

## Sexually transmitted diseases and anorectum

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### Abstract

Sexually transmitted diseases (STD) are a major public health problem because their incidence is increasing worldwide despite prevention campaigns and because they raise the risk of HIV infection. Anorectal localisations of STD are common among men who have sex with men (MSM) but can also be seen among heterosexuals (men or women). Transmission of such infections is due to anal sex or to other sexual behaviours like "fisting".

Although some pathogens (like Human Papillomavirus-HPV) are common in gastroenterologist/proctologist consultations, others are not so well-known. Furthermore during the last years, sexual risky behaviours have led to resurgence of old affections (like syphilis) or to emergence of unknown diseases (like lymphogranuloma venereum) in our countries.

This presentation tends to focus on clinical manifestation, diagnosis and treatment of different STD : HPV, Herpes Simplex Virus, *Neisseria gonorrhoeae*, *Chlamydia trachomatis* (in particularly lymphogranuloma venereum) and *Treponema pallidum*. (Acta gastroenterol. belg., 2009, 72, 413-419).

### Introduction

Sexually transmitted diseases (STD) remain a major public health problem all around the world despite prevention campaigns. This is a worrying problem because STD are not only associated with upper genital tract infections leading to infertility, obstetrical complications, genital and anal cancers but also with an elevated risk of transmission of human immunodeficiency virus (HIV) infection.

Anorectal localisations of STD are more common among men who have sex with men (MSM) but are not exclusively seen in this population and can also affect heterosexuals (men or women). In this localisation such infections are mainly due to anal sex but also to other sexual behaviours like "fisting".

Among these different pathogens, some are well-known by gastroenterologists and proctologists such as *Human Papillomavirus* (HPV) responsible of condyloma acuminata but others are unusual. Furthermore during the last years, sexual risky behaviours have led to resurgence of old affections (like syphilis) (1) or to emergence of unknown diseases in our country (like lymphogranuloma venereum) (2).

This article tends to focus on anorectal clinical manifestations, diagnosis and treatment of different STD : HPV, *Herpes Simplex Virus*, *Neisseria gonorrhoeae*, *Chlamydia trachomatis* (in particularly Lymphogranuloma Venereum) and *Treponema pallidum*.

Infections such Chancroid and Donovanosis respectively due to *Hemophilus ducreyi* and *Calymmato-*

*bacterium granulomatosis-Klebsiella granulomatosis* will not be dealt with because they are encountered only in tropical and subtropical areas.

Immunodeficiency due to HIV also leads to atypical, recurrent, extensive lesions that are resistant to treatment (3). These lesions will not be specifically studied here but co-infection with HIV must be searched in all case of STD especially in anorectal localisations because these lesions are associated with a higher risk of HIV transmission by rupture of the cutaneo-mucous barrier.

*Human Papillomavirus* (HPV) : Condylomata Acuminata

Condyloma Acuminata (anogenital warts) are the most frequent STD in developed countries (4). They are caused by *human papillomavirus* (HPV) infection, mainly HPV serotypes 6 and 11 (90%) but also HPV 16 and 18 with an oncogen power.

Acquisition of HPV infection is related to sexual activity and the infection is more common in immunosuppressed patients (5). Incubation period extends from 3 weeks to more than 12 months with possibility of latent infection.

Diagnosis is clinical by inspection of anal area (6). The lesions are skin-colored or pink ranging from smooth flattened papules to a papilliform, verrucous appearance. These lesions are well-known by gastroenterologists and proctologists. Lesions can vary in number, size and form. Application of a 5 percent acetic acid can facilitate identification but is not specific : lesions turn white. Anuscopy is mandatory for diagnosis of intra-anal lesions and other localisations must be checked (genitals, mouth).

The major risk of this infection is the evolution to squamous cell carcinoma (association with HPV 16 and 18) mainly in MSM and HIV-infected patients (7-8). Biopsies are recommended in doubtful diagnosis, in case of lack of response to therapy, large or atypical lesions, particularly in immunocompromised patients. Regular cytologic specimens of the anal canal should be

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Submission date : 23/06/2009

Acceptance date : 23/10/2009

recommended in high risk groups for screening of early neoplasia (9).

