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REVIEW

Infectious Proctitis: When to Suspect It Is Not Inflammatory Bowel Disease

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Abstract
Background Proctitis is a common problem and is most frequently associated with inflammatory bowel diseases. However, the incidence of infectious proctitis appears to be rising, especially in men who have sex with men. This may be due to the rise of people participating in receptive anal sex as well as the increase in sexually transmitted infections. The most frequently reported pathogens include *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Treponema pallidum*, and herpes simplex.
Diagnosis Symptoms of infectious proctitis can include rectal blood and mucous discharge, anorectal pain, ulcers, and occasionally lymphadenopathy and fever. History and physical examination are crucial in establishing a diagnosis, supported by endoscopy, histology, serology, culture and PCR.
Treatment Treatment with antibiotics or antivirals is usually initiated, either empirically or after establishing a diagnosis. Co-infections, HIV testing, and treatment of sexual partners should always be considered.

Keywords Chlamydia · Gonorrhea · Herpes simplex · Infectious proctitis · Lymphogranuloma venereum · Rectum · Syphilis

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Introduction

Proctitis is an inflammation of the lining of the rectum and is restricted to the distal 15 cm of the colon. Most commonly, proctitis will be associated with the idiopathic chronic inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis. In ulcerative colitis, the extent of large intestinal involvement varies, but approximately 30% of patients have inflammation involving the rectum only, termed "ulcerative proctitis". This condition often responds well to mesalamine suppositories. Crohn's disease of the rectum is associated with a more aggressive course of disease and often requires systemic immune-based therapy.

It is important for the clinician to realize that proctitis is not always associated with IBD. Other non-infectious causes of proctitis include radiation-associated proctitis or proctopathy, diversion colitis [1] and ischemia [2]. Infectious causes of proctitis include pathogens that usually cause a more extensive colitis rather than an isolated proctitis. Examples of these pathogens include *Escherichia coli, Shigella, Campylobacter,* and *Clostridium difficile*. These pathogens will not be discussed in the current review given the scope of this paper.

When should a physician be aware of isolated infectious proctitis? Frequently, the cause will be sexually transmitted and a careful sexual history can reveal important information that can already lead to a suggested diagnosis. Additionally, a recent traveling history, and a history of fever and diarrhea can provide clues suggesting an infectious proctitis. Unfortunately, symptoms can also be non-specific or even absent. For example, 11% of the rectal samples tested positive for either gonorrhea or Chlamydia in asymptomatic men who have sex with men, also referred to as "MSM" [3]. Finally, infectious proctitis should also

Table 1 Infectious proctitis

Cause	Diagnosis	First line treatment [4]
HSV-2	NAAT, viral culture	Symptomatic, or acyclovir 400 mg p.o. 3 times daily for 10 days
LGV	NAAT, immunofluorescence, culture	Doxycycline 100 mg p.o. twice daily for 3 weeks
Gonorrhea	Gram stain, NAAT, culture	Ceftriaxon 250 mg i.m. or cefixime 400 mg p.o.
Non-LGV Chlamydia	NAAT, culture	Doxycycline 100 mg p.o. twice daily for 1 week
Syphilis	Dark field microscopy, serology (VDRL, RPR)	2.4 million units of Penicillin G benzathine i.m.
Amoebiasis	Stool microscopy	Metronidazole 3 × 500 mg p.o. for 5–10 days

Causes, diagnostics and treatment

HSV-2 herpes simplex virus type 2, *LGV* lymphogranuloma venereum, *NAAT* nucleic acid amplification tests, *RPR* rapid plasma reagin, *VDRL* venereal disease research laboratory

be considered in patients who were initially diagnosed with IBD but are not responding to standard therapy as expected. If there is a high clinical suspicion for an infectious cause based on history and physical exam, empirical treatment should be initiated while awaiting the test results [4].

The most frequent causes for infectious proctitis are gonorrhea (30%), Chlamydia (19%), HSV-2 (16%), and syphilis (2%) (Table 1). Importantly, no identifiable infectious source is found in 45% of cases [5]. Co-infections are not uncommon, and 10% of the patients with infectious proctitis tested positive for two or more pathogens [5]. When proctitis is diagnosed, HIV testing is mandatory, since proctitis is associated with HIV infection. Additionally, the inflamed rectum increases the transmission of HIV by up to ninefold [6, 7].

