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CLINICAL MANAGEMENT OF SEXUALLY TRANSMITTED INFECTIONS AFFECTING THE ANORECTAL REGION

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INTRODUCTION

Intestinal infections can commonly occur as a result of sexual exposure involving anus, mouth or both. When considering "anal sex", different sexual activities can be taken into account, not limited to classical penile penetrative sex. Direct oral-anal contact (anilingus, colloquially referred as to "rimming") or sharing sex toys inserted in both genitalia and anus, sharing equipment for anorectal douching or oral ingestion of some pathogens transmitted during oral-genital sex after rectal intercourse are a well-known transmission route of sexually transmitted infection (STI) or intestinal infections. Frequency of anal interactions may vary, and it is inaccurately assumed that they reach a maximum among men who have sex with men (MsM). Causative pathogens span from classical enteric bacteria and protozoa, including *Shigella spp, Salmonella spp, Campylobacter spp, Giardia lamblia,* and *Entamoeba histolytica,* along with traditional sexually transmitted pathogens, such as *Neisseria gonorrhoeae, Chlamydia trachomatis, Treponema pallidum,* Herpes simplex virus, and Human papillomavirus. It is also well known that systemic infections like HIV and hepatitis A can be acquired by anal intercourse or anilingus. Consequently, intestinal infections represent a range of disorders responsible for intestinal diseases in men and women who engage in anal, oral , or both, sexual activity as well as a challenge to the clinicians and the surgeons whose goal is to provide adequate diagnostic and therapeutic care for these patients.

The spectrum of disease associated with each of these infections depends on a variety of factors, including the type of sexual intercourse, the number of partners and contacts, the immunologic competence of the individual, the pathogenicity of the agent, and the duration of the infection. Some of these infections induce a chronic asymptomatic carrier state that represents the human reservoir for most of these infections. The persistent, unrecognized transmission of intestinal infections from an asymptomatic subject to other subjects via anal intercourse or oral-anal sex in part explains the continued spread of these infections with clusters often geographically or socially limited. Furthermore, secondary transmission from higher risk groups via other traditional means of transmission, such as food contamination, extend the issue of intestinal infections to the entire community. In this short paper, I will focus predominately on infections acquired by anal sex.

Due to the long list of possible etiologies of intestinal symptoms, the approach to a sexually active patients with lower gastrointestinal symptoms must be comprehensive, including a full microbiologic evaluation based on symptoms and signs of disease; this approach should not be ignored among women and men who decline anal sexual activity, considering to investigate in a sensitive and respectful manner the patient's sexual history. It also should be noted that sexual behavior is a comprehensive human activity, so that pathogens can be spread to

other anatomical orifices in addition to the anus: these areas must not be forgotten in the clinical examination.
Infectious disorders of the lower digestive systems can be classically classified according the main involved tract: enteritis (inflammatory illness of the small intestine) proctitis (inflammation limited to the lower 10 cm of the rectum) or proctocolitis (inflammation present throughout segments of the colon and rectum) and perianal disease, (disorders involving the anus and perianal area). A list of infectious agents that are frequently associated with these intestinal syndromes is given in **Table 1**. Note that this list does not fully itemizes HPV related disease: these conditions are well known by proctologists and deserve little medical options other than surgical approach. Therefore, anal warts, as well as HIV and Hepatitis A, deserve a separate description.

Sexually Transmitted Pathogens determining Perianal Disease, Proctitis, Proctocolitis, Enteritis and systemic diseases

Bacteria	***Clinical Syndrome***	***Viruses***	***Clinical Syndrome***	***Protozoa and Helminthes***	***Clinical Syndrome***
Neisseria gonorrhoeae	Proctitis	Herpes simplex virus (HSV)	Perianal Diseases Proctitis	*Giardia lamblia*	Enteritis
Treponema pallidum	Perianal Diseases Proctitis	Human papillomavirus (HPV	Various perianal and anal canal diseases	*Entamoeba histolytica*	Proctocolitis
Chlamydia trachomatis	Proctitis	Cytomegalovirus (CMV)	Proctocolitis	*Dientamoeba fragilis*	Proctocolitis
Chlamydia trachomatis LGV serovars	Perianal Diseases Proctitis	Adenovirus	Enteritis	*Cystoisospora belli*	Enteritis
Klebsiella granulomatis	Perianal Diseases Proctitis	HAV & HBV	Hepatitis	*Cryptosporidia* spp	Proctocolitis Enteritis
Haemophilus ducreyi	Perianal diseases, Proctitis	HIV	AIDS and HIV related conditions	*Microsporidia spp*	Enteritis
Campylobacter spp	Proctocolitis			*Enterobious v.*	Appendicitis-pruritus ani
Salmonella spp.	Proctocolitis			*Strongyloides s.*	Enteritis
Shigella spp.	Proctocolitis				
Yersinia spp	Enteritis				

EPIDEMIOLOGICAL ASPECTS

Very few studies have been conducted on the prevalence of anal sex among humans. According to Halperin and coll. (1999), heterosexual women engage in unprotected receptive anal intercourse seven times more than MsM: this figure is far beyond then generally thought. More recent works confirm that American adult women report to engage in unprotected anal sex in proportion varying from 10% up to 43%. Adolescents also engage in anal sex: however, the prevalence of anal sex in this setting is not definite yet. Any kind of sexual contact (penile insertive intercourse, oral-anal sex, finger-anal sex, sharing sex toys) can be associated with intestinal infection. Perineal contamination by cervical-vaginal secretion is also a route of local transmission. Sexual transmission of enteric pathogens during anal sex was first suggested in the Sixties when several cases

