

2016 European guideline for the management of chancroid

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Guideline development

This guideline has been updated by reviewing the previous European chancroid guideline (2011) [1] CDC guidelines (2015) [2] BASHH guideline (2014) [3] and conducting a comprehensive literature search of publications from 2010 to April 2016.

Abstract

Chancroid is a sexually acquired disease caused by *Haemophilus ducreyi*. The infection is characterized by one or more genital ulcers, which are soft and painful, and regional lymphadenitis which may develop into buboes. The infection may easily be misidentified due to its rare occurrence in Europe and difficulties in detecting the causative pathogen. *H. ducreyi* is difficult to culture. Polymerase chain reaction (PCR) can demonstrate the bacterium in suspected cases. Antibiotics will usually be efficient for curing chancroid

New information in this guideline since 2011 edition:

- Chancroid is disappearing even from most countries where *Haemophilus ducreyi* was epidemic, with exceptional regions such as North India [4].

- Nevertheless recent sporadic case reports from Western Europe have been described, often initially misdiagnosed as genital herpes [5;6].
- In contrast to a sustained reduction in the proportion of GUD caused by *H. ducreyi*, this bacterium is increasingly found in tropical countries as a major cause of non-genital cutaneous ulcers especially in children [7].
- Management: There are no new data in the field of management

Epidemiology

Chancroid is a sexually transmitted infection (STI) caused by the small Gram-negative bacterium *Haemophilus ducreyi*. Recommendations for the diagnosis and management of chancroid has been given by a number of different institutions, including Centers for Diseases Control and Prevention [2], British Association for Sexual Health and HIV[3], and Public Health Agency of Canada [8] . In contrast to genital herpes the number of cases of chancroid is overall decreasing with rare exceptional regions such as Malawi with 15% of GUD [9]and North India with 24% of GUD [4]. A recent systematic review [7]analyzed 49 studies on chancroid. 35 were published during 1980-1999 and 14 during 2000-2014. The proportion of genital ulcers caused by *H. ducreyi* ranged in the earlier period from 0% in Thailand and China to 68.9% in South Africa. During the later time period, the proportion was low (<10%) except for Malawi. Overall, chancroid accounted for 8 cases (3%) of genital ulcers in an STD clinic in Paris from 1995 to 2005 [10].The substantial decrease has followed the recommendation to introduce syndromic management for treatment of GUD by the WHO after 2000 and after major social change [7]. Nevertheless, the global epidemiology of *H. ducreyi* is poorly documented due to difficulties in confirming microbiological diagnoses. Currently in Europe chancroid is restricted to rare sporadic cases [5;6]. Europeans may contract the disease while staying in countries with limited access to health services. As a number of persons travel from high-risk areas to work in the sex industry in Europe, the possibility of contracting chancroid in European countries should be considered. Recent studies have identified *H. ducreyi* as a previously unrecognized cause of nongenital skin ulcers in children in tropical areas [11;12]. *H. ducreyi* has been demonstrated in asymptomatic individuals [13]. Male circumcision is associated with reduced risk of contracting chancroid [14].

Clinical features

The incubation period for chancroid is short. Three to seven days after sexual intercourse with an infected person tender erythematous papules develop, most often on the prepuce and frenulum in men and on the vulva, cervix, and perianal area in women [15]. Extraanogenital chancroid has been reported in children and adults [16;17], and may represent an extraordinary diagnostic challenge, as clinical suspicion of chancroid may be low and the infection is not sexually transmitted. DNA from *H. ducreyi* has even been demonstrated in oesophageal lesions [18]. The significance of this finding is uncertain. The papules quickly progress into pustules, which rupture after a few days and develop into superficial ulcers with ragged and undermined edges. The bases of the ulcers are granulomatous with purulent exudates. The ulcers are soft and painful and may persist for months if left untreated. Secondary superinfections may cause induration. Autoinoculation from primary lesions on opposing skin may result in so-called “kissing ulcers”. Inguinal lymphadenitis, usually unilateral and painful, develops in approximately half of the patients, and may further progress into buboes. Fluctuant buboes may rupture spontaneously. According to CDC [2], a probable diagnosis of chancroid, for both clinical and surveillance purposes, could be made if all of the following criteria are met:

- 1) the patient has one or more painful genital ulcers;
- 2) the clinical presentation, appearance of genital ulcers and, if present, regional lymphadenopathy are typical for chancroid;
- 3) the patient has no evidence of *T. pallidum* infection by darkfield examination or nucleic acid amplification test (NAAT) of ulcer exudate or by a serologic test for syphilis performed at least 7 days after onset of ulcers; and
- 4) a NAAT for HSV or HSV culture performed on the ulcer exudate is negative (IV, C).

