2007 EUROPEAN GUIDELINE (IUSTI/WHO) ON THE MANAGEMENT OF PROCTITIS, PROCTOCOLITIS AND ENTERITIS CAUSED BY SEXUALLY TRANSMISSIBLE PATHOGENS

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INTRODUCTION

Men and women may be at risk of sexually transmissible anorectal or intestinal infections through a variety of sexual practices, including receptive anal intercourse and oral-anal sexual contact. These infections may lead to symptomatic proctitis, proctocolitis or enteritis.

AETIOLOGY

Sexually transmissible causes of proctitis, proctocolitis and enteritis.

Causes of distal proctitis	Causes of proctocolitis	Causes of enteritis
Neisseria gonorrhoeae	*Shigella* spp.	*Giardia duodenalis*
Chlamydia trachomatis: Genotype A-K Genotype L (LGV*)	*Campylobacter* spp.	*Cryptosporidium* spp.
Treponema pallidum	*Salmonella* spp.	
Herpes simplex virus	*Entamoeba histolytica*	
	Cryptosporidium spp.	
	Cytomegalovirus†	

*LGV = lymphogranuloma venereum.
† In severely immunocompromised patients (in the context of HIV infection, $CD4^+$ T-cell count $<100/mm^3$)[1].

Note: ***IT IS IMPORTANT TO NOTE THAT SEVERAL STIs MAY CO-EXIST[2].***

CLINICAL FEATURES OF PROCTITIS, PROCTOCOLITIS, AND ENTERITIS

1. Symptoms (history):

(a) In patients with *acute proctitis* (inflammation of the rectum) are:

- Mucopurulent anal discharge.
- Anorectal bleeding.
- Constipation.
- A sensation of rectal fullness or of incomplete defaecation.
- Tenesmus.

In patients with mild proctitis (and in those with chronic proctitis), there may only be:

- A history of mucus streaking of the stool.
- Constipation.
- Sometimes a feeling of incomplete defaecation.

The presence of the additional features mentioned above (i.e. discharge, bleeding, tenesmus) suggests more severe proctitis.

(b) In patients with *acute proctocolitis* (inflammation of the rectum and colon):

- Small volume diarrhoea.
- Lower abdominal pain.
- Abdominal tenderness.
- Anorectal bleeding.
- Sensation of incomplete defaecation.

(d) In patients with *enteritis* (inflammation of the small intestine):

- Large volume, watery diarrhoea.
- Mid-abdominal cramps.
- Nausea with or without vomiting.
- Malaise.
- Weight loss.

2. Signs (findings at clinical examination: anoscopy is recommended):

(a) Distal proctitis (that is proctitis confined to the distal 12-15 cm of the rectum):

- Mucopus in lumen of rectum.
- Loss of normal vascular pattern (although note that the vascular pattern may not be apparent in the distal 10 cm of the normal rectum).
- Mucosal oedema.
- Contact bleeding.
- Sometimes ulceration.
- Sometimes an inflammatory mass (as in syphilis and lymphogranuloma venereum [LGV][3])

(b) *Proctocolitis*:

As of a distal proctitis, but the inflammatory changes extend beyond the rectosigmoid junction.

(c) *Enteritis:*

The rectal mucosa appears normal unless there is concurrent infection with organisms causing proctitis.

DIAGNOSTIC TESTS FOR THE PATHOGENS CAUSING PROCTITIS, PROCTOCOLITIS AND ENTERITIS

Rectal gonorrhoea

- Gram-negative diplococci may be seen within the cytoplasm of neutrophilic granulocytes, permitting a *presumptive* diagnosis of rectal gonorrhoea (the predictive value of a positive smear is about 87%, but the sensitivity is <60% (Level IIb, Grade B)[4].
- Material for culture for *Neisseria gonorrhoeae* should be obtained either by the passage of a swab through the anal canal into the distal rectum, or under direct vision through an anoscope[5].
- The use of nucleic acid amplification tests (NAATs) have not yet been adequately validated for use on rectal specimens, and their use cannot be currently recommended.