Treatment is based on systematic repetitive destruction of any lesion by chemical or physical destruction (podophyllin, 5-fluorouracil, cryotherapy, electrocoagulation), immunological therapy (Imiquimod®) or surgical excision. No evidence exists for superiority of one type of treatment to another (10) and preferred approach depends on number and size of lesions and physician habits. Electrosurgery is probably the most frequent option in proctology.

Recurrences are frequent (about 30 to 70% within 6 months of treatment) (11) but hope comes from recent availability of two vaccine preparation for HPV : Gardasil® (HPV 6, 11, 16 and 18) and Cervarix® (HPV 16 and 18). Now in Belgium such vaccine is refunded for girls between 12 and 18 years.

#### *Herpes Simplex Virus (HSV-1 and HSV-2)*

Anorectogenital localizations of HSV are mainly due to HSV-2 (60 to 80% of cases) but HSV-1 can also be seen in this area. Contamination can be direct (sexual contact) or indirect (soiled linen, sex toys). Anal herpes (proctitis) is unusual and mainly due to anal sexual contact, especially in MSM. Recurrence is rare in this area.

In 80% of cases primary infection is asymptomatic with an average incubation of 4 days after exposure. In 10% of cases, primary infection leads to severe clinical manifestations lasting several weeks. It is clinically characterised by ephemeral bilateral painful vesicular eruption, often unnoticed, leaving place to multiple painful erosions or ulcerations in low rectum, perianal or anal areas. Association with systemic symptoms (fever, headache, malaise, myalgias) and regional symptoms (dysuria, constipation, tender inguinal lymphadenitis) is suggestive.

Recurrent infection is relatively asymptomatic : ephemeral vesicles followed by polycyclic ulceration often in a unilateral rather than a bilateral distribution. Systemic symptoms are infrequent in this condition (12-13).

Clinical diagnosis (pain !) should be confirmed with laboratory testing. Different techniques can be used :

- a Tzanck smear can be done by scraping lesions and laying on a slide in order to search cytopathic effect of the virus (multinucleate giant cells). However utility of such a test is limited due to low sensitivity and specificity (14).
- Viral culture can be done by sampling of vesicular fluid placed in adequate media and quickly brought to the laboratory. Such a technique requires intact vesicles and is therefore difficult in anal area where vesicles are ephemeral.
- Ag detection by direct fluorescence antibody or by Polymerase Chain Reaction (PCR) assay have emerged as more sensitive methods to confirm HSV

infection in muco-cutaneous sites. Sample can be performed by using a dried swab.

Serology is of little interest. A positive serology indicates a present or past infection.

In case of primary infection, treatment consists of aciclovir 400 mg per os (PO) three times a day or 200 mg five times a day or valaciclovir 1000 mg twice a day during 7 to 10 days with a local application of Isobetadine® or Diaseptyl gel (15). Symptomatic treatment with analgesics and antipyretics must be associated.

#### *Neisseria gonorrhoeae : Gonorrhoea*

*Neisseria gonorrhoeae* is a gram-negative aerobic diplococcus bacterium responsible of gonorrhoea. Reservoir is strictly human and transmission is due to sexual contact with infected lesions. Incubation period is from two to five days in men and between for 8 to 10 days in women. Despite effective antibiotic therapy, *Neisseria gonorrhoeae* remains a common STD in Europe and USA especially in urban areas (16).

Gonococcal infections are associated with several clinical manifestations depending infection site (Table 1). Infection in women is often asymptomatic compared to men (17). Genital infections are generally symptomatic in men with penile discharge in 90% of cases. Extragenital infections (pharynx, rectum) are usually asymptomatic but a small percentage of patients may present pharyngitis or proctitis. Proctitis is characterized by mucopurulent discharge, tenesmus, constipation and intense anorectal pain. At clinical examination, proctitis is characterized by anal diffuse congestion with superficial ulcerations and purulent secretions. In clinical practice minor forms are more frequent with discrete hemorrhagic rectitis or purulent secretions on normal rectal mucosa (12).

