorrhoeae* culture and they should be performed to confirm positive gram stains [4,8].

Over the last decades, significant concerns about an increasing prevalence of antibiotic-resistant *N. gonorrhoeae* have been raised in the medical literature [9,14]. Cultures should be obtained in cases of suspected or confirmed treatment failure [8].

Antibiotic treatment should be started upon diagnosis (Table 1). Ceftriaxone (a single intramuscular dose) is the standard of care for treatment of gonorrhea. Although the 2020 gonorrhea guideline recommends azithromycin 2 g combined with ceftriaxone, this is no longer recommended [15]. However, in IP, when *N. gonorrhoeae* is suspected, instead of azithromycin, doxycycline could be added, as it is superior against (suspected) *C. trachomatis* infections, and to avoid azithromycin resistance in undiagnosed coinfection with *Mycoplasma genitalium (M. genitalium)*.

To promote treatment adherence and reduce transmission, empirical treatment covering *N. gonorrhoeae* and *C. trachomatis* should be offered, as previously described [4]. A test of cure is generally unnecessary in uncomplicated disease, except if poor treatment adherence or persisting infection is suspected [9]. Nevertheless, precise information should be given to the patient and a close follow up should be maintained.

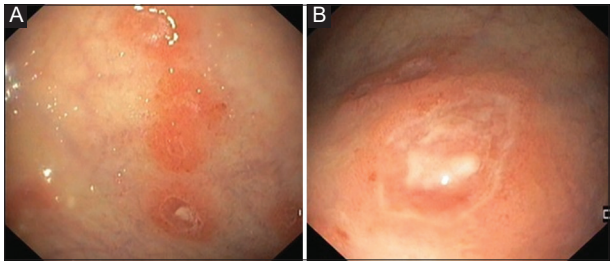

Figure 4 Endoscopic findings of *Neisseria gonorrhoeae* positive infectious proctitis with several superficial hyperemic ulcers (A, B)

C. trachomatis

Infection by *C. trachomatis* represents the most diagnosed STI worldwide, with over 100 million people infected each year [16]. The incidence of *C. trachomatis* infection has been rising over the last decades [10]. Anorectal infection is more common in young women and MSM [4]. Rectal infection occurs as a consequence of receptive anal intercourse, and symptoms occur after an incubation period of 7-10 days [11]. Like other STIs, women with chlamydial urethritis or cervicitis may present with simultaneous rectal infection due to direct spreading [12]. Rectal chlamydia infection has been shown to account for approximately 20% of all IP cases, frequently in association with other agents [5].

C. trachomatis is an intracellular bacterium presenting 15 different serovars. Serovars A-K are responsible for non-LGV infections, whereas L1-L3 serovars are responsible for LGV. This subtype of *C. trachomatis* infection is particularly prevalent in HIV-positive LGV patients and is often associated with other concomitant STIs [17,18].

Non-LGV serovars produce inflammation restricted to the epithelium and are often asymptomatic. Nevertheless, symptomatic patients may complain of anal pain, mucopurulent or bloody discharge and tenesmus [8,11].

LGV is an invasive and systemic infection, generating systemic symptoms more frequently compared to infection by non-LGV serovars. The clinical presentation of LGV is often divided into 3 stages. The first stage is characterized by the presence of anal and/or genital ulcers or papules at the site of inoculation. The appearance of the characteristic painful inguinal or femoral lymphadenopathy (*buboes*) is typical of the second stage of infection [11]. At this stage, anorectal ulcers may also appear. Symptoms at this stage may include mucopurulent or bloody discharge, anal pain, malaise, myalgia, and fever [8,11]. When untreated, the final stage may include the development of rectal abscesses, granulomas, fistulae, and strictures.