Symptoms, Diagnostics, and Treatment Per Cause

Herpes Simplex

The herpes simplex virus (HSV) consists of two types, HSV-1 and HSV-2. Both types are DNA viruses and members of the herpes family. Although, there is significant overlap, HSV-1 is generally associated with labial, oral, and ocular lesions, and HSV-2 accounts for most anogenital lesions. HSV-2 is transmitted by anal receptive intercourse and risk factors for infection include female sex, older age, less education, poverty, cocaine use, and a greater lifetime number of sexual partners [8]. The seroprevalence of HSV-2 in the United States was 16.2% from 2005 to 2008 according to the US Centers for Disease Control and Prevention (CDC). Of importance, 81% of patients who tested positive were not aware of this diagnosis and this finding has obvious implications for transmission to others [4, 9]. In a retrospective chart review, Davis et al. [10] identified 26 MSM with a suspected diagnosis of proctitis and 29% were diagnosed with herpes simplex proctitis.

Symptoms of HSV-proctitis start 1–3 weeks after exposure and include severe anorectal pain, tenesmus, constipation, perianal ulcerations, fever, difficulty in urinating, inguinal lymphadenopathy and the presence of diffuse ulcerative or discrete vesicular or pustular lesions in the distal 5 cm of the rectum [11]. Crusting of the lesions is followed by healing after 2 weeks. After the start of antibody production to HSV-2, the virus becomes latent. Although, latent HSV-2 can be reactivated leading to a recurrence of proctitis, subsequent episodes of proctitis usually follow a milder course. Most HSV-proctitides are indeed primary infections. This was demonstrated in 23 patients with HSV-proctitis, and 85% showed serologic signs of a primary infection [11].

Endoscopy in HSV proctitis may reveal vesicles, mucopurulent exudates and ulcers, and also allows for obtaining rectal tissue for smear and histology. Historically, the diagnosis of HSV was based on a Tzanck smear of samples from an ulcer base. A positive smear would reveal multinucleated giant cells or intranuclear inclusion bodies. However, the sensitivity and specificity of this test are limited. Histopathology on mucosal biopsies can confirm the findings of the Tzanck smear. In current practice, PCR assays for HSV DNA and viral cultures are commonly used, with PCR demonstrating the best sensitivity. Alternatively, serology can be used. Current HSV serologic assays are based on the HSV-specific glycoprotein G2 (HSV-2) and glycoprotein G1 (HSV-1) and can accurately distinguish HSV-1 from HSV-2.

Treatment of HSV-associated proctitis is mainly symptomatic. Oral analgesics can be used for pain relief. Episodic antiviral therapy can be considered as well, but it is important to realize that this will not eradicate HSV or decrease the risk of recurrence. Furthermore, patients without immune deficiencies will generally follow a self-limiting course of disease. HIV-infected individuals might benefit from antiviral therapy, as it can shorten the duration of symptoms as well as the period of viral shedding [12]. CDC recommended treatment regimens are mainly aimed at genital herpes and are not specifically designed for proctitis. These regimens include 7–10 days schedules with either acyclovir 400 mg orally 3 times daily, or famciclovir 250 mg orally 3 times daily, or valacyclovir 1 g orally twice daily [4]. Daily antiviral suppressive therapy should be considered in immune compromised patients, since

these patients are at increased risk for reactivation and shedding of virus [12]. This strategy can decrease the number of recurrences as well as transmission. Specific counseling for HSV should cover the topics of recurrent outbreaks, asymptomatic shedding, and risk for other sexually transmitted infections if safe sex practices are not followed. An HIV test is mandatory in case of anorectal herpes infection given the significant association between the two infections [13]. It has been hypothesized that antiviral treatment for HSV-2 can decrease rates of HIV. Unfortunately, acyclovir treatment did not decrease the acquisition of HIV in HSV-2 infected women and MSM, although it did decrease the occurrence of genital ulcers by 73% [14].

Lymphogranuloma Venereum (LGV)

Since 2003, the incidence of LGV has shown a remarkable increase in the Western world, especially in MSM [15–17]. *Chlamydia trachomatis* serotypes L1–L3 are the responsible pathogens for LGV and especially serotype L2 has been implicated in the recent outbreak [18]. LGV patients are frequently HIV-positive MSM with proctitis and approximately 50% carry other sexually transmitted infections (STIs) as well [15, 19]. The significant association between HIV and LGV was underscored in a recent meta-analysis. This report included 13 studies and the prevalence of HIV among LGV cases varied from 67 to 100% [20].