of enteric protozoan infection were described among MsM in New York City. In the following years a number of epidemiological reports described enteric infections caused by fecal contamination that might occur during anilingus or fellatio following anal intercourse in MsM residing in the United States, Great Britain, Canada, and Europe. Anorectal sexually transmitted infections in men have long been traditionally known to be caused by rectal intercourse with individuals who harbor urethral infection. The role of fomites in transmission, which may occur with use of shared unsterile equipment for rectal douching or colonic stimulation, remains unknown. The role of receptive anal intercourse among women in the transmission of HIV virus is not fully documented as well as among MsM. And again, very little is known about the other rectal STIs. However, it should be remembered that anal intercourse must be considered a high risk practice for HIV in any individual. Since the majority of studies have been carried out amongst MsM, we can assume that the risk of acquiring STI through anal sex in women might be similar to the risk in MsM as a prudential measure. Multiple pathogens may be present in up to a quarter of the symptomatic patients. Infections can be present along with a wide range of masking anorectal conditions like fissures, fistulae, perirectal abscesses, ulcerations and several dermatological conditions. Overall, the prevalence of anorectal infection among symptomatic sexually anal active people may range from 20% up to 95% according to several studies. Many factors are responsible for the high prevalence rates of enteric infections in MsM, perhaps the better studied vulnerable population from this point of view. The changing pattern of human relationships, along with the increase of promiscuity and anonymity of sexual contacts, constitute significant risk factors that expose men (and women as well) to repetitive infections with enteric pathogens. Asymptomatic carriage of intestinal infection is another common problem that hinders public health efforts to control these infections. Furthermore, failure of physicians to recognize patients at risk or their possibility of harboring intestinal pathogens is one of the most important factor responsible for the continued transmission of these infections. This is particularly amplified in countries where the cultural atmosphere tends to ignore some aspects of human sexuality that are considered improper or morally charged with prejudice. Thus, physicians who do not obtain a sexual history or who are reluctant to perform an anorectal examination including anoscopy, will frequently fail to detect a sexually transmitted infection. Patients also could be reluctant to disclose their intimate behaviors. As a consequence, with these limitations, a thorough sexual history and extensive physical examination are mandatory in all sexually active patients presenting anal complaint, regardless of age, sex and appearance!

CLINICAL SYNDROMES

1- PROCTITIS

Anorectal Gonorrhea

Infection of the rectum with *N. gonorrhoeae* may result in either symptomatic or asymptomatic disease. The prevalence of rectal infection ranges between 6% and 45% among MsM men attending gay's venues like saunas or sexually transmitted disease clinics. Rates among women range from 26% to 63%. However, it should be remembered that rectal colonization can occur as a result of spread of vaginal secretion in women with primary cervical infection. Asymptomatic infection of the rectum constitutes a major reservoir of gonococcal infection in MsM.
Anorectal symptoms are usually mild and include constipation, anorectal discomfort or itching, tenesmus, and mucopurulent discharge. Mild bleeding occasionally occurs. Co-infection with other pathogens is common so that, signs and symptoms might be amplified by other more severe causes (herpes e.g.). On anoscopy, the rectal mucosa may appear completely normal or erythematosus with mucopurulent and/or small ulcerations at the anorectal junction

close to the columns of Morgagni. Histological findings on rectal biopsy are often unspecific and show only mild inflammation. Complications such as fistulae, perirectal abscess, rectal stricture, and disseminated gonococcal infections have occasionally been reported. Presumptive diagnosis is simply made by swabbing the distal rectum mucosa and rolling the swab on a slide: Gram stain confirms the presence or absence of leukocytes and intracellular gram-negative diplococci. Among patients with anorectal symptoms, the anoscope should be used to examine the rectum and to obtain exudates for culture on selective media. Nowadays, more modern molecular techniques as nucleic acid amplification techniques (NAAT) are the tests of choice for the detection of gonococcal infections.These tests can be performed in several settings (public and private practices) thanks to limited storage and management requirements. Treatment of gonococcal infection of the rectum consists of antibiotic listed in **table 2**.

Anorectal Herpes

Anorectal Herpes simplex virus infection is a very frequent cause of proctitis among MsM. The prevalence of anal herpes may vary from 20% up to 30% of MsM with anorectal symptoms. Data on women are very limited. Anorectal herpes is usually acquired by anal intercourse, although oral-anal contact with an individual with oral herpes could lead to anorectal infection. In the recent years the frequency of HSV type I over type II is significantly increased.
Herpes infection may involve the perianal area, anal canal, and/or rectum. Symptoms are quite prominent in most cases and include anal pain, constipation, rectal discharge, hematochezia, fever, and seldom neurological symptoms. Other findings that are significantly more frequent in men with HSV proctitis include perianal ulcerations, inguinal adenopathy (57%), fever (48%), difficulty in urinating (48%), sacral paresthesia (26%), and the presence of diffuse ulcerative, discrete vesicular or pustular lesions in the distal 5 cm of the rectum (50%). The clinical course of first anorectal herpes episode is usually self-limited, resolving in 2-3 weeks. Recurrences are frequently seen but tend to be less severe compared to the initial episode.
Diagnosis is based on the clinical history and the appearance of herpetic vesicles or ulcerations confirmed by the recovery of herpes on viral culture or by specific PCR testing. Histological examination of rectal biopsies frequently reveals intranuclear inclusion bodies, perivascular mononuclear cell infiltrates, and focal ulcerative changes. Diagnosis must not rely on serology only: paired sera can demonstrate seroconversion by a fourfold or greater rise in antibody titer, but their clinical usefulness is nowadays very limited.
Treatment includes analgesics and sitz baths; the use of oral acyclovir, or its derivatives, is effective in shortening the duration of symptoms and viral shedding of anorectal herpes.
Progressive mucocutaneous herpes involving the anorectal area has been described in patients with HIV/AIDS. These infections cause severe progressive large destructive ulcerations, unless antiviral intervention is undertaken. Mucocutaneous herpes in AIDS patients will respond to acyclovir, but recurrences are frequently experienced once therapy has stopped. Thus, it is recommended that for HIV/AIDS patients, intravenous acyclovir should be administered during the acute episode. The patient should then be placed on oral acyclovir for up to 6 months for suppression of recurrences.