The proctoscopic and endoscopic appearance of rectal mucosa infected by non-LGV *C. trachomatis* is non-specific, including erythema and friability. In addition to these findings, infection by LGV specimens may lead to the presence of ulceration, granulomas and abscesses [8] (Fig. 5). Longstanding

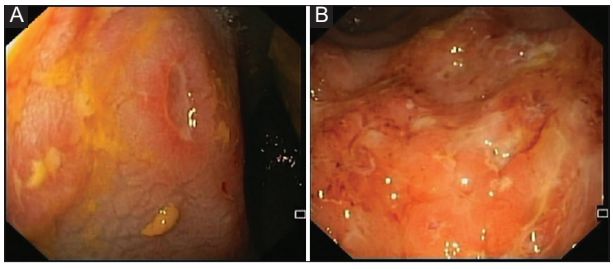

Figure 5 Endoscopic findings of *Chlamydia trachomatis (C. trachomatis)*-positive infectious proctitis. (A) An ulcer with well-defined borders present in proctosigmoidoscopy of non-*Lymphogranuloma venereum* (LGV) *C. trachomatis* infectious proctitis (IP). (B) Multiple hyperemic ulcers (some of them with deep ulcers) in the rectal mucosa of a patient diagnosed with LGV *C. trachomatis*-positive IP

LGV, leading to granulomas, fistulae and structuring, can generate an endoscopic, radiologic, and even histological appearances resembling Crohn's disease [6].

Upon clinical suspicion, microbiologic testing should be performed to achieve a definite diagnosis. NAATs are the most sensitive tests for the diagnosis of *C. trachomatis* infection. Rectal specimens can be obtained by clinician-collected swabs or rectal tissue sampling [4]. NAATs are particularly important, as they enable the genotyping of *C. trachomatis,* thus allowing the identification of LGV serotypes [7]. The current guidelines from the Centers for Disease Control and Prevention (CDC) recommend annual screening for women under 25 and men who engage in receptive anorectal sexual activity [4].

Treatment should be provided for all patients with proven *C. trachomatis* infection. Oral doxycycline 100 mg b.i.d. for 7 days is the first-line treatment directed toward non-LGV *C. trachomatis* [4,16]. This therapeutic course should be extended to 21 days if an LGV serovar is diagnosed.

A test of cure is generally unnecessary, except in the case of complicated disease, pregnancy, suspected poor treatment compliance or need of treatment with second-line therapies. Nonetheless, information regarding the disease course, as well as partner notification and treatment should be given to the patient.

HSV

HSV infection manifests near the mucocutaneous junctions; therefore, proctitis due to HSV results in extension of the disease from the perianal region to the anal canal and rectum. Anorectal HSV infection is more common in an immunosuppressed population that practices receptive anal intercourse.

Both serotypes (HSV-1 and HSV-2) can be found in the anogenital area [8]. Although most cases of recurrent genital herpes are caused by HSV-2, an increased proportion of HSV-1 anogenital herpetic infections has been observed, especially in young women and MSM [4].

Symptoms described in HSV proctitis are anorectal pain, tenesmus, exudate, rectal bleeding, and sacral paresthesia. The presence of painful vesicular lesions or ulcers in the perianal area is a clue to the diagnosis (Fig. 6). Inguinal lymphadenopathies can also be present [12]. The endoscopic findings of rectal mucosa could be erythema, mucosal edema and ulcerations.

People with symptoms of acute proctitis with painful perianal or mucosal ulcers detected on proctological examination should receive presumptive treatment for genital herpes [7]. The diagnosis of anorectal HSV infection can be performed using PCR, which has a higher sensitivity compared to the gold standard test (culture virus in rectal tissue) [19]. Treatment options are acyclovir 400 mg t.i.d., valganciclovir 500 mg b.i.d., or famciclovir 250 mg t.i.d., for 5-10 days [8,20]. Intravenous treatment must be considered only in cases of severe HSV, such as disseminated disease, pneumonitis, hepatitis, and meningoencephalitis (Table 2) [20].

Ideally, therapy should be administered within the first 24 h of appearance of the lesion or during the prodrome (burning sensation or pain) to shorten the duration of injuries [7]. The healthcare provider should discuss the importance of abstaining from sexual activity with uninfected partners when lesions or prodromal symptoms are present [7].

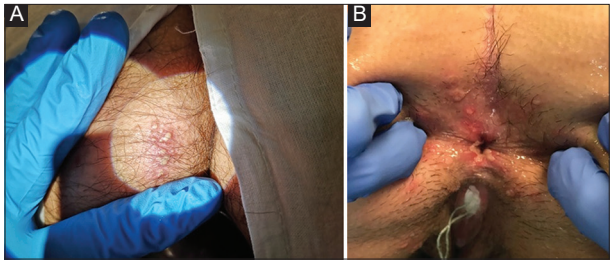

Figure 6 Perianal vesicles (A) and vesicular eruptions in the anal canal (B) in 2 immunosuppressed patients infected with Herpes simplex virus-2

T. pallidum

Syphilis is a chronic bacterial infection caused by a spirochete, *T. pallidum*, whose incidence has risen steadily in recent years in Western Europe and the Americas, mainly in the MSM population [21]. Patients may be completely asymptomatic, and diagnosis is made as a result of incidental screening. When patients are symptomatic, the signs or symptoms may vary according to the stage of the disease [22,23].