Rectal chlamydial infection

(a) By genotype trachomatis (genotype A-K):

- The diagnosis is made by the detection of specific DNA sequences by a nucleic acid amplification test (NAAT) in rectal material collected as in the case of gonorrhoea (see above) (Level IV, Grade C). However, testing of rectal swabs has not yet been approved by the Food and Drug Administration (FDA) in the United States and protocols for testing rectal specimens are not included in the manufacturer's kit inserts.

(b) By genotype lymphogranuloma venereum (LGV; genotype L):

- Specimens that test positive for *Chlamydia trachomatis* in a NAAT should be characterised further (genotyping for LGV) (Level IIa, Level B). Genotyping of positive *C. trachomatis* NAAT material for LGV is possible in specific laboratories in many European countries (contact European Surveillance for STI, i.e. ESSTI; website: **www.essti.org/**).
- The histology of LGV proctitis may resemble Crohn's disease, but the appearance is non-specific [3,6].

Anorectal syphilis

- Dark-field microscopy for treponemes, or a (multiplex) NAAT for *Treponema pallidum* DNA from biopsy material or exudate from an ulcerated lesion may be used[7].
- Specific serological tests such as an IgG antitreponemal antibody enzyme immunoassay with confirmation by another specific treponemal antibody test support a diagnosis of syphilitic proctitis.

Anorectal herpes simplex virus infection

- Nucleic acid amplification by PCR should be used routinely, as it is a more sensitive test than culture (Level IIa, Grade B)[8].

Bacterial infections causing proctocolitis

- Culture of *Shigella* spp., *Salmonella* spp., or *Campylobacter* spp. from faecal samples yields the diagnosis.

Amoebiasis

- Microscopical examination for the trophozoites of *Entamoeba histolytica* of diarrhoeal stool specimens, rectal exudate or scrapings from rectal ulcers should be attempted.
- Cysts of the protozoan may be found in diarrhoeal stools or in formed faeces. It is important to differentiate between *E. histolytica* and the non-pathogenic amoeba *Entamoeba dispar* that resembles *E. histolytica* morphologically.

Cytomegalovirus infection

- The finding of typical intranuclear inclusion bodies in rectal or colonic biopsies enables one to make the diagnosis.

Giardiasis

- Fluid stools samples should be examined microscopically for the trophozoites and cysts of *Giardia duodenalis*.
- Only cysts are found in formed samples.
- Repeated examinations (at least three) are often necessary before a diagnosis is made.
- Although antigen detection tests are available that are more sensitive than the microscopical examination of a single stool sample[9], at least two faecal samples should be submitted for protozoological examination (Level IIa, Grade B).

Cryptosporidiosis

- Faecal samples are examined after staining for the oocysts of this protozoan.
- The discovery of various stages of the life cycle of the organism within the enterocytes on histological examination of jejunal, colonic or rectal biopsies is diagnostic.
- Enzyme immunoassays and direct immunofluorescence tests for the detection of cryptosporidial antigens that have high sensitivity are commercially available[9,10] (Level Ib, Grade A).

Non-specific proctitis

In some patients with symptoms and signs of a distal proctitis, a causative organism cannot be detected. These individuals are said to have non-specific proctitis.

MANAGEMENT OF THE INFECTIONS

(a) Those causing PROCTITIS:

- In all cases of proctitis (symptomatic or asymptomatic) caused by a sexually transmitted pathogen, patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications for the health of themselves and their partner(s). This should be reinforced by giving clear and accurate written information.
- Patients should be advised to avoid unprotected sexual intercourse until they and their partner(s) have completed treatment and follow-up.

For the prevention of proctitis caused by an STI, condom use for anal intercourse should be encouraged (III), and regular sexual health checks should be offered to those individuals who have frequent changes of sexual partners. The use of gloves for "fisting" should be encouraged.