Anorectal gonorrhoeal infections are unusual amongst heterosexual men and typically occur more frequently in MSM who engage anoreceptive intercourse.

For proctitis, diagnosis is made by mean of a culture for *Neisseria gonorrhoeae*. This can be done by taking a rectal sample of purulent secretions with a simple dry swab through anoscopy or blindly by inserting the swab 3 to 4 cm into rectal vault. It requires a direct transfer to laboratory and allows antibiotic susceptibilities assessment.

Another method is a DNA amplification using PCR. It requires a rectal swab with special adapted transport medium (like BD Probetec ET® *Chlamydia trachomatis* and *Neisseria gonorrhoeae* Amplified DNA Assay Collection Kit). Sensibility and specificity of this technique is very good (equal performance to culture) and sample storage and transport is less critical (conservation between 2° and 27°C, transport in 48h, the sooner is the better) (18).

No indirect diagnosis (serology) is available.

Treatment consists of a “minute” antibiotherapy with a single intramuscular (IM) dose of ceftriaxone

Table 1. — Clinical manifestations of Gonococcal infections and potential complications

	Infection	Complications
♂	Acute urethritis with penile discharge in 90% Proctitis Pharyngitis	Bacteraemia Septic arthritis
♀	Cervical Infection Urethritis Proctitis	Bacteraemia Septic arthritis Pelvic inflammatory disease (salpingitis, endometritis, ovarian absces)

Table 2. — Serovars of *Chlamydia trachomatis* with clinical presentation and classical geographic distribution

Serovars	Infection	Geographic repartition
A to C	Trachoma	Mostly Africa, Asia
D to K	♀ urethritis, cervical infection, salpingitis, endometritis ♂ urethritis, proctitis, prostatitis, epididymitis	World-wide
L1 to L3	Lymphogranuloma Venereum	Mostly tropical and subtropical areas

(Rocephine®) 125 mg or cefotaxime (Claforan®) 500 mg or spectinomycine (Trobicin®). Other alternatives consist of doxycycline 100 mg PO twice a day for 7 days or azithromycine 2 gr PO in a single dose (with bad tolerance due to significant gastrointestinal side effects) (15).

Due to rising rates of gonococcal resistance, use of fluoroquinolones (Ciproxine® 500 mg PO twice a day or Tarivid® PO twice a day for 5 to 7 days) for the treatment of gonorrhoeal infections is no longer advised (19).

#### *Chlamydia trachomatis* : Lymphogranuloma Venereum

*Chlamydia trachomatis* is a gram-negative intracellular bacterium. Man is its natural host. Transmission is due to sexual contact with infectious lesions (vaginal, oral or anal sex) but is also indirect by sharing of sex toys or by high risk sexual practices like “fisting” (complete fist penetration).

Several serovars of *Chlamydia trachomatis* are known (20) (Table 2) :

- Serovars A to C are present in Africa and Asia and are responsible of trachoma, an ocular affection.
- Serovars D to K have a world-wide distribution and are responsible of usually benign and often asymptomatic urogenital and rectal infections.
- Serovars L1 to L3 are causing lymphogranuloma venereum (LGV) and are mostly present in tropical and subtropical areas.

Since 2004, epidemiological outbreaks of LGV have been reported in the Netherlands and other developed countries (Belgium, France, Germany, United Kingdom,

North America) (2 ; 21-34). Most cases were encountered among MSM with high risk sexual behaviours (unprotected anal sex, meeting sex partners on the internet, multiple partners in gay leather scene). They were often associated with other STD (mainly HIV but also syphilis or hepatitis C) (35-36) and most of the cases were characterised by bloody proctitis mimicking inflammatory bowel disease.