In primary syphilis that appears within 3 months (average 2-3 weeks) after direct contact with another person's infectious skin lesions, an anogenital lesion is typically solitary, painless, ulcerative and indurated, with a clean base and discharge of serous fluid (chancre) [24,25]. Regional lymphadenopathy may also be present in the genitalia, mouth or rectum [24].

If not identified and properly treated, infection may progress to the secondary stage, typically in 6-12 weeks. In fact, secondary syphilis is the most common recognized clinical syndrome of syphilis, particularly among women or MSM. In this stage, a multisystem disease is described and can include several manifestations, such as maculopapular rash (typically palmoplantar), oral ulceration, proctitis and *condylomata lata* (wart-like papules commonly located in the perianal or genital area) [22,23]. Tertiary infection, which may occur several years after primary or secondary disease, can have major neurological or cardiovascular sequelae [22,23].

Syphilitic proctitis is rarely reported, but is being recognized more frequently because of the increasing incidence of syphilis among MSM. The signs and symptoms of proctitis are nonspecific, such as rectal bleeding, rectal pain, mucus and rectal fullness. The endoscopic appearance of the rectum may include edema, erythema, multiple friable erosions or ulcerations [26].

The presumptive diagnosis of syphilis is made using serologic tests that should include nontreponemal and treponemal tests (Table 2). For those without prior syphilis, either test can be used as the initial screening test. Confirmatory testing is necessary given the potential for false-positive screening test results (dark field microscopy/direct fluorescent antibody

Table 2 Summary of recommendations for the diagnosis and treatment of infectious proctitis

Pathogen	Diagnosis	Symptoms/Proctologic findings	Treatment (1st line)	Treatment (2nd line)	Notes
N. gonorrhoeae	NAATs (swab/tissue sampling) Gram stains Culture	Symptoms: up to 84% asymptomatic; pain associated with defecation, tenesmus, mucopurulent discharge, pruritus Proctologic exam/ endoscopy: Unspecific; purulent discharge, loss of vascular pattern, erythema, friability. Less frequently, ulceration.	Ceftriaxone 1 g i.m.[1]	Cefoxitine 2 g i.m. + Probenecid 1g p.o. (single dose) Cefotaxime 500 mg i.m. (single dose) Cefixime 400 PO + azithromycin 2 g p.o. (single dose) Gentamicin 240 mg IM + azithromycin 2 g p.o. (single dose)[2] Ciprofloxacin 500 mg p.o. (single dose)[2,3]	Negative gram stains do not rule out infection in asymptomatic patients. Agent to be covered by empiric (syndromic) antibiotic treatment. TOC is generally unnecessary in uncomplicated cases.
Non-LGV C. trachomatis	NAATs (swab/tissue sampling)	Symptoms: up to 50% asymptomatic or paucisymptomatic; anal pain, tenesmus, blood and mucous discharge Proctologic exam/ endoscopy: Unspecific; erythema, friability	Doxycycline 100 mg b.i.d. for 7 days[3] Azithromycin 1 g p.o. (single dose)	Levofloxacin 500 mg p.o. q.d. for 7 days[3] Ofloxacin 200 mg p.o. b.i.d. for 7 days[3] Erythromycin 500 mg p.o. b.i.d. for 7 days Amoxicillin 500 mg p.o. t.i.d. for 7 days	Agent to be covered by empiric (syndromic) antibiotic treatment. TOC is generally unnecessary in uncomplicated cases.
LGV C. trachomatis	NAATs (swab/ tissue sampling)	Symptoms: anal pain, painful inguinal adenopathy (75%), mucopurulent discharge, bloody discharge, tenesmus, fever, pain Proctologic exam/endoscopy: Unspecific; erythema, friability and ulceration. Longstanding LGV can lead to colorectal fistulae and fibrotic strictures and abscesses (can mimic Crohn's disease).	Doxycycline 100 mg b.i.d. for 21 days[3]	Azithromycin 1 g p.o. per week for 3 weeks Erythromycin 400 mg p.o. q.i.d. for 21 days. Moxifloxacin 400 mg p.o. q.d. for 21 days[3] Rifampicin 600 mg p.o. q.d. for 21 days	May mimic the clinical, endoscopic and histologic appearance of Crohn's disease. TOC is generally unnecessary in uncomplicated cases.
Herpes simplex	NAATs (swab/tissue sampling)	Symptoms: severe anal pain, painful anogenital, vesicles tenesmus, bleeding constipation, difficulty in urinating, sacral paresthesias, lymphadenopathy. Severe cases can present with perianal erythema and ulcerations. Proctologic exam/ endoscopy: Coalesced vesicles and Pustules. Mucosal edema and ulcerations (distal rectum - 10 cm).	Acyclovir 400 mg p.o. t.i.d. for 5-10 days Famciclovir 250 mg p.o. t.i.d. for 5-10 days Valaciclovir 500 mg p.o. b.i.d. for 5-10 days Episodic therapy for recurrent infection Acyclovir 800 mg p.o. t.i.d. for 2 days Famciclovir 1 g p.o. b.i.d. 1 day HIV patients Acyclovir 400 mg p.o. f.i.d. for 7-10 days Valaciclovir 500-1000 mg p.o. b.i.d. for 10 days		Parenteral therapy should be considered in patients with more severe clinical manifestations (central nervous system disease, disseminated HSV or hepatitis). No role for topical therapy. Analgesics and sitz baths can be considered in severe primary episodes with painful lesions.