The first symptoms of LGV usually include anal ulceration at the site of inoculation. However, if this stays unnoticed, patients may then present (often after resolution of the initial ulcer) with painful inguinal and/or femoral lymphadenopathy, also referred to as "buboes". Of importance, 25% of the patients with LGV will not develop lymphadenopathy and during the recent outbreak of LGV, most patients had almost exclusively rectal symptoms rather than the classical bubonic form. This observation was confirmed in a study that enrolled 263 UK patients with a diagnosis of LGV where 96% of patients suffered from proctitis [21]. The symptoms of this infection include mucous and bloody rectal discharge, anal pain, constipation, fever, and tenesmus. Longstanding LGV can lead to granulomas, colorectal fistulae and fibrotic strictures, which can create histological, endoscopic and radiological views that can mimic Crohn's disease [22, 23]. This was illustrated in a recent report that described 12 patients with an initial diagnosis of Crohn's disease, but this diagnosis was subsequently reversed to LGV in all patients [24].

Currently, the gold standard for the diagnosis of LGV is nucleic acid amplification tests (NAAT). Alternatively, serology, culture or immunofluorescence of rectal swabs or lymph node aspirate can be considered. Additional genotyping might be required to distinguish LGV from non-LGV; this distinction has implications for the duration of treatment differs as outlined below.

Treatment is often started empirically, consisting of a course of doxycycline 100 mg twice daily for 3 weeks. Alternatively, erythromycin 500 mg orally four times daily for 3 weeks can be considered; this option is recommended for pregnant women [4]. Asymptomatic sexual partners should also be treated with a course of doxycycline, 100 mg twice daily for 1 week. The length of treatment for LGV was initially established empirically, but recently it was demonstrated that rectal *Chlamydia* RNA persisted for not more than 16 days during treatment with doxycycline [25]. This finding supports the current recommendation for a 3-week regime of doxycycline.

Non-LGV Chlamydia

Chlamydia trachomatis is the most common STI in the United States. *Chlamydia* is an intracellular bacterium and serovars A–K are responsible for the non-LGV infections. A rectal infection occurs after anal receptive intercourse and symptoms usually start 7–10 days after infection. In case of proctitis, patients can complain of anal pain, tenesmus, blood and mucous discharge, and sometimes fever. However, the infection can also remain asymptomatic in up to 50% of infected patients [26].

Sigmoidoscopy can reveal nonspecific findings like friable erythematous mucosa with ulcerations, but biopsies can reveal granulomas which may make the distinction between *Chlamydia* proctitis and Crohn's disease difficult. The diagnosis is usually based on culture or NAAT on rectal swabs.

The treatment consists of doxycycline, 100 mg twice daily for 1 week. Alternatively, a one-time dose of 1 g of oral azithromycin can be considered, both options show comparable efficacy [27]. Due to the frequent co-infection with *Neisseria gonorrhoeae*, empiric treatment for gonorrhea is recommended in patients with non-LGV, as well as the treatment of sexual partners.

Syphilis

Syphilis is caused by the spirochete *Treponema pallidum* and can be contracted during anal receptive intercourse. Anal ulcers can occur after 2–6 weeks. The typical appearance is a single painless anal ulcer (chancre), but symptoms like discharge, bleeding, significant pain and itching can occur as well. Ulcers are typically located at the anal verge but can also be located more proximally in the rectum.

In untreated patients, secondary syphilis can occur 6–8 weeks after the healing of the initial ulcer. This

secondary stage is characterized by a widespread maculopapular rash, classically located at the palms of hands and feet. Genital and anorectal condylomata lata can be recognized as whitish warty lesions preferentially located near the initial chancre. Systemic symptoms like fever, night sweats and weight loss are not uncommon.

Treponema pallidum can not be cultured, but scrapings of affected tissue can reveal spirochetes with the use of dark-field examination. Non-treponemal serologic tests are most commonly used to establish a diagnosis. Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin (RPR) tests are used to diagnose an initial infection and to monitor response to therapy. A fourfold change in titer should be detected in order to demonstrate a clinically significant difference. Therefore, sequential serologic tests in individual patients should be performed by using the same testing method. Specific treponemal antigen tests, like the fluorescent treponemal antibody absorption test (FTA-ABS), are confirmatory and are required to identify false-positive VDRL or RPR tests. FTA-ABS will stay positive in most patients after the first infection.