***Chlamydia trachomatis* Proctitis**

Gastrointestinal infection with C. *trachomatis* has been reported with both the lymphogranuloma venereum (LGV) serotypes and the non-LGV serotypes. Prevalence rates of 5% to 15% have been reported for anorectal chlamydial infection in MsM, and up to 30% in heterosexual women. *Chlamydia* proctitis with non-LGV serotypes is nearly clinically identical to the picture described for N. *gonorrhoeae* infection. The infection is usually asymptomatic or may induce mild symptoms, including anorectal discharge, tenesmus, and anorectal discomfort. In symptomatic individuals, anoscopy and/or sigmoidoscopy may be completely normal or reveals mild inflammation with small erosions or follicles in the lower 10 cm of the rectum.
In contrast, LGV infections of the rectum are frequently invasive diseases and induce a severe proctitis and proctocolitis. The deep

rectal involvement explains severe anorectal pain, bloody mucopurulent discharge, tenesmus, and occasionally diarrhea or constipation. Inguinal adenopathy is very common. Systemic symptoms (general malaise, fever, muscle pain) are also frequent.
Anoscopy and sigmoidoscopy reveal diffuse friability of the mucosa with aphtous ulcerations of the rectum, scattered pseudo-polypoid areas and bleeding surfaces, which occasionally extends to the descending colon. Strictures and fistulae may become prominent in chronic cases and may easily be misdiagnosed as inflammatory bowel disease, as well as rectal cancer. Histological picture shows diffuse inflammation with cryptitis, giant cells, and granulomas, similar to the histopathological appearance of Crohn's disease or IBD. Modern diagnosis is based on NAAT for the detection of C. trachomatis in the rectum. Serology sometimes can be used as a surrogate in the diagnosis of LGV infection. Treatment consists of antibiotic up to 3 weeks for LGV infections, shorter course for non-LGV serotypes. Patients should be followed carefully with repeated anoscopies ad sigmoidoscopies, particularly when the differential diagnosis between LGV and inflammatory bowel disease is uncertain.

Anorectal Syphilis

Infection of the anorectal area by *Treponema pallidum* is perhaps one of the most frequently misdiagnosed lesions in MsM. Anorectal syphilis usually presents as a painless indurated lesion (“chancre”) approximately 2 up to 12 weeks after sexual exposure by contact. Symptoms are usually absent during the primary stage of anorectal syphilis; when present minor anal pain or discomfort, constipation, rectal bleeding, and occasionally rectal discharge could be referred. Primary anorectal syphilis may appear as single or multiple perianal ulcers in the anal canal or rectum. Typically, anal chancres are undetected by the physician due to failure to examine the anal area; alternatively, they are misdiagnosed as traumatic lesions, fissures, or anal herpes. If undiagnosed, the primary chancre disappears, and secondary syphilis may become manifest in the perianal areas as raised wet patches, or discrete polyps, smooth lobulated masses, or rectal mucosal ulcerations. Perirectal and digital rectal examination, along with anoscopy, may raise the clinical suspicion and suggest the correct diagnosis when considering sexual habits of the patients and the local epidemiological data. Detection of motile treponemes by dark-field examination is not useful for the evaluation of perianal and anal lesions since nonpathogenic treponemes may be present and are difficult to differentiate from *T. pallidum.* Today the detection of Treponema by molecular techniques (PCR) is the mainstay of direct diagnosis in the rectum. Biopsies of any rectal lesions or masses should be processed for silver staining or immunofluorescence using anti-*T.pallidum* antisera. Diagnosis of anorectal syphilis is confirmed by serological test (both treponemal and non treponemal tests). The recommended treatment of syphilis is still based on intramuscular benzathine penicillin. Careful serologic follow-up and re-examination of intestinal infections at regular intervals (1-3 and 6 months) is necessary to document eradication of infection.

Condylomata Acuminata

Anal warts are common in individuals who practice anal intercourse. Prevalence among MsM seen by proctologists may be up 50%. These lesions are caused by Human papillomaviruses, which are easily transmitted from person to person, and are recognized as clustering raised pink to brown papules. Perianal itching or anorectal discomfort may be associated with the presence of anal warts; more frequently they are asymptomatic but psychologically distressing the patient. Nor laboratory diagnosis is required, neither genotyping (by molecular probes) is recommended. Many topical treatments are effective for perianal warts, Cryotherapy with liquid nitrogen spray is perhaps the most widespread and easily available for perianal and intra-anal warts. However, Laser therapy and surgical excision have been recommended for most cases. Several other dermatological and pre cancer lesions are related to HPV infection: however, their description and management deserve elsewhere a more specialist consideration.

2- PROCTOCOLITIS

Enteric Pathogens

When the inflammation of the rectum extends beyond 15 cm into the sigmoid colon and descending colon, the condition is referred to proctocolitis. Infections with *Shigella spp, Salmonella spp, Campylobacter spp,* and occasionally *E. histolytica* or *Chlamydia t*. var. LGV, are frequently associated with proctocolitis. All of these organisms are invasive species and frequently produce hemorrhagic ulcerations of the colon and rectum. Infected patients frequently complain of lower abdominal discomfort, pain, and bloody diarrhea. Systemic symptoms of fever, chills, and myalgia, in association with a history of diarrhea, nausea, and cramps, are frequently present. Sigmoidoscopy or colonoscopy may reveal discrete ulcerations and mucopus. Rectal biopsies frequently show nonspecific inflammation with polymorphonuclear leukocyte infiltration of the lamina propria, with occasional cryptitis and giant cells. Granulomas are rarely, if ever, seen except for LGV.

Although several species of *Shigella* are responsible for human disease, S. *sonnei* and S. *flexneri* account for most of the infections seen in MsM in some areas. Clinically, shigellosis presents with an abrupt onset of diarrhea, fever, nausea, and cramps. Diarrhea is usually watery but may contain mucus or blood, Diagnosis is made by culturing the organism from the stool onto selective media. Treatment is usually supportive, but antibiotics may be beneficial in severe cases. Due to widespread development of resistance, selection of antibiotics should be based on regional antibiotic sensitivities.

