

Guideline on the Management of Chancroid

Developed by the IUSTI-Europe Guideline Editorial Board

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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 August 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. Nucleic acid amplification tests can demonstrate the bacterium in suspected cases. Antibiotics are usually effective in curing chancroid.

New information in this guideline since 2011 edition:

- Chancroid is disappearing even from most countries where *Haemophilus ducreyi* was previously epidemic, with the exception of North India and Malawi.^{4,5}
- Nevertheless recent sporadic case reports from Western Europe have been described, often initially misdiagnosed as genital herpes.^{5-6,7}
- In contrast to a sustained reduction in the proportion of genital ulcer disease (GUD) caused by *H. ducreyi*, the bacterium is increasingly found in tropical countries- especially the South pacific region- as a common cause of non-genital cutaneous ulcers most yespecially in children.^{8,7}
- Management: There are no new data for the management of chancroid.

Kommentiert [HM1]: I think the Malawi ref should be added here.

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 have 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.^{9,8} In contrast to genital herpes, the number of cases of chancroid is decreasing overall with rare exceptions such as Malawi with 15% of GUD^{5,9} and North India with 24% of GUD.⁴ The study from Malawi was published in 2013, although using data from 2004-6. A recent systematic review^{7,8} 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 in prevalence has followed the introduction of syndromic management for treating GUD by the WHO, and major social changes after 2000.^{8,7} Nevertheless, the global epidemiology of *H. ducreyi* is poorly documented due to difficulties in confirming a microbiological diagnosis. Currently in Europe chancroid is restricted to rare sporadic cases.^{5-6,7} As a number of people travel from high-risk areas to work in the sex industry in Europe, the possibility of contracting chancroid in European countries should also be considered. Recent studies have identified *H. ducreyi* as a previously unrecognized cause of non-genital 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 The genital 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 exudate. The ulcers are soft and painful and may persist for months if left untreated. Secondary superinfection 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 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, can 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, or antigen detection tests are comparable to nucleic acid detection, the latter is preferable to identify alternative diagnoses. Such diagnostic tests are available in many European countries. Extra-anogenital skin ulcers due to *H. ducreyi* (or cutaneous chancroid) has have reported in children and adults,^{16,17} and may represent a particular diagnostic challenge, as clinical suspicion maybe low and the infection is

not sexually transmitted. DNA from *H. ducreyi* has even been demonstrated in oesophageal lesions¹⁸ although the significance of this finding is uncertain. No adverse effects of chancroid on pregnancy outcome or on the foetus have been reported.

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 diagnosis.

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 strains differ in their 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 a 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 sent 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 (III, B).²²⁻²⁴

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 detection rates than culture. As these methods do not depend on live bacteria, samples may be analyzed in laboratories placed ~~in~~ remotely from the patient, which is relevant in Europe where only a few laboratories provide NAATs for *H. ducreyi*. Specimens should be obtained as described for culture; no specific transport medium is required unless special procedures related to individual NAATs indicate otherwise. Specimens taken for culture may also be used for NAATs. The exudate from the ulcer should be collected by vigorous rubbing of the base of the lesion with a sterile cotton-tipped swab. Various different in-house PCR methods have been described, some of which have the advantage of simultaneously testing for other relevant pathogens, in particular *Treponema pallidum* and herpes simplex virus (III, B).²⁵⁻³⁰

Serology.

Detection of antibodies against *H. ducreyi* is not helpful for the diagnosis of acute chancroid, as has been demonstrated by experimental inoculation of the bacterium into volunteers.³¹

Management

Information, explanation and advice should be given to 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 available.

Therapy

Since the 1970s, beta-lactamase producing strains of *H. ducreyi* emerged and treatment failures were common. Subsequently, further plasmid-mediated resistance to tetracycline, sulfonamides, chloramphenicol, and aminoglycosides also has been reported.³² Little is known about chromosomally mediated resistance in *H. ducreyi*, but decreased susceptibilities to various antibiotics in absence of identifiable resistance plasmids suggests evolving of such mechanisms. Based on in vitro susceptibility the most active drugs against *H. ducreyi* are azithromycin, ceftriaxone, ciprofloxacin and erythromycin. Worldwide, several isolates with intermediate resistance to either ciprofloxacin or erythromycin have been reported.

Successful treatment for chancroid cures the infection and resolves the clinical symptoms. In advanced cases, scarring can occur, 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.³³ The antibiotics treatment should be based on local epidemiology 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 as well as for children and adolescents less than 18 years where erythromycin or ceftriaxone regimens should be used. The multiple day regimens are recommended for HIV positive patients rather than the single dose treatments.³⁴

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.³⁵ Azithromycin and ceftriaxone were equally effective in healing ulcers for which cultures were negative, and azithromycin was as effective as ceftriaxone 23 days post-treatment (Ib, A). Although no antimicrobial susceptibility data for *H. ducreyi* have been published for two decades, it is still assumed that the infection will respond adequately to treatment with the recommended regimens.³⁶

Adjunctive therapy

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 alternative³⁷ but some authorities believe that it may lead to sinus formation. Antibiotic cover is recommended if this is done (IV, C).

Partner notification

Sexual 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 in the 10 days preceding the patient's onset of symptoms (IV, C).³ Partners should also be offered testing for other STIs, including HIV.

Follow-up

All patients diagnosed with chancroid should be followed up after 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 anogenital 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 (target 95% for all)

- All cases of suspected chancroid should be subjected to laboratory investigations.
- Sexual contacts within 10 days preceding the patient's onset of symptoms~~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.

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Appendices:

Composition of editorial board:

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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

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Kommentiert [HM2]: I cannot find ref 33 from WHO. However, this website from 2005 seems to be the syndromic management of genital ulcer: <http://apps.who.int/iris/bitstream/10665/43116/1/9241592656.pdf> page 109-113 (accessed 27 November 2016)