Rectal gonorrhoea

- *Therapy, Partner Notification and Follow-up:* Patient management should follow that recommended for uncomplicated anogenital gonorrhoea (see 2005 update of European Guideline IUSTI/WHO on Gonorrhoea: **www.iusti.org)**. Concurrent treatment for chlamydial infection should also be given unless this infection has been excluded by microbiological testing (III).

Rectal chlamydial infection

- *Therapy:*

  (a) Genotype trachoma (Level IV, Grade C):

  - Azithromycin 1g orally as a single dose, or
  - Doxycycline 100mg orally twice daily for seven days.

Good data on the efficacy of these drugs or indeed of any antimicrobial agent in the treatment of anorectal chlamydial infection are lacking.

See also the European IUSTI/WHO Guideline 2001 on *C. trachomatis* infection: **www.iusti.org**.

(b) Genotype lymphogranuloma venereum (level IIb, Grade B):

- Doxycycline 100mg orally twice daily for 21 days, or
- Tetracycline 500mg orally four times per day for 21 days, or
- Erythromycin 500mg orally four times per day for 21 days.

See the European IUSTI/WHO Guideline for the Management of Tropical Genito-ulcerative Diseases: **www.iusti.org**.

- *Partner notification:* Contact tracing should be pursued in all patients identified with chlamydial infection, genotype trachomatis as well as LGV, at initial diagnosis. All partners for the preceding 3 months should be traced (Level IV, Grade C).

- *Follow-up:*

  - In the case of LGV, at least one follow-up assessment should be performed.
  - A test of cure is recommended at least 4 weeks after completion of antimicrobial therapy (Level IV, Grade C) of chlamydial infection, genotype trachomatis as well as LGV.
  - It is recommended that an HCV RNA test is performed when the LGV diagnosis is confirmed and 1, 3 and 6 months later[11,12]. Serological tests for syphilis and HIV should also be undertaken at diagnosis, 1 and 3 months later.

Anorectal syphilis

- *Therapy, Partner Notification and Follow-up:* See the European IUSTI/WHO Guideline for the Management of Syphilis (**www.iusti.org**)

Note: In all patients with syphilis, HIV testing is recommended.

Anorectal herpes simplex virus infection

- *Therapy:* It seems reasonable to follow the recommendations given in the European IUSTI/WHO Guideline 2001 for the Management of Genital Herpes (**www.iusti.org**).

Note: In all patients with anorectal HSV infection, HIV testing is recommended

(b) Those causing PROCTOCOLITIS:

Bacterial infections

- In the prevention of spread of the bacterial pathogens, careful hand washing after defaecation, frequent disinfection of toilet seats, taps and door handles should be encouraged. Good hygiene, notably washing, before and after sexual contact should be promoted. The use of barriers such as dental dams during oral-anal contact should be encouraged (Level IV, Grade C).

  - *Therapy:*

    - Antimicrobial therapy is often unnecessary in the treatment of *Shigella* and *Salmonella* infections, but when indicated (for example in those with bloody diarrhoea, and in individuals with AIDS or sickle cell disease), the choice of drug should be informed by knowledge of the pattern of antimicrobial resistance in the population.
    - For campylobacter infection:

      - erythromycin 500mg orally four times per daily for 7 days, or
      - ciprofloxacin 250mg twice daily for 7 days.

Treatment of these infections is usually indicated in HIV-infected individuals[13] (Level IV, Grade C).

- *Partner notification:* The possible source of infection should be ascertained if possible, in the knowledge that many infected individuals are symptomless. In most instances, sexual partners within the week preceding the onset of symptoms should be screened for infection.

- *Follow-up:* This is usually unnecessary, but in the case of food handlers with shigellosis, three consecutive negative stool samples taken not less than 24 hours apart, and at least 2 days after cessation of antimicrobial therapy should be obtained before they are allowed back to work (Level IV, Grade C).

Amoebiasis

- *Therapy:*

  - Metronidazole 800mg orally three times daily for 5-8 days (Level IIa, Grade B), or
  - Tinidazole 2g in a single oral dose daily for 5-8 days
  - Diloxanide furoate 500mg orally three times daily for 10 days should be given simultaneously to eliminate all infection from the bowel (Level IIa, Grade B).