Treatment of the first two stages of syphilis consists of a single intramuscular injection with 2.4 million units of Penicillin G benzathine. In case of penicillin allergy, a 2-week regimen of doxycycline, 100 mg twice daily, can be considered. Follow-up by VDRL or RPR in order to monitor response to treatment should take place every 3 months for the first year. Repeat syphilis infections are not uncommon, and 6.7% of MSM with an initial diagnosis of rectal syphilis experienced a recurrence within a year and the chance of a recurrence is increased fivefold if an HIV co-infection is present [28].

Gonococcal Proctitis

Gonorrhea is the second most commonly reported bacterial STI. *N. gonorrhoeae* is a gram-negative diplococcus and can cause gonococcal proctitis. It is contracted by anal receptive intercourse and the infection is most common in females and MSM. After 5–7 days of incubation, patients usually report tenesmus, mucopurulent discharge, pruritus and pain.

The evaluation of gonococcal proctitis includes a gram stain of mucosal biopsies or discharge which can demonstrate intracellular gram-negative diplococcus. A culture is the preferred method of diagnosis, since this will also provide information about the antibiotic susceptibility. Alternatively, NAAT can confirm the presence of the gonococci (Table 1).

Treatment consists of a single intramuscular dose of ceftriaxone (250 mg), or alternatively, cefixime (400 mg p.o. single dose). Fluoroquinolones are not recommended for the treatment of gonorrhea given the antibiotic resistance [4]. This resistance is common in parts of Europe and South–East Asia and is increasing in the United States. Of concern, resistance of *N. gonorrhoeae* to oral cephalosporin and azithromycin has been reported recently as well. However, this is not the case for i.m. ceftriaxone [29]. Recent sexual partners should be treated as well. Chlamydial co-infection is common; therefore empiric treatment for Chlamydia should also be initiated [30, 31]. Patients should be retested in case of persistent symptoms after therapy for gonorrhea, since recurrence is not uncommon.

Conclusions

The rising incidence of infectious proctitides, especially in MSM, warrants physicians to consider infectious causes when they diagnose proctitis. The symptoms of infectious proctitis may mimic IBD, and complicated LGV is often mistaken for Crohn's disease. History and physical examination should assess sexual habits, including receptive anal intercourse, as well as anogenital lesions and lymphadenopathy. If the diagnosis is clear based on these findings, empirical treatment should be started. Meanwhile, diagnostics like endoscopy, culture and PCR on rectal swabs and serology can be utilized to further establish a cause. Treatment usually consists of antibiotics or antivirals. Special considerations in these matters are allergies, pregnancy and antibiotic susceptibility. The long-term prognosis of infectious proctitis is excellent but can be affected by patient and doctors delay, especially in case of LGV. HIV testing is mandatory and co-infections are not uncommon and should always be considered.

References

1. Thorsen AJ. Noninfectious colitides: collagenous colitis, lymphocytic colitis, diversion colitis, and chemically induced colitis. *Clin Colon Rectal Surg*. 2007;20:47–57.
2. Sharif S, Hyser M. Ischemic proctitis: case series and literature review. *Am Surg*. 2006;72:1241–1247.
3. Mimiaga MJ, Mayer KH, Reisner SL, et al. Asymptomatic gonorrhea and chlamydial infections detected by nucleic acid amplification tests among Boston area men who have sex with men. *Sex Transm Dis*. 2008;35:495–498.
4. Workowski KA, Berman S. Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep*. 2010;59:1–110.
5. Klausner JD, Kohn R, Kent C. Etiology of clinical proctitis among men who have sex with men. *Clin Infect Dis*. 2004;38:300–302.
6. Craib KJ, Meddings DR, Strathdee SA, et al. Rectal gonorrhoea as an independent risk factor for HIV infection in a cohort of homosexual men. *Genitourin Med*. 1995;71:150–154.
7. Schwarcz SK, Kellogg TA, McFarland W, et al. Characterization of sexually transmitted disease clinic patients with recent human immunodeficiency virus infection. *J Infect Dis*. 2002;186:1019–1022.