However, as neither specificity nor sensitivity of microscopy, serology, and antigen detection tests are comparable to nucleic acid detection, the latter is preferable for the diagnosis of agents of genital ulcers that may either cause the disease or co-infect the patient. Such diagnostic tests are available in many European countries.

Diagnosis

Microscopy.

H. ducreyi appears as small gram-negative rods. Microscopy may be done on ulcer swabs. Due to low sensitivity and specificity microscopy is, however, not recommended for diagnostic purpose.

Culture.

H. ducreyi is a very fastidious bacterium, and selective, enriched culture media are required for its isolation. Several different media have been used to isolate *H. ducreyi* from clinical specimens [19;20]. As different strains show different ability to grow on different media, a combination of at least two different media may be used for optimal recovery rates. Samples should be taken with a cotton-tipped swab from the base at the undermined edge of a lesion after cleansing by flushing with sterile saline. *H. ducreyi* will only survive few hours on the swab, and bedside inoculation of culture plates followed by immediate incubation can be done to reduce loss of viable bacteria during transportation. However, bedside plating is often not possible, and the swab should then be send to the laboratory in an appropriate transport medium, e.g. Amies or Stuarts medium [21]. Minimizing transport time and keeping the specimen at 4° C during transit will increase the chance of positive culture of *H. ducreyi*. Inoculated culture plates should be incubated at 33° C in a humid atmosphere containing 5% CO₂ for more than three days. Culture of material from buboes obtained by puncture and aspiration is less sensitive than culture from ulcers. Culture of *H. ducreyi* ensures a definite diagnosis of chancroid, but it does not rule out other concomitant infections. Culture is particularly important when further characterization of the bacterium such as antimicrobial susceptibility pattern is needed, e.g. in cases of therapeutic failure.

A definitive diagnosis of chancroid requires the identification of *H. ducreyi* on culture media; however, the advent of more sensitive DNA amplification techniques has demonstrated that the sensitivity of culture of *H. ducreyi* reaches only 75% at best [22-24](III, B).

NAAT.

Nucleic acid amplification techniques are excellent for demonstrating *H. ducreyi* in clinical sample material. Individual strain specific growth requirements do not influence the outcome of NAATs and NAATs show higher positive rates than culture. As these methods do not depend on live bacteria, samples may be analyzed in laboratories placed in remote distance from the patient, which is relevant in Europe as only few laboratories may establish NAATs for *H. ducreyi* due to the rare occurrence of chancroid. Specimens should be obtained as described for culture; no specific transport medium is required unless special procedures related to individual NAATs indicate otherwise. Specimens used for culture may be subjected to NAATs after inoculation on culture plates. The exudate from the ulcer is to be collected by vigorous rubbing of the base of the lesion with a sterile cotton-tipped swab that should be inserted into prelabelled cryotubes containing 0.5 ml transport medium to lyse the organisms and optimise DNA stability; the swabs could then be frozen (at -20°C) for transport to the laboratories [11].

Various different in-house PCR methods have been described, some of which having the advantage of simultaneously testing for other relevant pathogens, in particular *Treponema pallidum* and herpes simplex virus [25-30]. (III, B).

Serology.

Detection of antibodies against *H. ducreyi* is not relevant for the individual diagnosis of acute chancroid as demonstrated by experimental inoculation of the bacterium into volunteers [31].

Management

Information, explanation and advice for the patient

Patients should be informed that chancroid is a bacterial infection that is sexually transmitted but curable with antibiotics and that it is a cofactor for HIV transmission, as are genital herpes and syphilis (IV, C).

Symptoms should resolve within 1-2 weeks of commencing antibiotic therapy (III, B).