- *Partner notification:* All partners within the preceding 3-4 months should be assessed (Level IV, Grade C).

- *Follow-up:* Stool samples should be examined after treatment and at monthly intervals for 3 months (Level IV, Grade C). Stools should remain negative during that period.

Cytomegalovirus

HIV testing is recommended and refer to an infectious diseases specialist.

(c) <u>Those causing ENTERITIS</u>:

- In the prevention of infections causing enteritis, advice on good hygiene (see under Bacterial Infections above) should be given to the patient.
- HIV-infected patients should avoid contact with human and animal faeces, and should wash their hands carefully after handling pets to avoid acquisition of cryptosporidiosis[14]. They should also avoid oral-anal sexual contact (Level IV, Grade C).

Giardiasis

- *Therapy:*

  - Metronidazole 2g orally as a single dose daily for 3 days, or
  - Metronidazole 400mg orally three times per day for 5 days (Level IIa, grade B), or
  - Tinidazole 2g orally as a single oral dose (Level IIa, grade B).

- *Partner notification:* As the infected sexual partner is often symptomless partner notification should be undertaken in all cases. All partners within the preceding month should be assessed for patients with symptomatic infection.

- *Follow-up:* Three negative consecutive stool samples taken not less than 24 hours apart should be obtained to confirm cure (Level IV, Grade C).

Cryptosporidiosis

- *Therapy:* In the immunocompetent patient, the condition is self-limiting. Initiation of highly active antiretroviral therapy is often helpful in HIV-associated chronic cryptosporidiosis[15](Level III, Grade B).

- *Partner notification:* The value of partner notification in patients with cryptosporidiosis is uncertain.

- *Follow-up:* In the immunocompetent patient this is unnecessary.

SYNDROMIC MANAGEMENT OF THE PATIENT WITH ANORECTAL AND/OR INTESTINAL SYMPTOMS IN WHOM A SEXUALLY TRANSMISSIBLE CAUSE IS SUSPECTED.

History

A consideration of the patient's symptoms (see above) is often helpful in determining whether the patient has proctitis, proctocolitis or enteritis. A sexual history is, of course, important.

Physical examination and diagnostic tests

- Palpate the abdomen:
  - Tenderness over the colon suggests colitis.
- Inspect the perianal region:
  - Perianal ulceration may suggest syphilis, HSV infection, or LGV.
- If proctitis is suspected, anoscopy should be performed to inspect for mucosal inflammation and infiltration/swelling and/or ulceration.
- If possible, stained smears (Gram or Giemsa) of rectal exudate should be made and the number of polymorphs in light microscopical high power field (magnification, x1000) noted; >10 cells suggests proctitis[16]. If Gram-negative diplococci are seen within the cytoplasm of neutrophilic granulocytes a *presumptive* diagnosis of rectal gonorrhoea may be made.
- Ideally, microbiological tests for the various infections detailed above should be taken.

When facilities for the organismal diagnosis of an STI are unavailable or limited, or when a syndromic treatment approach is considered imperative, rigid sigmoidoscopy should be undertaken, if available. This usually allows differentiation between a distal proctitis and a proctocolitis and will inform on a rational treatment choice.

Treatment

(A) *Specific treatment:* In the case of patients with mild symptoms, and when microbiological investigations are possible, it is best to await the results of these tests before initiating specific therapy.

(B) *Syndromic treatment:* In patients with more severe symptoms, or when microbiological testing is impossible, or if there are persistent symptoms and signs but microbiological tests are negative, or if the patient is unable to attend when test results are available, syndromic treatment (empirical therapy) should be given:

Distal proctitis:

(i) Mild symptoms and signs:

a) Ceftriaxone 250mg as single intramuscular injection, **OR** cefotaxime 1,000mg as single intramuscular injection (2nd choice for i.m. treatment), **OR** cefixime 400mg as a single oral dose, **OR** cefuroxim axetil 1,000mg as a single oral dose (2nd choice for oral treatment).