Serovars L1 to L3 induce a lymphoproliferative reaction and LGV is predominantly a disease of lymphatic tissue in contrast to other serovars leading to limited mucosal infection. Clinical course of LGV is classically considered as occurring in three stages. After an incubation period of 3 to 30 days, primary stage is characterised by a transient often unnoticed painless herpes-like genital or anal papule or erosion. This lesion spontaneously heals within a few days. Secondary stage appears between 2 to 6 weeks after infection by extension of infection to regional lymph nodes. General systemic signs are usually present (fever, shivers, asthenia, arthralgia, myalgia). Patients developed painful inguinal and/or femoral usually unilateral lymphadenitis which can evolve to abscess and eventually give rise to draining fistulae (buboes). In female cases, retroperitoneal lymph nodes can be seen and cervical lymphadenitis is possible with oral sexual intercourse. In MSM, an anorectal syndrome occurs with hemorrhagic proctocolitis with mucopurulent rectal discharge, anal pain, constipation and/or tenesmus (Figs. 1-3) (12, 37). This can be mistaken for inflammatory bowel disease. “Lymphoroids” (like haemorrhoid lesions caused by lymphatic obstruction) can often appear or other lesions like chronic atypical fissures with irregular indurate edges (Fig. 4). Without treatment, tertiary stage is characterised by evolution to fibrosis, fistulae and strictures in the anogenital tract. Late complications include genital elephantiasis, frozen pelvis and important destruction of the genital tract.

Direct diagnosis can be made either by culture, by immunofluorescence or by DNA amplification. Culture is only done in specialised laboratories. It allows determination of serovars but requires mandatory rapid transport. It is not done in usual clinical practice. Aspirates from buboes can be evaluated by immunofluorescence but this technique is relatively insensitive. The best technique is to trace the presence of *Chlamydia trachomatis* by DNA amplification using PCR test. It requires to do a smear through anoscopy or rectoscopy and to place rectal swab in a special adapted transport medium (like BD Probetec ET® *Chlamydia trachomatis* and *Neisseria gonorrhoeae* Amplified DNA Assay Collection Kit, which allows PCR *Chlamydia trachomatis* and *Neisseria gonorrhoeae* with the same sample). PCR can also be done on buboes aspirates.

Serology (IgG and IgA) is only of indirect help : high titer levels (> 1:256) are in favour of LGV diagnosis. Lower titer levels may result from old affection or other serovar infection.



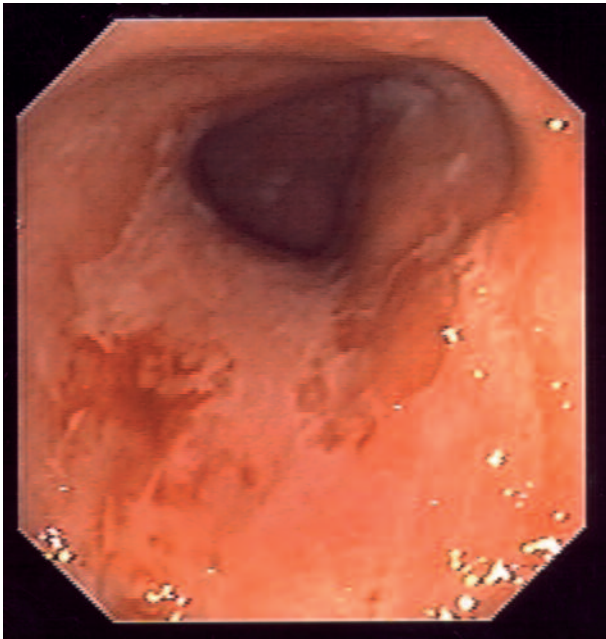


Fig. 1. — Lymphogranuloma venereum proctitis in a young MSM patient (MSM = men who have sex with men).



Fig. 2. — Pelvic CT scan in a young MSM patient with lymphogranuloma venereum : thickening of rectal wall accompanied by perirectal adenitis (MSM = men who have sex with men).