Campylobacter jejuni is a curved gram-negative rod that is isolated from 4% to 9% of patients with acute diarrhea. Sexual transmission of this organism has been documented in animals and in humans. More recent studies have also identified an atypical form of *Campylobacter,* referred as *Campylobacter-like* organisms that are frequently isolated from MsM with and without intestinal symptoms, and rarely from heterosexual men and women. Two of these *Campylobacter-like* organisms have been speciated following DNA homology tests and are referred to as C. *cinaedi* and C, *fennelliae.* These organisms resemble C. *jejuni* morphologically in most biochemical tests, but differ in sensitivity to cephalothin, growth temperature requirements, and DNA homology.

Infection with *Campylobacter* usually presents with fever, chills, myalgia, abdominal pain and diarrhea. Fecal leukocytes are usually present, and the diagnosis is confirmed by isolating the organisms from the stool by culture on selective media. Although the need for antimicrobial therapy has not been fully established in humans, antibiotic has been recommended for severe symptomatic cases.

Salmonellae have been recovered from the stool of symptomatic MsM, and the same serotype has been recovered from asymptomatic sexual partners with whom no housing, food, or water were shared. Symptomatic individuals present with fever, abdominal pain, faint rash and diarrhea. Cases of *Salmonella enteritidis* have been commonly reported in AIDS patients. Diagnosis of *Salmonella* infection is made by culturing the organisms from the stool on selective media. Treatment of salmonellosis must be individualized depending on severity of symptoms and antibiotic sensitivity of the isolate. Since asymptomatic carriers are common, tracing of sexual partners of infected individuals is particularly important.

Several protozoans are of rarer detection: we only report the suggested treatment in **Table 2**, since the clinical presentation does not differ from other pathogens.

Entamoeba histolytica Infection

In selected surveys involving MsM, the prevalence of infection with *E. histolytica* has been documented to range between 25% and 40%. Colonization with nonpathogenic *E. dispar* is very frequent as well. The prevalence of infection correlates with a history of anilingus or fecal-oral contact. *E. histolytica* results in asymptomatic carrier state in over half of the infected individuals. In symptomatic patients, diarrhea, tenesmus, abdominal cramps, bloody stool and

anorectal discharge become prominent after one to three weeks following sexual contact. Fever is observed in up to 35% of cases. Fulminant colitis may occur with a high mortality rate. Anoscopy and sigmoidoscopy may reveal focal or diffusely friable ulcerative mucosa, which may resemble inflammatory bowel disease. Extra intestinal symptoms and disseminated disease are extremely rare among MsM infected with *E. histolytica.*
The pathogenicity of the trophozoites is based on the ability to penetrate through the intestinal mucosa, and to kill both epithelial cells and inflammatory cells.
Diagnosis is based on microscopic demonstration of *E. histolytica* in the stool (minimum three specimens collected on separate days) or antigen detection by very sensitive and specific monoclonal antibody. ELISA or immunofluorescence serology reveal antibodies that are detectable within the first week of disease and tend to persist for years. Molecular tests have a limited role in clinical practice today, whereas histological samples obtained during sigmoidoscopy or colonoscopy may show nonspecific mucosal thickening associated with inflammation. Both asymptomatic and symptomatic patients must be treated with the aim to eliminate the pathogen and to eradicate the intestinal carriage. The recommended treatment for symptomatic disease is reported in **Table 2**.

3- ENTERITIS

Enteritis is an inflammatory illness of the duodenum, jejunum, and/or ileum with no involvement of the distal colon. G. *lamblia* is one of the most frequently identified pathogens associated with enteritis in MsM. In addition, *Cryptosporidium spp, Cystoisospora spp, Microsporidium spp,* Cytomegalovirus, and *Mycobacterium avium-intracellulare* have also been found to cause diffuse enteritis in MsM with AIDS. Infection caused by *Yersinia enterocolitica*, *Y. pseudotuberculosis* and *Campylobacter spp* are rarer.

Giardia lamblia

G. *lamblia* appears to be sexually transmitted through oral-anal contact and is found to have a variable prevalence rate among MsM. Symptoms of giardiasis include diarrhea, abdominal cramps, bloating, and nausea. Although it is associated with a malabsorption syndrome, its pathogenesis is poorly understood. Disruption of intestinal motility, mechanical blockade, competition for nutrition, and flattening of microvilli have all been postulated as possible mechanisms of pathogenicity.
Diagnosis depends on the finding of ova and parasite in stool, duodenal aspirate, biopsy, or the string test (Enterotest). Since these assays are frequently time-consuming and lack sensitivity, an enzyme-linked immunosorbent assay (ELISA) has been developed for the detection of *Giardia* antigen in stool specimens. Compared with multiple ova and parasite stool examination, the ELISA has a sensitivity and specificity of 92% and 98%, respectively. Treatment consists of antibiotics (see **Table 2**); however, these drugs are associated with 10% to 15% failure rate, and follow-up stool examination is required following treatment.

Cryptosporidium spp and Microsporidium spp

Cryptosporidia are tiny (4-5 µm) protozoan parasites that primarily inhabit the microvillus region of epithelial cells. Cryptosporidia have been described as causing enterocolitis in over 16 species of animals but human infection was not reported until 1916, when it was identified in an immunocompromised patient. With the recognition of AIDS, multiple cases of *Cryptosporidium spp* enteritis have been identified in immunocompromised MsM. A very similar history can be outlined for Microsporidia, ubiquitous intracellular spore-forming organisms that include more than 150 genera and more than 1300 species. Again, transmission can occur through person to person contact and the role of sexual transmission is unclear. *Cryptosporidium* or *Microsporidium* infections are strongly related to a suspected underlying HIV infection. These protozoa may induce self-limited infection in immunocompetent patients, as well as severe, debilitating diarrhea in immunocompromised patients. In the immunocompetent, diarrhea and abdominal cramps usually resolves in 10 to 14 days. However, in the immunocom-promised patient, such as an AIDS patient,