PLUS:

b) Azithromycin 1g as single oral dose, **OR** doxycycline 100mg twice daily by mouth for seven days.

PLUS (especially if there are associated clinical features such as fever, paraesthesiae in the distribution of the sacral nerves, or hesitancy of urination **):**

c) Valaciclovir 500mg given orally twice daily for 5-10 days.

(ii) Moderate to severe symptoms and signs:

If proctitis symptoms are severe, particularly with rectal ulceration and associated with fever, treat with:

a) Ceftriaxone 250mg as single intramuscular injection, **OR** cefotaxime 1,000mg as single intramuscular injection (2nd choice for i.m. treatment), **OR** cefixime 400mg as a single oral dose, **OR** cefuroxim axetil 1,000mg as a single oral dose (2nd choice for oral treatment).

PLUS

b) Doxycycline 100mg by mouth twice daily for 21 days, **OR** tetracycline 500mg by mouth four times per day, **OR** erythromycin base 500mg four times per day for 21 days.

PLUS

c) Valaciclovir 500mg given orally twice daily for 5-10 days.

Note:
If rapid diagnostic tests are supportive of the diagnosis of early syphilis or if, at a later visit serology supports a diagnosis of early syphilis: benzathine penicillin 2.4 million units i.m. (1.2 million units into each buttock), provided the history excludes possible penicillin anaphylaxis.

Proctocolitis

- If the patient has recently visited a geographical area where amoebiasis is prevalent, or if he or she is a sexual contact with a person who has returned from such an area, consider amoebiasis and refer to an appropriate specialist.
- In cases associated with bacterial pathogens, fluid replacement is the most important aspect of treatment. When symptoms are severe, antimicrobial therapy may be required.