(Contd...)

Table 2 *(Continued)*

Pathogen	Diagnosis	Symptoms/Proctologic findings	Treatment (1st line)	Treatment (2nd line)	Notes
T. pallidum	Nontreponemal (RPR, VDRL, TRUST) and treponemal tests (FTA-ABS, TPPA) Tissue biopsy with staining for *T. pallidum*	Symptoms: primary anorectal syphilis – anogenital pain, discharge, defecatory urgency, tenesmus. Proctologic exam/ endoscopy: broad based ulcers between anal verge and dentate line. Potential confusion with anal fissure but off the midline and associated with rectal symptoms	Penicillin G benzathine 2.4 million units i.m. once Late syphilis: Penicillin G benzathine 2.4 million units i.m. once weekly for 3 weeks	Doxycycline 100 mg p.o. b.i.d. for 14 days[4] Late syphilis: Ceftriaxone 1 g b.i.d. i.m. or i.v. for 10-14 days	Clinical exam and serologic testing with nontreponemal test (RPR) at 6 and 12 months. In case of late syphilis also at 24 months.
M. genitalium	NAATs (swab/tissue sampling)	Symptoms: unspecific; paucisymptomatic *vs* Chlamydia and Neisseria infections Proctologic exam/ endoscopy: Unspecific features in the rectal mucosa.	Azithromycin 500 mg p.o. (day 1) followed by 250 mg 2-5 days p.o.	Second line: Moxifloxacin 400 mg q.d. for 7 days (oral)[5] Third line: Pristinamycin 1 g, q.i.d. for 10 days (oral) Minocycline 100 mg b.i.d. for 14 days (oral)[3] Doxycycline 100 mg b.i.d. for 14 days (oral)[3]	Consider after exclusion of *N. gonorrhoeae* and *C. trachomatis* as causative pathogen European guidelines consider a test of cure, 3 weeks after treatment. CDC recommendations endorsed TOC in patient with persistent symptoms and signs after treatment.
Monkeypox	NAATs (swab skin or anorectal lesion)	Symptoms: prodromic stage - fever, lethargy, myalgias, headache and lymphadenopathy; anogenital lesions, severe rectal pain Proctologic exam/ endoscopy: Unspecific; erythema, evolutive perianal lesions (macules, vesicles, pustules, ulcers), friability, ulceration, and abscesses.	Tecovirimat 200 mg, 3 capsules (600 mg) b.i.d. for 14 days[6]	Second line: Brincidofovir – not approved in Europe	Tecovirimat capsules should be taken within 30 minutes after a meal.