Cryptosporidium and Microsporidia infection results in prolonged watery diarrhea that eventually results in dehydration and debilitation. Rarely, extra intestinal infections by Microsporidia has been reported (ocular, cerebral and myositis). The mechanism by which these organisms produce diarrhea is unknown. Very little mucosal injury is evident except for villous atrophy, which is insufficient to account for the diarrhea.
Diagnosis of *Cryptosporidium* infection is based on detection of the organism by microbiological techniques or by use of a modified acid-fast stain of diarrheal stool. In addition, the diagnosis can be established from histologic examination of the small bowel or rectal mucosa.
Since *Cryptosporidium* infection is self-limited in immunocompetent individuals, no treatment is required. Although treatment is indicated in immunocompromised patients, no single drug has been proven to be 100% efficacious. Specific treatment for Microsporidia are available (see **Table 2**)

Cystoisospora belli

Another coccidian parasite frequently seen in MsM with enteritis is *C. belli.* The clinical manifestations of this infection are nearly identical to those described for *Cryptosporidium.* Diagnosis of infection is established via acid-fast staining of the stool or by the sugar flotation concentration assays. Treatment for *Cystoisospora* infection is indicated only among immunosuppressed patients; however, among immunocompetent with long-lasting symptoms, antibiotic treatment with cotrimoxazole is effective in eradicating the pathogen.

M. avium-intracellulare (MAI)

MAI is an atypical mycobacterium that has been identified in severely immunocompromised hosts, including AIDS patients. The gastrointestinal tract and lymph nodes appear to be the most common involved sites. Infections of the intestinal tract frequently result in steatorrhea and malabsorption. The clinical and radiographic features of this disease mimic Whipple's disease. The main histologic features on small bowel biopsy include increased numbers of macrophages within the lamina propria which are filled with periodic acid-Schiff (PAS) and acid-fast-positive staining organisms. Diagnosis is therefore dependent on culture, and histological evidence by acid-fast staining of mucosal biopsies. At present, no single effective therapy is available for this infection, and frequently six antituberculous drugs are used in an unsuccessful attempt to control the infection.

PRINCIPLES OF MANAGEMENT

Since the wide-ranging spectrum of pathogens causing gastrointestinal disease among sexually anal active people, only a systemic approach to diagnosis and therapy will be successful in the care of these patients. An algorithm outlining the approach to the diagnosis and treatment of intestinal disorders is provided in Figure 1. This was designed to help differentiate the infectious etiologies of proctitis, proctocolitis, and enteritis, Additional steps must be undertaken in patients who are immunocompromised and may have opportunistic infections and/or malignancies.
First, the medical history should consider the type of sexual activity, preference and number of sexual partners, types of sexual practices, and past history of sexually transmitted infections. The exploration of sexuality must be an integral part of today medical history, and it may provide critical information in the evaluation of intestinal disease for most individuals. The medical history should also attempt to differentiate among clinical syndromes of proctitis, proctocolitis and enteritis. However, the assessment of symptoms rarely might suggest one or another etiologic infectious agent. Examination of the patient should include inspection of the anus, digital rectal examination, and anoscopy, avoiding use of bacteriostatic lubricants, which might interfere with microbiologic studies. External examination may reveal the presence of

herpetiform lesions, anal warts, or syphilitic chancres, General mucosal abnormalities, including friability, mucosal exudates, discrete polyps, ulcerations, or fissures, should be carefully examined for microbiological sampling and/or biopsies.

The presence of proctitis is manifested by inflammation limited to the distal rectum. Initial laboratory screening tests should include a bed-side rectal Gram stain for evaluation of polymorphonuclear leukocytes and intracellular gram-negative bacilli, reflective of infection with N. *gonorrhoeae.* Then, samples for C. *trachomatis* and HSV detection by molecular diagnosis should be performed in addition to cultures or NAAT for *N. gonorrhoeae.* Empiric therapy for such infections, pending culture results, might include a combined antimicrobial regimen active against both rectal gonorrhea and chlamydial infection. Rectal mass lesions or mucosal induration suggest LGV and secondary syphilis: in this latter case other manifestations of secondary syphilis might be detected on skin or other body districts. However, if serological test are negative, repeated tests for syphilis are indicated up to two weeks. HSV proctitis is frequently a clinically distinctive syndrome, presenting, as already above outlined, with severe anorectal pain, multiple perianal ulcerations, focal or diffuse ulcerations, fever, inguinal lymphadenopathy, dysuria, impotence, and paresthesia in the S4 to S5 distribution. LGV may also produce severe proctitis, perianal or rectal ulcerations, fever, and inguinal lymphadenopathy, but it is not associated with neurologic symptoms and often causes proctocolitis rather than proctitis. If perianal rectal ulcers are found in association with proctitis, LGV, rectal syphilis or HSV infection should always be suspected.

If proctocolitis is evident, with mucosal lesions extending beyond 10 to 15 cm in the rectum, rectal samples should be performed for the CT/LGV serotypes, and stool cultures for *Shigella, Salmonella* and *Campylobacter* should be obtained. In addition, stools should be carefully examined for *E. histolytica.* Recent antibiotic use or the presence of mucosal membranes dictate an evaluation for *Clostridium difficile* infection. Therapeutic options for proctocolitis, pending culture results, are varied and will be influenced by local differences in the prevalence of enteric pathogens and the patterns of antimicrobial susceptibility of these pathogens. In severe cases, presumptive treatment has been advocated, but specific choice of antimicrobials should be based on identification of the etiologic agent. Patients who have normal anoscopic findings and symptoms suggestive of enteritis should be carefully evaluated for G. *lamblia, Cryptosporidium, Isospora,* cytomegalovirus, and *M. avium-intracellulare.* Stool for ova and parasite examination should be obtained, with a notation to the microbiology laboratory to use specialized techniques for identification of *Cryptosporidium* and *Isospora. C*ultures for Mycobacteria should always be obtained in immunocompromised patients.

The finding of proctitis, proctocolitis and long lasting enteritis must suggest proper HIV counseling and testing. Blood testing is advised in any sexually active patient regardless sexual orientation: however, it should be always strongly offered to MsM.