8. Fleming DT, McQuillan GM, Johnson RE, et al. Herpes simplex virus type 2 in the United States, 1976–1994. *N Engl J Med*. 1997;337:1105–1111.
9. Xu F, Sternberg MR, Gottlieb SL, Berman SM, Markowitz LE, Forhan SE, Taylor LD. Seroprevalence of herpes simplex virus type 2 among persons aged 14–49 years—United States, 2005–2008. Centers for Disease Control and Prevention (CDC), Morbidity and Mortality Weekly Report. 2010;59: 456–459.
10. Davis TW, Goldstone SE. Sexually transmitted infections as a cause of proctitis in men who have sex with men. *Dis Colon Rectum*. 2009;52:507–512.
11. Goodell SE, Quinn TC, Mkrtichian E, Schuffler MD, Holmes KK, Corey L. Herpes simplex virus proctitis in homosexual men. Clinical, sigmoidoscopic, and histopathological features. *N Engl J Med*. 1983;308:868–871.
12. Lavery EA, Coyle WJ. Herpes simplex virus and the alimentary tract. *Curr Gastroenterol Rep*. 2008;10:417–423.
13. Stamm WE, Handsfield HH, Rompalo AM, Ashley RL, Roberts PL, Corey L. The association between genital ulcer disease and acquisition of HIV infection in homosexual men. *JAMA*. 1988;260:1429–1433.
14. Celum C, Wald A, Lingappa JR, et al. Acyclovir and transmission of HIV-1 from persons infected with HIV-1 and HSV-2. *N Engl J Med*. 2010;362:427–439.
15. White JA. Manifestations and management of lymphogranuloma venereum. *Curr Opin Infect Dis*. 2009;22:57–66.
16. Vall-Mayans M, Caballero E, Sanz B. The emergence of lymphogranuloma venereum in Europe. *Lancet*. 2009;374:356.
17. Nieuwenhuis RF, Ossewaarde JM, Gotz HM, et al. Resurgence of lymphogranuloma venereum in western Europe: an outbreak of *Chlamydia trachomatis* serovar l2 proctitis in the Netherlands among men who have sex with men. *Clin Infect Dis*. 2004;39: 996–1003.
18. Mabey D, Peeling RW. Lymphogranuloma venereum. *Sex Transm Infect*. 2002;78:90–92.
19. Martin-Iguacel R, Llibre JM, Nielsen H, et al. Lymphogranuloma venereum proctocolitis: a silent endemic disease in men who have sex with men in industrialised countries. *Eur J Clin Microbiol Infect Dis*. 2010;29:917–925.
20. Ronn MM, Ward H. The association between lymphogranuloma venereum and HIV among men who have sex with men: systematic review and meta-analysis. *BMC Infect Dis*. 2011;11:70.
21. Ward H, Martin I, Macdonald N, et al. Lymphogranuloma venereum in the United Kingdom. *Clin Infect Dis*. 2007;44:26–32.
22. Ahdoot A, Kotler DP, Suh JS, Kutler C, Flamholz R. Lymphogranuloma venereum in human immunodeficiency virus-infected individuals in New York City. *J Clin Gastroenterol*. 2006;40: 385–390.
23. Hoie S, Knudsen LS, Gerstoft J. Lymphogranuloma venereum proctitis: a differential diagnose to inflammatory bowel disease. *Scand J Gastroenterol*. 2011;46:503–510.
24. Soni S, Srirajaskanthan R, Lucas SB, Alexander S, Wong T, White JA. Lymphogranuloma venereum proctitis masquerading as inflammatory bowel disease in 12 homosexual men. *Aliment Pharmacol Ther*. 2010;32:59–65.
25. de Vries HJ, Smelov V, Middelburg JG, Pleijster J, Speksnijder AG, Morre SA. Delayed microbial cure of lymphogranuloma venereum proctitis with doxycycline treatment. *Clin Infect Dis*. 2009;48:e53–e56.
26. Miller WC, Zenilman JM. Epidemiology of chlamydial infection, gonorrhea, and trichomoniasis in the United States-2005. *Infect Dis Clin North Am*. 2005;19:281–296.
27. Lau CY, Qureshi AK. Azithromycin versus doxycycline for genital chlamydial infections: a meta-analysis of randomized clinical trials. *Sex Transm Dis*. 2002;29:497–502.
28. Phipps W, Kent CK, Kohn R, Klausner JD. Risk factors for repeat syphilis in men who have sex with men, San Francisco. *Sex Transm Dis*. 2009;36:331–335.
29. Deguchi T, Nakane K, Yasuda M, Maeda S. Emergence and spread of drug resistant *Neisseria gonorrhoeae*. *J Urol*. 2010;184: 851–858. Quiz 1235.
30. Lyss SB, Kamb ML, Peterman TA, et al. *Chlamydia trachomatis* among patients infected with and treated for *Neisseria gonorrhoeae* in sexually transmitted disease clinics in the United States. *Ann Intern Med*. 2003;139:178–185.
31. McMillan A, Young H. Clinical correlates of rectal gonococcal and chlamydial infections. *Int J STD AIDS*. 2006;17:387–390.