Doxycycline 100 mg PO twice a day during 21 days is the recommended treatment in case of LGV (30). Azithromycin 1 gr PO weekly for 3 weeks may be effective as well as during pregnancy (15). Buboës may require needle aspiration or incision and drainage.

Awaiting results of laboratory testing, empiric therapy in case of clinical syndrome consistent with LGV proctocolitis is made of doxycycline® 100 mg PO twice a day



Fig. 3. — Abdominal CT scan in a young MSM patient with lymphogranuloma venereum : multiple abdominal lymphadenitis with inflammation of the mesentery (MSM = men who have sex with men).



Fig. 4. — Atypical fissure due to *Chlamydia trachomatis*

+ ceftriaxone 125 mg IM in a single dose. Persons who have had sexual contact with patient within 60 days should be examined, tested and treated by doxycycline 100 mg PO twice a day for 7 days or azithromycin 1 gr PO in a single dose.

#### *Treponema pallidum* : Syphilis

Syphilis is a chronic infection caused by *Treponema pallidum*, a non cultivable helicoïdal spirochete. Transmission is interhuman mainly by direct contact with infectious lesions during sexual intercourse. In the past, endemic contamination was rare in our countries with mainly imported infections (migrants or infection acquired outside Europe by tourism). Since 1999, out-

breaks were documented in Western Europe (Netherlands, Belgium, France, Germany, Republic of Ireland, United Kingdom, Denmark) especially among MSM (50 to 80% of cases), particularly patients co-infected by HIV (50%) (1 ; 38-44). Average incubation period is 21 days (lasting from 10 to 90 days) (45).

Different stages of infection are distinguished :

- Early syphilis is defined as the stages occurring within the first year after acquisition. It includes primary syphilis, secondary syphilis and early latent syphilis (an asymptomatic phase).
- Late syphilis includes stages developing after the first year of acquisition. It includes late latent syphilis (an asymptomatic phase) and tertiary syphilis.

Primary syphilis is characterised by apparition of a painless papule at the site of inoculation that soon ulcerates to produce classical chancre (one to two cm ulcer with a raised, indurate margin and non-exsudative base). It is associated with regional adenopathy (often bilateral). Various atypical aspects can really be seen even pseudotumoral aspect in the rectum (46-47). Chancre may be unnoticed and heals spontaneously within three to six weeks.

Secondary syphilis will develop within weeks to a few months later. Secondary syphilis can produce a wide variety of symptoms (48). Rash is the most characteristic symptom : classically symmetric macular or papular eruption involving the entire trunk and extremities, including palms and soles. Large, raised, gray to white lesions may develop in mucuous membranes in the mouth and perineum (the so-called "condylomata lata"). Systemic symptoms are present : fever, headache, malaise, anorexia, myalgias, weight loss. Most patients with secondary syphilis have lymph node enlargement (posterior cervical, axillary, inguinal and femoral nodes). Other clinical manifestations can be encountered : alopecia, synovitis, osteitis, glomerulonephritis, uveitis.

Tertiary syphilis may appear from 1 to 30 years after contamination with central nervous system involvement (neurosyphilis, particularly general paresis and tabes dorsalis), cardiovascular involvement (aortitis) and gummatous syphilis (granulomatous, nodular lesions in a variety of organs) (49).

The diagnosis of syphilis is complicated by the fact that *Treponema pallidum* is a non cultivable bacteria. Diagnosis can be made either directly (direct visualization of the organism in clinical specimens) and indirectly by serology.

Direct diagnosis is based on darkfield microscopy examination of exudates collected on moist lesions (50). It requires rapid examination and serious experience and therefore is rarely done. Immunofluorescence and PCR techniques exist but are not available in Belgium.

Indirect diagnosis (serology) is used in current daily practice. Following tests are distinguished (Table 3) :

- Non treponemal tests based upon the serum reactivity from patients with syphilis to a cardiolipin-cholesterol-lecithin antigen : VDRL (Venereal Disease Research Laboratory) and RPR (Rapid Plasma Reagin) tests.
- Treponemal tests which are more complex and are usually used as confirmation tests : TPHA (*Treponema pallidum* Haemagglutination Assay), TPPA (*Treponema pallidum* Particle Agglutination Assay), FTA-abs (Fluorescent Treponemal Antibody Absorption), Elisa (Enzyme-Linked Immunosorbent Assay).