Among HIV positive subjects the involvement of the entire gastrointestinal tract is the rule, so that a wise physician must start with a careful oral examination to check presence of thrush and/or oral lesions of Kaposi's sarcoma. Dysphagia or odynophagia may suggest the presence of esophageal candidiasis and/or esophageal involvement with cytomegalovirus or HSV infection. Systemic and/or abdominal lymphadenopathy in the presence or absence of occult gastrointestinal blood loss should suggest gastrointestinal neoplasms, including Kaposi's sarcoma and gastrointestinal lymphomas. Careful radiographic examinations of the esophagus, small bowel, and colon, as well as endoscopy and colonoscopy, may be warranted in these highly suspect patients.

To conclude, identification of any of the enteric pathogens should result in specific therapeutic regimens. Failure to respond to specific antimicrobial regimen may represent drug resistance, or more commonly, the presence of additional pathogens, necessitating a more comprehensive microbiologic and immunologic evaluation. If symptoms persist after eradication of infection, or if no pathogens are identified, one must then consider a broader spectrum of clinical entities, from dermatological perianal conditions to idiopathic inflammatory

bowel disease or neoplastic lesions, and thus specific diagnostic and therapeutic approaches to these diseases must be performed.

PREVENTION

Because of the relatively high prevalence of asymptomatic anorectal carriage of pathogenic organisms, a concerted effort involving clinicians and public health authorities is necessary to control these infections at least among higher risk group like MsM. Effective education of physicians, surgeons and patients about the different modes of transmission of these pathogens is necessary, along with a basic knowledge of the more modern reliable and available laboratory techniques for the diagnosis of these infections. The role of the proctologist should not be limited to deal with anal complaints: above the sphincter there is a whole patient…. so that surgeons may play an important role in participating into a network of multidisciplinary professionals dealing with prevention and care issues. Recognition of the importance of sexual transmission of enteric pathogens is a prerequisite in designing public health programs that will effectively prevent their spread to the community at large.