Patients should abstain from any sexual contact until they and their partner(s) have completed therapy (IV, C).

Testing for syphilis and herpes simplex virus should always be done in patients suspected to suffer from chancroid, both because the three diseases may clinically be difficult to distinguish from each other and because co-infections occur (IV, C). As mentioned above, tests based on nucleic acid detection are preferable if accessible.

Therapy

Successful treatment for chancroid cures the infection and resolves the clinical symptoms. In advanced cases, scarring can result, despite successful therapy. The World Health Organization has proposed syndromic approaches for treatment of genital ulcers to be used in settings, where appropriate laboratory diagnosis is not available [32]. The antibiotics treatment should be based on local aetiologies and antibiotic susceptibility patterns.

Several antibiotic regimens have been recommended for confirmed cases of chancroid:

- First line –
 - Ceftriaxone as a single intramuscular injection of 250 mg (Ib, A)
 - or
 - Azithromycin, as single 1 g oral dose, (Ib, A)

The response is generally good although failures, especially in HIV positive individuals, have been reported.

- Second line –
 - Ciprofloxacin 500 mg orally twice a day for three days (Ib, B),
 - or
 - erythromycin orally 500 mg four times a day for seven days (Ib, B)

Azithromycin and ceftriaxone offer the advantage of single-dose therapy. Children can be treated with ceftriaxone. Ciprofloxacin is contraindicated for pregnant and lactating women. The multiple days regimens are recommended for HIV positive patients rather than the single dose treatments [33].

An unblinded, prospective study designed to determine the efficacy of single-dose azithromycin for the treatment of chancroid was done in 133 patients who were randomized to receive 250 mg of ceftriaxone im or 1 g of azithromycin orally, both given as a single dose [34]. Azithromycin and ceftriaxone were equally effective in healing ulcers for which cultures were negative and after 23 days of treatment azithromycin was as effective as ceftriaxone for the treatment of chancroid (Ib, A)

Adjunctive therapy

All patients and in particular those who suffer from HIV infection and other immunosuppressive conditions should be carefully followed up by clinical examination [35] (IV, C).

Patients with fluctuant buboes will experience symptomatic relief if these are emptied. Needle aspiration is effective but may need to be repeated. Incision and drainage is an alternative [36]but some authorities believe that it may lead to sinus formation. Antibiotic cover is recommended if this is done (IV, C).

Partner notification

Sex partners of patients who have chancroid should be examined and treated, regardless of whether symptoms of the disease are present, if they had sexual contact with the patient during the 10 days preceding the patient's onset of symptoms [3] (IV, C). Partners should also be offered test for other STIs, including HIV.

Follow-up

All patients diagnosed with chancroid should be followed up at the end of treatment:

- to ensure resolution of symptoms and signs of infection; successful treatment should improve symptoms within 3 to 7 days. A test of cure is not necessary.
- to evaluate healing that might be slower for some HIV-infected patients and uncircumcised men.
- to document treatment failure, considering antibiotic resistance, re-infection, other causes of ano-genital ulcers, or an underlying immunodeficiency.

- to check that adequate partner notification has been completed.
- to address any patient concerns.
- to arrange suitable testing for syphilis and HIV.

Prevention/health promotion

Patients diagnosed with chancroid should be counselled regarding prevention of other STIs:

- Offer regular sexual health screening.
- Patients should be retested for syphilis and HIV 3 months after the diagnosis of chancroid, if the initial test results were negative.
- Condom use should be demonstrated and promoted.

Auditable Outcome Measures

- All cases of suspected chancroid should be subjected to laboratory investigations.
Target 100 % .
- Sexual contacts within 3 months should be traced, tested and treated.
- HIV and syphilis serological testing should be offered, as well as screening for concomitant STIs.
- Suspected or confirmed cases of chancroid should be reported and relevant surveillance data collected according to local and national guidelines.

Appendices:

Composition of editorial board:

www.iusti.org/regions/Europe/pdf/2013/Editorial_Board.pdf

List of contributing organisations:

www.iusti.org/regions/Europe/euroguidelines.htm

Tables of levels of evidence and grading of recommendations:
www.iusti.org/regions/Europe/pdf/2013/Levels_of_Evidence.pdf

Statement on declarations of interest: None

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