VDRL and RPR are used in screening and to monitor the response to therapy because they are quantitative tests (51). They become positive at 15 days of chancre. TPHA or TPPA are used only as initial confirmation tests and become positive at 10 days of chancre. FTA-abs IgM is essentially used for diagnosis of congenital syphilis or in recent infections because of rapid positivity ( $\leq 7$  days of chancre). Elisa IgM and IgG tests could be used for routine screening but this must still be confirmed. They become positive at  $\leq 7$  days of chancre.

In clinical practice VDRL and TPHA are the mostly used tests with interpretation depending of both results (Table 4). Evolutive syphilis is signed by a positive TPHA with a highly positive VDRL. In case of doubt, it is necessary to control the tests after 15 days.

Treatment of primary syphilis is based on a single dose of Benzathine Penicillin G (2,4 million units IM) (15). Secondary syphilis requires same injection of Benzathine Penicillin G 2,4 millions units IM once a

Table 3. — Serologic tests for Syphilis : type of tests, precocity and interest

	Type	Precocity	Interest
Non Treponemal Tests	VDRL or RPR	Positive at 15 days of chancre	Screening and treatment follow-up (quantitative value)
Treponemal Tests	TPHA or TPPA	positive at 10 days of chancre	Initial confirmation only
	FTA – ABS IgM	Positive $\leq 7$ days of chancre	Recent infections (chancre) or Congenital Syphilis
ELISA test (EIA)	IgM + IgG	Positive $\leq 7$ days of chancre	Routine screening only (must be confirmed)

Table 4. — Clinical interpretation of TPHA and VDRL tests for syphilis

Reactions	Interpretations
TPHA - /VDRL -	No Syphilis Primary Syphilis within 5 to 10 first days of chancre (if contact < 3 weeks => do FTA-ABS)
TPHA - /VDRL ++ to +++	Probable false-positive
TPHA + /VDRL - (or low titer of antibodies)	Serologic sequel : cured syphilis Primary syphilis within 10 to 15 first days of chancre Tertiary syphilis
TPHA + /VDRL + to +++ (or high titers of antibodies)	Evolutionary Syphilis

week during three weeks. Neurosyphilis therapy consists in daily intravenous (IV) injection of Penicillin G 18-24 million units during 10 to 14 days. During penicillin therapy, a Jarisch-Herxheimer reaction (acute febrile reaction frequently accompanied by headache and myalgias) can occur within the first 24 hours.

In case of penicillin allergy, these options have been proposed :

- Erythromycine 500 mg PO four times daily for 14 days or Azithromycin single oral dose of 2 gr (no longer recommended due to development of macrolide resistance).
- Doxycycline 100 mg PO twice daily for 14 days (or 28 days if late latent syphilis).
- Ceftriaxone 1 gr daily IV or IM for 8-10 days (not well documented and possible crossed allergy).

In case of neurosyphilis, a drug desensitization should be considered.

All patients should be clinically and serologically examined again every three months during one year. A four-fold reduction in titer of the non-treponemal antibody test (VDRL) after 6-12 months is considered as an appropriate response.

As any other STD, an attempt to find out and treat sexual partners of patients is mandatory.

## Conclusion

Each anorectitis in MSM is a sexually transmitted disease by default until proof to the contrary. Gastroenterologists and proctologists should know anorectal clinical aspect of STD and be aware of of this current epidemic.

Multiple concomitant contamination are common making a search of *HSV*, *Neisseria Gonorrhoeae*, *Chlamydia trachomatis* (direct diagnosis), Syphilis (serology) but also contamination by HIV, hepatitis B and hepatitis C mandatory.

Primary prevention is a condom use and awareness amongst the high risk population (MSM).

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