TABLE 2

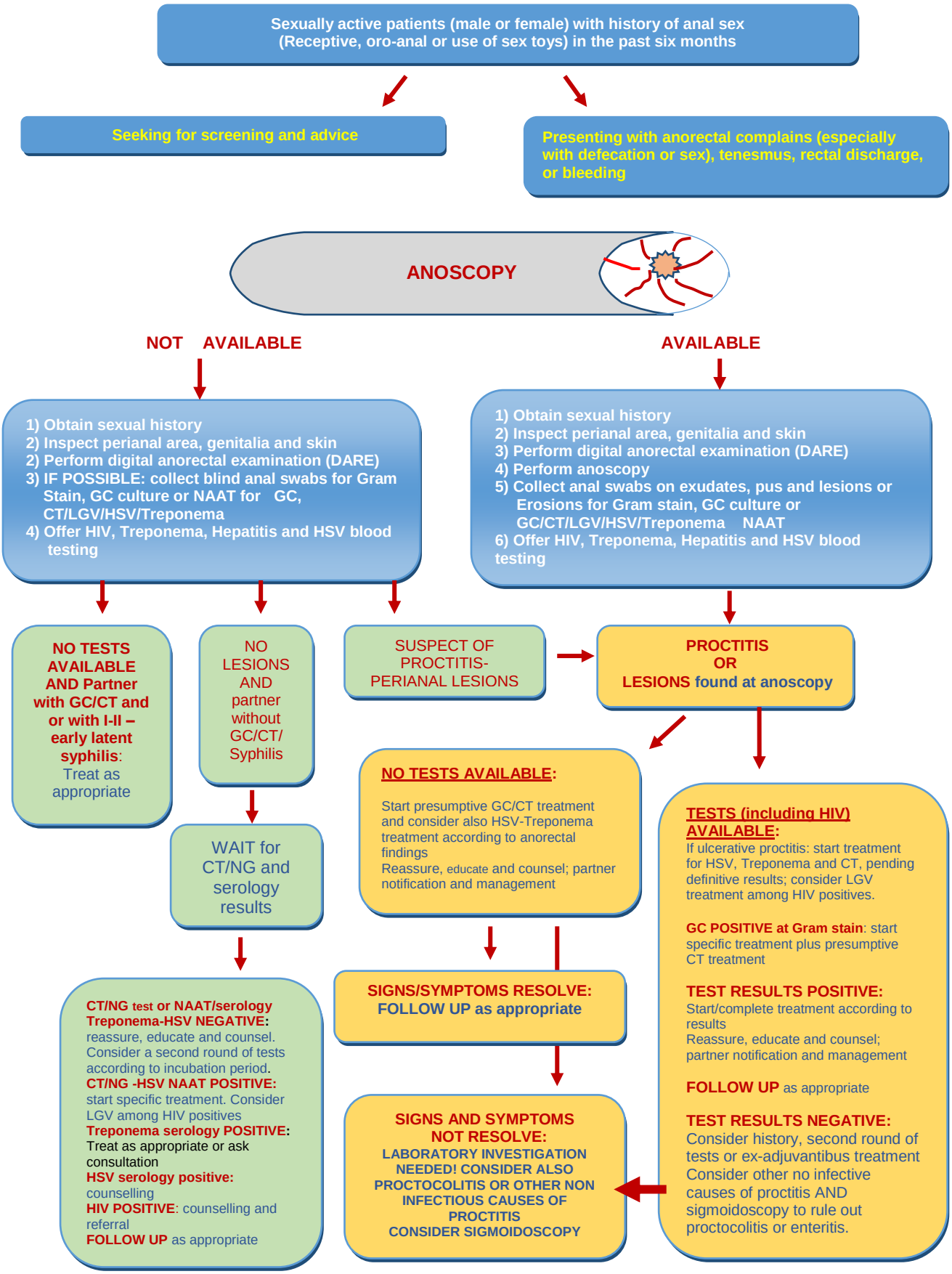
SUMMARY OF SUGGESTED TREATMENT OPTIONS FOR SEXUALLY TRANSMITTED PATHOGENS

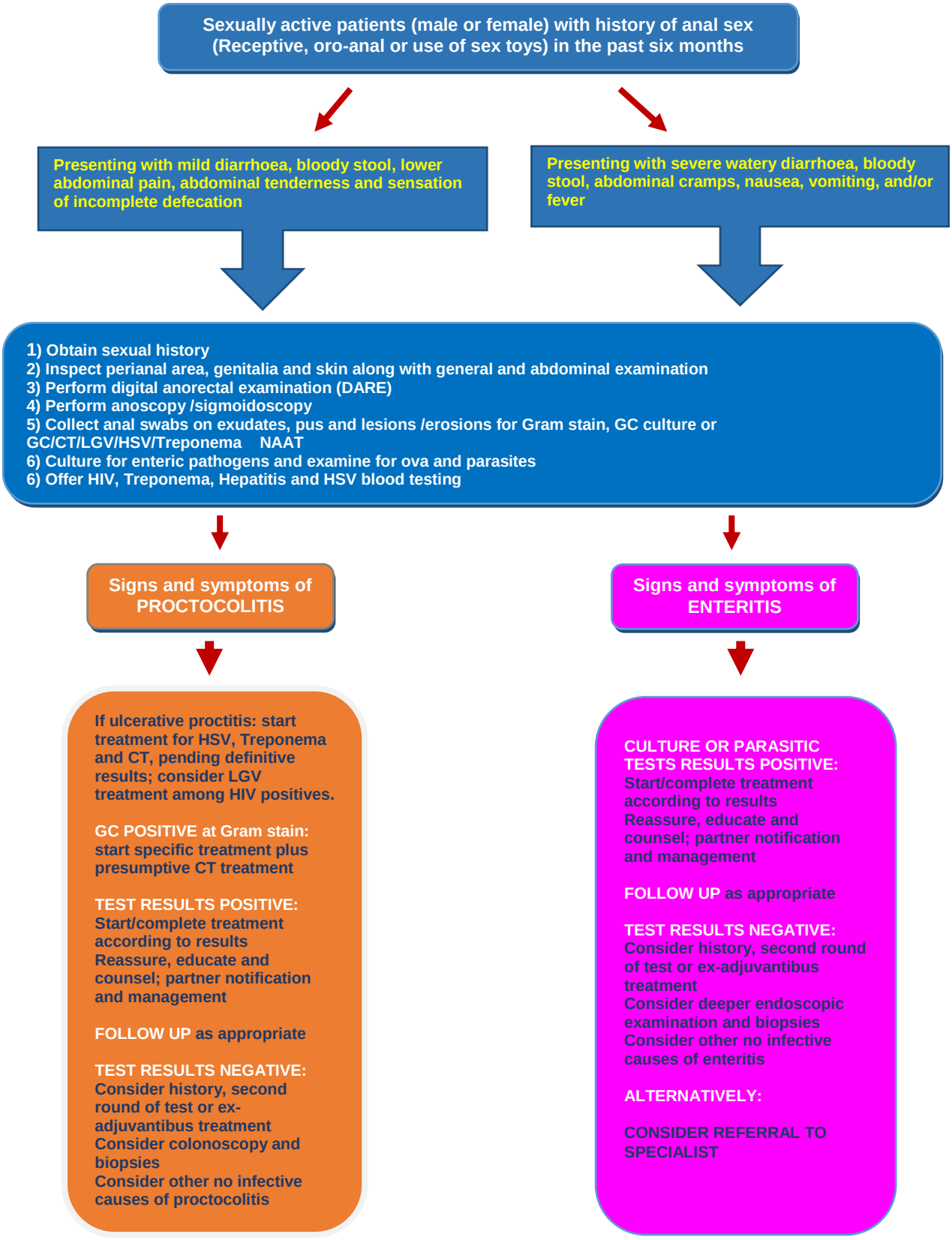
Bacteria	*First Choice treatment*	*Alternative treatment*	*Notes*
Neisseria gonorrhoeae	Ceftriaxone 500 mg IM together with azithromycin 2 g PO both as single dose	Cefixime 400 mg PO together with azithromycin 2 g PO both as a single dose. Patients with a history of penicillin anaphylaxis or cephalosporin allergy: Spectinomycin 2 g IM as a single dose together with azithromycin 2 g PO as single dose	Fluoroquinolones are not recommended because of the worldwide high prevalence of quinolone resistance
Treponema pallidum	Primary-secondary syphilis : Benzathine penicillin G 2.4 million units IM (one injection of 2.4 million units or 1.2 million units in each buttock) on day 1 – repeat at day 8 and day 15 if duration of syphilis is unknown (latent stages)	Only in case of penicillin allergy or parenteral treatment refused: Doxycycline 200 mg daily (either 100 mg bid or as a single 200 mg dose) PO for 14 days.	Ceftriaxone 500 mg -1 g IV daily for 10 days in case of bleeding disorders. Do not hesitate to refer the patient to the infectious disease specialist or dermatologist.
Chlamydia trachomatis	Doxycycline 100 mg PO bid for 7 days	Azithromycin 1g PO as single dose	
Chlamydia trachomatis LGV serovars	Doxycycline 100 mg PO bid for 21 days	Erythromycin 500 mg PO qid for 21 days	Always to be considered among HIV positive MsM
Klebsiella granulomatis	Azithromycin 1 g weekly or 500mg daily PO until complete healing is achieved	Doxycycline 100mg PO bid Co-trimoxazole 160/800mg PO bid	Do not hesitate to refer the patient to the infectious disease specialist or dermatologist.
Haemophilus ducreyi	Ceftriaxone IM 250 mg as single dose	Azithromycin 1g PO as single dose Ciprofloxacin of 500 mg PO bid for 3 days	Needle aspiration of buboes is effective but may need to be repeated. Incision and drainage is an alternative but it may lead to sinus formation.