[1]Center for Disease Control and Prevention guidelines recommend ceftriaxone 500 mg for people with a weight <150 kg and 1 g for people with weighing ≥150 kg. Combining ceftriaxone with azithromycin is no longer recommended

[2]Alternatives for patients with history of severe allergic reactions to beta-lactams

[3]Contraindicated during pregnancy

[4]Penicillin allergy or parenteral treatment refused

[5]Moxifloxacin is recommended as second-line treatment in the presence of macrolide resistance mutations and failure of azithromycin therapy and first option for complicated infections (14 days)

[6]For adults and pediatric patients weighing at least 40 kg (13 to <25 Kg: 200 mg b.i.d.; 25 to <40 Kg: 400 mg b.i.d.). Common adverse reactions in healthy adult subjects (≥2%) were headache, nausea, abdominal pain, and vomiting. No dosage adjustment is required for patients with mild, moderate or severe renal impairment or patients with end-stage renal disease requiring hemodialysis

CDC, Centers for Disease Control and Prevention; FTA-ABS, fluorescent treponemal antibody absorption; i.m., intramuscular; NAATs, nucleic acid amplification tests; p.o., per os; RPR, rapid plasma regain; TOC, test of cure; TPPA, T. pallidum particle agglutination; TRUST, toluidine red unheated serum test; VDRL, Venereal Disease Research Laboratory

testing) or PCR of ulcer exudate, *condylomata* exudate or rectal biopsies [27].

First-line treatment of primary and secondary syphilis is penicillin G benzathine, 2.4 million units i.m. q.d. Second-line therapy with doxycycline or ceftriaxone can be considered (Table 2) [28].

M. genitalium

M. genitalium is a sexually transmitted pathogen that is a cause of non-chlamydial, non-gonococcal urogenital infections in men (10-35%) and genital tract infection in women, including pelvic inflammatory disease and associated female reproductive complications, such as spontaneous abortion, pre-term birth and infertility [29,30]. Proctitis when present is clinically less pronounced or asymptomatic [29,31,32].

The pathogenic role of *M. genitalium* in proctitis has been described, but not completely clearly and without a strong association [29-31,33]. Recently, an Australian study showed high rates of *M. genitalium* coinfection with *C. trachomatis* and *N. gonorrhoeae* in the rectum, with *M. genitalium* present in 13-14% of MSM [29].

There is no evidence that asymptomatic infection warrants treatment, and many patients will spontaneously clear the organism [30]. Therefore, asymptomatic screening is not recommended and testing for *M. genitalium* is only indicated in symptomatic proctitis after exclusion of other common etiologies. The detection of *M. genitalium*-specific nucleic acid in clinical specimens by NAATs is the best diagnosis method, which should be followed (if possible) with an assay for macrolide resistance mutations [34]. In *M. genitalium* infection, proctoscopy shows unspecific findings in rectal mucosae, similar to other infections (e.g., erythema, erosions and mucopurulent exudate).

Regarding therapy, only a few antimicrobial classes have activity against mycoplasma. Azithromycin has a cure rate of 85-95%; however, macrolide resistance is an urgent emerging problem worldwide [4]. The current guidelines recommend an extended course of azithromycin (500 mg on day 1, followed by 250 mg for 2-5 days) as primary choice of treatment for uncomplicated *M. genitalium* infection in the absence of macrolide resistance mutations or resistance testing [34]. Moxifloxacin is recommended as second-line treatment in case of macrolide resistance mutations or failure of azithromycin therapy, and as first option for complicated *M. genitalium* infection. There are few options for persistent *M. genitalium* infection after azithromycin and moxifloxacin (Table 2).

Pristinamycin is a streptogramin and the best evaluated third-line treatment (1 g q.i.d. for 10 days). Minocycline (100 mg b.i.d. for 14 days), or an extended doxycycline regimen, can be an alternative therapy in this scenario [4,34].

On the other hand, a resistance-guided sequential therapy is recommended if treatment is indicated before the results of microbiological investigation are available. This approach is based on doxycycline as initial empiric therapy (100 mg b.i.d. for 7 days), which reduces the organism load, followed by high-dose azithromycin (1 g on day 1, followed by 500 mg daily for 2-4 days), or moxifloxacin for macrolide resistance cases [4,34]. Two large studies achieved a microbial cure of 92-95% with resistance-guided sequential therapy supporting this strategy.