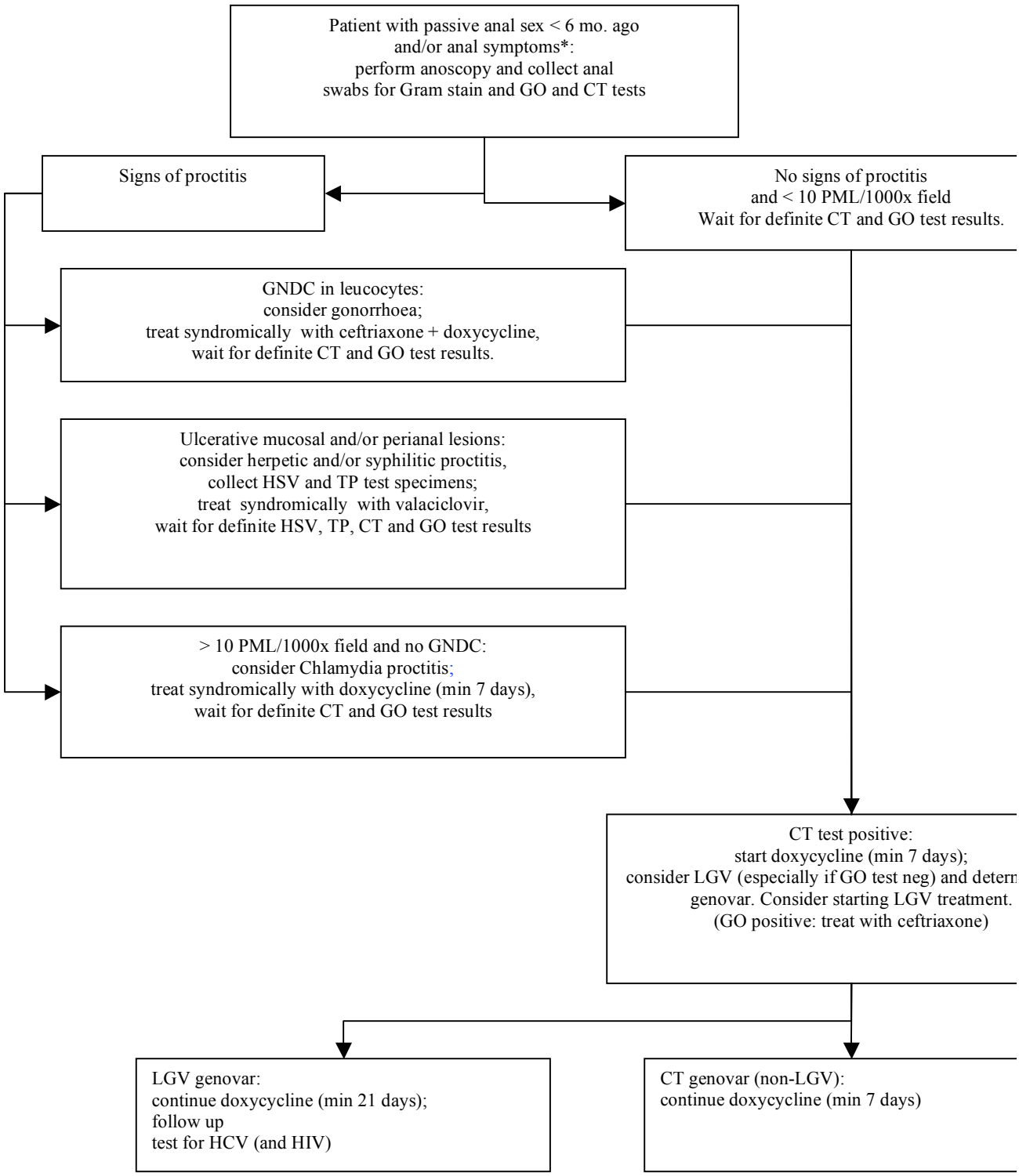
Enteritis

- Treat with metronidazole or tinidazole.
- Failure to respond symptomatically within four weeks should prompt further investigations by a gastroenterologist.

REFERENCES

1. Goodgame RW. Gastrointestinal cytomegalovirus disease. *Ann Int Med* 1993; **119**: 924-935.
2. Quinn TC, Stamm WE, Goodell SE, *et al*. The polymicrobial origin of intestinal infections in homosexual men. *N Engl J Med* 1983; **309**: 576-582.
3. Nieuwenhuis RF, Ossewaarde JM, Gotz HM, *et al*. Resurgence of lymphogranuloma venereum in Western Europe: an outbreak of *Chlamydia trachomatis* serovar L_2 proctitis in The Netherlands. *Clin Infect Dis* 2004; **39**: 996-1003.
4. McMillan A, Young H. Gonorrhea in the homosexual man: frequency of infection by culture site. *Sex Transm Dis* 1978; **5**: 146-150.
5. Deheragoda P. Diagnosis of rectal gonorrhoea by blind anorectal swabs compared with direct vision swabs taken via a proctoscope. *British Journal of Venereal Diseases* 1977; **53**: 311-313.
6. Geller SA, Zimmerman MJ, Cohen A. Rectal biopsy in early *lymphogranuloma venereum* proctitis. *Am J Gastroenterol* 1980; **74**: 433-435.
7. Palmer HM, Higgins SP, Herring AJ, Kingston MA. Use of PCR in the diagnosis of early syphilis in the United Kingdom. *Sex Transm Infect* 2003; **79**: 479-483.
8. Ramaswamy M, McDonald C, Smith M, *et al*. Diagnosis of genital herpes by real time PCR in routine clinical practice. *Sex Transm Infect* 2004; **80:** 406-410.
9. Garcia LS, Shimizu RY, Novak S, Carroll M, Chan F. Commercial assay for detection of *Giardia lamblia* and *Cryptosporidium parvum* antigens in human fecal specimens by rapid solid-phase qualitative immunochromatography. *J Clin Microbiol* 2003; **41**: 209-212.
10. Kehl KS, Cicirello H, Havens PL. Comparison of four different methods for the detection of *Cryptosporidium* species. *J Clin Microbiol* 1995; **33**: 416-418.
11. Van der Bij AK, Spaargaren J, Morre SA, *et al*. Anorectal lymphogranuloma venereum in men who have sex with men: diagnostic and clinical implications. A retrospective case-control study. *Clin Inf Dis* 2006; **42**: 186-194.
12. Gotz HM, van Doornum G, Niesters HG, den Hoolander JG, Thio HB, de Zwart O. A cluster of acute hepatitis C virus infection among men who have sex with men – results from contact tracing and public health implications. *AIDS* 2005; **19**: 969-974.
13. Angulo FJ, Swerdlow DL. Bacterial enteric infections in persons infected with human immunodeficiency virus. *Clin Infect Dis* 1995; **21 Suppl 1**: S84-93.
14. Kaplan JE, Masur H, Holmes KK. Guidelines for preventing opportunistic infections among HIV-infected persons. 2002. *MMWR* 2002; **51 (RR08)**: 1-46.
15. Miao YM, Awad-El-Kariem FM, Franzen C, *et al*. Eradication of cryptosporidia and microsporidia following successful antiretroviral therapy. *JAIDS* 2000; **25**: 124-129.
16. McMillan A, Gilmour HM, Slatford K, McNeillage GJC. Proctitis in homosexual men. A diagnostic problem. *British Journal of Venereal Diseases* 1983; **59**: 260-264.