			Do not hesitate to refer the patient to the infectious disease specialist or dermatologist.
Campylobacter spp	Azithromycin 500 mg PO qd x 3 days	Ciprofloxacin 750 mg PO bid x 3 days Levofloxacin 500 mg PO qd x 3 days	Treatment should be warranted only for patients with severe clinical conditions.
Salmonella spp.	Ciprofloxacin 500 mg PO bid x 3-7 days Levofloxacin 500 mg PO qd x 3 – 7 days(14 days in immunocompromised hosts)	Co-trimoxazole 1 c PO bid x 10 gg	Fluid and electrolyte replacement is essential as well as antibiotic treatment- Treatment is essential in patients with: • More than 9 stools per day • High fever • Need for hospitalization
Shigella spp.	Ciprofloxacin 750 mg PO qd x 3 days	Azithromycin 500 mg PO qd x 3 days	Treat immunocompromised for 7 – 10 days
Yersinia spp	Ciprofloxacin 500 mg PO bid x 5 days	Co-trimoxazole 10mg-50mg/kg bid PO x 5 days Doxycycline 100 mg PO bid+ gentamicin 5 mg/Kg qd x 5 days	Optimal treatment strategies are unclear. Most of the cases do not require antibiotic treatment. Individual therapy should be guided according to clinical severity. Referral to infectious disease specialist highly recommended.
Viruses	***First Choice treatment***	***Alternative treatment***	***Notes***
Herpes simplex virus (HSV)	First episode (for 7-10 days) Acyclovir 200 mg PO five times a day Acyclovir 400 mg PO tid Famciclovir 250 mg PO tid Valaciclovir 500mg bid PO Recurrent disease (for 3-5 days) acyclovir 200 mg five times daily Acyclovir 400 mg tid Valaciclovir 500 mg bid Famciclovir 125 mg bid.	Short course oral therapies are available for recurrences : Acyclovir 800 mg tid for 2 days Famciclovir 1 g bid for one day Valaciclovir 500 mg bid for 3 days	Suppressive therapy: seek specialist advise
Cytomegalovirus (CMV)	Ganciclovir :see notes	Cidofovir :see notes	Among immunosuppressed patients only: referral to infectious disease specialist highly recommended
Protozoa and Helminths	***First Choice treatment***	***Alternative treatment***	***Notes***
Giardia lamblia	Tinidazole 2 g PO once Metronidazole 500 mg PO bid x 5-7 days	Albendazole 400 mg PO qd x 5 days Paromomycin 10-25 mg/kg/die PO in 3 divided doses x5-10 days	

Entamoeba histolytica	Metronidazole 500-750 mg PO tid x 7-10 days Tinidazole 2 g PO dose x 3 days BOTH followed by Paromomycin 25-35 mg/kg die PO in three divided doses x 7 days	Nitazoxanide (not available in Italy)	Referral to infectious disease specialist highly recommended
Dientamoeba fragilis	Paromomycin 25-35 mg/kg die PO in three divided doses x 7 days	Metronidazole 500-750 mg PO tid x 7-10 days Iodoquinol 650 mg PO tid x 20 days (not available in Italy)	Referral to infectious disease specialist highly recommended
Cystoisospora belli spp	Co-trimoxazole 1 c PO bid x 10 days OR Co-trimoxazole 1 c PO qid x 10 days (more severe cases) Co-trimoxazole 1 c PO qid x10 days then bid x 3 weeks (particularly among AIDS patients.	Ciprofloxacin 500 mg PO bid x 5 days	Referral to infectious disease specialist highly recommended
Cryptosporidia spp	None: see notes	None: see notes	Referral to infectious disease specialist highly recommended
Microsporidia	Albendazole 400 mg PO bid x 3 weeks	See notes	Referral to infectious disease specialist highly recommended

FIGURE 1: MANAGEMENT OF PATIENTS WITH INTESTINAL SEXUALLY TRANSMITTED INFECTION




Sexually active patients (male or female) with history of anal sex (Receptive, oro-anal or use of sex toys) in the past six months
Presenting with mild diarrhoea, bloody stool, lower abdominal pain, abdominal tenderness and sensation of incomplete defecation
Presenting with severe watery diarrhoea, bloody stool, abdominal cramps, nausea, vomiting, and/or fever
1) Obtain sexual history
2) Inspect perianal area, genitalia and skin along with general and abdominal examination
3) Perform digital anorectal examination (DARE)
4) Perform anoscopy /sigmoidoscopy
5) Collect anal swabs on exudates, pus and lesions /erosions for Gram stain, GC culture or GC/CT/LGV/HSV/Treponema NAAT
6) Culture for enteric pathogens and examine for ova and parasites
6) Offer HIV, Treponema, Hepatitis and HSV blood testing
Signs and symptoms of PROCTOCOLITIS
Signs and symptoms of ENTERITIS
If ulcerative proctitis: start treatment for HSV, Treponema and CT, pending definitive results; consider LGV treatment among HIV positives.
GC POSITIVE at Gram stain: start specific treatment plus presumptive CT treatment
TEST RESULTS POSITIVE: Start/complete treatment according to results
Reassure, educate and counsel; partner notification and management
FOLLOW UP as appropriate
TEST RESULTS NEGATIVE: Consider history, second round of test or ex-adjuvantibus treatment
Consider colonoscopy and biopsies
Consider other no infective causes of proctocolitis
CULTURE OR PARASITIC TESTS RESULTS POSITIVE: Start/complete treatment according to results
Reassure, educate and counsel; partner notification and management
FOLLOW UP as appropriate
TEST RESULTS NEGATIVE: Consider history, second round of test or ex-adjuvantibus treatment
Consider deeper endoscopic examination and biopsies
Consider other no infective causes of enteritis
ALTERNATIVELY:
CONSIDER REFERRAL TO SPECIALIST

SUGGESTED READINGS:

1. Rompalo A, Quinn T. Sexually Transmitted Intestinal Syndromes. In: Sexually Transmitted Diseases, King Holmes at al. 4th ed. , 2008

2. De Vries HJC, Zingoni A, White JA, et al. 2013 European Guideline on the management of proctitis, proctocolitis and enteritis caused by sexually transmissible pathogens. Int J STD AIDS 2014 25: 465.

3. Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2010. MMWR 2010; 59/No. RR-12