According to the European guidelines, a test of cure, 3 weeks after the completion of treatment, should be considered in all patients, given the high prevalence of resistance present either pre-treatment or developing during treatment, with the consequent risk of spread of resistance [34]. In contrast, CDC recommendations only suggest test of cure in patient with persistent symptoms and signs after treatment.

Monkeypox

Monkeypox is a zoonotic viral infection caused by an orthopoxvirus of the family Poxviridae. Until May 2022, it was an occasional, endemic disease, mainly from Central and West African countries, with small outbreaks described. Since the beginning of the recent outbreak, more than 83,500 cases have been reported worldwide. They are mainly linked to groups of MSM, suggesting an important role for sexual transmission [35].

Clinical manifestations usually appear after an incubation period of 5-24 days, characterized by biphasic pattern with a prodromal phase of fever, lethargy, myalgias, headache and lymphadenopathy, followed by skin eruption 2-4 days later. Skin lesions follow a typical pattern of evolution, starting as macules and progressing into papules, vesicles, pustules and ulcers [36,37]. New clinical presentations of monkeypox infection have been identified, including perianal lesions, severe rectal pain, proctitis, pharyngitis, and penile edema [37].

The incidence of proctitis and/or proctalgia in patients with monkeypox in different series ranged from 22-37% [34-36]. In a recent prospective observational study that included 181 patients with Monkeypox virus (MPXV) infection, 78% had lesions in the anogenital region and 43% in the oral and perioral region. About 39% of them had complications requiring treatment and 25% had proctitis, the most common complication. Patients reporting anal-receptive sex were more likely than others to have proctitis and early systemic symptoms before developing skin lesions [34].

The diagnosis of MPXV infection can be performed by PCR, with detection of MPXV DNA in the skin or an anorectal lesion. Additionally, small series showed a high detection of MPXV DNA in anorectal specimens, even in patients without rectal disease [38].

There is no specific treatment for monkeypox infections. However, monkeypox and smallpox viruses are genetically similar and consequently the antiviral drugs (e.g., tecovirimat, brincidofovir, cidofovir) and vaccines developed to protect against smallpox, may be used in severe illness or immunocompromised individuals.

Antiviral therapy is recommended for patients with or at risk for severe disease and those with infection in anatomic sites

(e.g., mouth, pharynx, anogenital area) that may be associated with severe pain or result in sequelae (e.g., scarring, strictures). Currently, tecovirimat, also known as TPOXX, is the treatment of choice for pediatric and adult MPXV infection, and the only drug authorized in Europe [39,40]. Tecovirimat inhibits the activity of a protein called VP37, found on the surface of orthopoxviruses, which is required for the formation of an infectious virus particle. The dose of tecovirimat depends on body weight (Table 2) and it is given typically for 14 days, but should be individualized based on the clinical response and tolerability [39]. Most patients with monkeypox disease will have mild and self-limited disease, with supportive care [41].

Other important issues

Physicians have a critical role to play in improving the health outcomes in MSM. Testing for other infections (HIV, hepatitis C, and HAV status) and counseling about vaccination (HAV and hepatitis B) after a diagnosis of IP are important issues to take into consideration. Also, some concerns about human papillomavirus (HPV) infection and related disorders should be considered.

HIV and hepatitis C infections

Testing for HIV infection is mandatory upon suspected diagnosis of IP [7]. The relationship between HIV status and the incidence of anorectal venereal infections is bidirectional: HIV-positive patients have a higher incidence of anorectal STIs and recurrence is more common in this subset of patients, while the inflamed mucosa in the setting of IP appears to increase HIV transmission 9-fold [42-44]. The patient should be offered treatment as soon as possible, and partners sharing risk factors with that patient should be encouraged to undergo evaluation [4]. In addition, it is important to perform serology for hepatitis C in MSM with a diagnosis of IP, as it is also considered a STI.

Hepatitis A serology and vaccination

Hepatitis A is a self-limited infection transmitted primarily by the fecal–oral route and sometimes results in epidemic outbreaks. Transmission of HAV can occur during sexual activity, probably due to fecal–oral contact. In MSM and patients living with HIV vaccination should be recommended, as they are considered risk groups for hepatitis A infection [41]. Prevaccination serologic testing for hepatitis A immunity before vaccination is not routinely recommended; however, it can be considered as a way to reduce costs.