FLOWCHART EUROPEAN GUIDELINE FOR SYMPTOMATIC PROCTITIS



* Symptomatic proctitis, symptoms:
(a) In patients with *acute proctitis* (inflammation of the rectum):

- Mucopurulent anal discharge.
- Anorectal bleeding.
- Constipation.
- A sensation of rectal fullness or of incomplete defaecation.
- Tenesmus.

(b) In patients with *mild proctitis* (and in those with chronic proctitis), there may only be:

- A history of mucus streaking of the stool.
- Constipation
- Sometimes a feeling of incomplete defaecation.
-

Abbreviations

CT= Chlamydia trachomatis
GNDC= Gram negative diplococci
GO= Gonorrhoea
HSV= Herpes simplex virus
PML= Polymorphonuclear leukocytes
TP= Treponema pallidum

Levels of evidence and grading of recommendations

Levels of Evidence

Ia: Evidence obtained from meta-analysis of randomised controlled trials.
Ib: Evidence obtained from at least one randomised controlled trial.
IIa: Evidence obtained from at east one well designed study without randomisation.
IIb: Evidence obtained from at least one other type of well designed quasi-experimental study.
III: Evidence obtained from well designed non-experimental descriptive studies such as comparative studies, correlation studies, and case-control studies.
IV: Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

Grading of Recommendations

A (Evidence levels Ia, Ib) Requires at least one randomised controlled trial as part of the body of literature of overall quality and consistency addressing the specific recommendation.

B (Evidence levels IIa, IIb, III) Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.

C (Evidence IV) Requires evidence form expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality.

Search strategy employed:

Medline search. Key words: proctocolitis, proctitis, anorectal diseases, men who have sex with men, *Chlamydia trachomatis*, lymphogranuloma venereum, *Neisseria gonorrhoeae*, *Treponema pallidum*, *Entamoeba histolytica*, amoebiasis, *Giardia duodenalis*, giardiasis, cryptosporidiosis, herpes simplex virus infection, genital herpes, salmonellosis, campylobacter infections, shigellosis, cytomegalovirus.

Review of UK national guidelines (2001) for the management of gonorrhoea, syphilis, genital herpes, chlamydial infection, tropical genitor-ulcerative diseases (www.bashh.org).

Review of IUSTI/WHO Guideline (2001) for the management of gonorrhoea, syphilis, genital herpes, chlamydial infection, tropical genitor-ulcerative diseases (www.iusti.org).

Review of US Centers for Disease Control Sexually Transmitted Diseases Treatment Guidelines 2006 for the management of gonorrhoea, syphilis, genital herpes, chlamydial infection, lymphogranuloma venereum, proctocolitis, proctitis and enteritis (www.cdc.gov/std/).

Declarations of interest:
None declared

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