Currently, there are 2 monovalent vaccines (Havrix® and Vaqta®), administered in a 2-dose series at 0 and 6-12 months [45]. A combined hepatitis A+B vaccine (Twinrix®) has been developed as a 3-dose series for adults aged ≥18 years at risk for hepatitis A or B virus infections, administered in a 0, 1 and 6-month schedule [45].

HPV infection and related disorders

Although HPV does not cause symptomatic inflammation or a proctitis syndrome, it is important to consider this infection, mainly in the MSM population. As a matter of fact, MSM are at high risk for HPV-related disorders such as anal warts or dysplasia. In addition, anal cancer (generally of the squamous cell type) is more common in MSM than in the general population, and the risk increases dramatically among those who have HIV [46]. Moreover, the symptoms of anal cancer can also be similar to those present in an IP, such as bleeding and tenesmus. Therefore, anal Pap testing in all MSM with anorectal symptoms should be performed, if it has not been done within the past 12 months. There are only limited data to support general screening recommendations for anal Pap testing in MSM or other populations [4].

International recommendations for HPV vaccination include all adolescents at age 11 or 12 years and catch-up vaccination through age 26 years for those not previously vaccinated. MSM adults aged 26-45 years (not previously vaccinated) should be considered for HPV vaccination and clinical decision-making involving the patient and a clinician is recommended. Providers and patients should be aware that HPV vaccination after 26 years, at the data of writing of this protocol, is not covered by the public health system, and this may also affect the decision to vaccinate.

Currently, there are 2 vaccines available: Cervarix® (targets high-risk genotypes 16 and 18) and Gardasil 9® (targets genotypes 6, 11, 16, 18, 31, 33, 45, 52 and 58), of which the latter is the more recommended. A 2-dose vaccine schedule (at 0- and 6–12-month intervals) is recommended for persons who initiate vaccination before their 15th birthday. A 3-dose vaccine schedule (at 0-, 1–2- and 6-month intervals) is recommended for immunocompromised persons, regardless the of age of initiation [47].

Differential diagnosis

The symptoms of IP, including rectal blood, mucous discharge and anorectal pain, may appear in other causes of proctitis, such as IBD. Indeed, the distinction between these diseases can be challenging in some cases, as IP and IBD share some overlapping endoscopic and histologic features [6,48]. According to symptoms, signs and physical examination, other differential diagnoses should be considered, such as traumatic proctitis due to the use of sex toys and douching, radiation proctitis, rectal malignancy, solitary rectal ulcer syndrome, diversion colitis, ischemia or Cytomegalovirus infections (particularly in severely immunocompromised patients or in the context of HIV infection with low CD4+ T-cell counts). Therefore, the differential diagnosis should be supported by a combination of clinical history and physical examination, as well as endoscopic, serologic, and microbiologic findings.

In terms of diagnosis, distinguishing between IBD and IP is the most challenging scenario. However, a prompt and correct diagnosis is crucial to ensure appropriate management and optimal outcomes for each clinical scenario.

Regarding clinical history, some authors conclude that a history of HIV-positive MSM, anal pain and anal discharge are discriminating features of infectious colitis [48]. If patients complain of abdominal cramping and diarrhea, it is important to distinguish proctitis from proctocolitis and enteritis. These infections, caused by *Campylobacter*, *Shigella*, *Salmonella*, *Giardia,* and *Entamoeba histolytica*, are not considered STIs, but sexual transmission can occur in MSM populations. Considering the histological findings, intense lymphohistiocytic infiltrate with prominent plasma cells, lymphoid aggregates and only minimal active chronic crypt centric damage, are more suggestive of IP than IBD [48].

Considering that both conditions can coexist and in order to reduce the cases of IP incorrectly diagnosed as IBD, some authors recommend HIV testing for every MSM patient with IBD suspicion. Moreover, all patients with IBD in the colorectal tract, even confirmed by endoscopy and histopathology, should be tested for STIs using molecular and serological methods [49]. Patients initially diagnosed with IBD not responding to standard therapy as expected, should also be tested for STIs.

Concluding remarks

The incidence of STIs is rising, especially in high-risk groups, such as patients living with HIV, MSM, and people with multiple sexual partners. The correct identification and treatment of these patients is important, not only for the individual patient, but also in terms of public health. A diligent diagnostic assessment is key for an efficient therapeutic approach.

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