

## **2010 European guideline for the management of chancroid**

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## 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<sup>1</sup>, British Association for Sexual Health and HIV<sup>2</sup>, and Public Health Agency of Canada<sup>3</sup>.

In contrast to genital herpes the number of cases of chancroid is overall decreasing, and the eradication of chancroid is considered a feasible objective<sup>4</sup>. However, chancroid is still a cause of genital ulcers in resource poor countries, especially in South East Asia and Africa (e.g. Botswana<sup>5</sup>), where outbreaks have been occurring among sex workers in the cities, including capitals such as Nairobi<sup>6</sup>. Europeans may contract the disease while staying in these areas.

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. Using an improved culture medium, Hafaz et al.<sup>7</sup> found a higher number of chancroid cases than expected in Sheffield, and also demonstrated that many of the patients had concurrent infections with other sexually transmitted diseases, especially herpes simplex infections. Overall, chancroid accounted for 8 cases (3%) of genital ulcers in an STD clinic in Paris from 1995 to 2005<sup>8</sup>. In the U.K. the Health Protection Agency has reported a total of 450 cases diagnosed in Genito–Urinary Medicine clinics in the years 1995 – 2000<sup>9</sup>. Local outbreaks have been reported from various parts of Europe, including Rotterdam<sup>10</sup> and Greenland<sup>11</sup>.

Non-sexual transmission has been reported<sup>12,13</sup>. *H. ducreyi* has been demonstrated in asymptomatic individuals<sup>14</sup>. Male circumcision is associated with reduced risk of contracting chancroid<sup>15</sup>.

## **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. Extra-anogenital chancroid has been reported in children and adults<sup>12,13</sup>, and may represent an extraordinary diagnostic challenge, as clinical suspicion of chancroid may be low. DNA from *H. ducreyi* has even been demonstrated in oesophageal lesions<sup>16</sup>. 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 apposing 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<sup>1</sup>, 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 patient has no evidence of *T. pallidum* infection by darkfield examination of ulcer exudate or by a serologic test for syphilis performed at least 7 days after onset of ulcers; 3) the clinical presentation, appearance of genital ulcers and, if present, regional lymphadenopathy are typical for chancroid; and 4) a test for HSV performed on the ulcer exudates 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<sup>17,18</sup>. 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<sup>19</sup>. 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% CO<sub>2</sub> 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<sup>20-22</sup> (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 analysed 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.

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<sup>23-27</sup> (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<sup>28</sup>.

## **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<sup>29</sup>. 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 can be administered as a single intramuscular injection of 250 mg (Ib, A). The response is generally good although failures, especially in HIV positive individuals, have been reported.
  - Alternatively, azithromycin, as single 1 g oral dose, seems clinically at least as efficient as ceftriaxone (Ib, A)
- Second line - Ciprofloxacin can be used as a three-day course of 500 mg orally twice a day (Ib, B), or erythromycin may be used orally as 500 mg three or four times a day for seven days (Ib, B)

Azithromycin and ceftriaxone offer the advantage of single-dose therapy. Children and pregnant and lactating women can be treated with ceftriaxone. Ciprofloxacin is contraindicated for pregnant and lactating women.

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<sup>30</sup>. 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)

An open-label prospective study to examine the efficacy of a single 2-gm dose of spectinomycin for treatment of chancroid resulted in a 98% cure rate 14 days after treatment<sup>31</sup> (III, B). The results of another study with 5.0 g of granulated thiamphenicol, orally, in a single dose, indicated a high cure rate with a low incidence of side effects<sup>32</sup> (IIb, B). In clinical trials, fleroxacin has been evaluated in the treatment of chancroid (single oral doses of 200 or 400 mg) with bacteriological cure rates around 80%<sup>33</sup> (III, B).

#### 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<sup>34</sup> (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<sup>35</sup> 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<sup>2</sup> (IV, C).

### **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.

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**Declaration of interest**

None to declare

## Appendix 1

### **Search strategy**

The previous European IUSTI guideline titled “European Guideline for the Management of Tropical Genito-ulcerative diseases” from October 2001 was used as a basis for the current guideline, as it was “The 2007 National Guideline for the Management of Chancroid” produced by the British Association for Sexual Health and HIV ([www.bash.org](http://www.bash.org)). MEDLINE and PubMed searches were performed from 2007 to December 2009 using the MeSH heading “chancroid” including all documents and subheadings. A Cochrane search showed 61 clinical trials published between 1951 and 1999 but no systematic reviews on chancroid.

## Appendix 2

### LEVELS OF EVIDENCE AND GRADING OF RECOMMENDATIONS

#### **Levels of evidence**

Ia: Evidence obtained from meta-analysis of randomized controlled trials (RCTs);

Ib: Evidence obtained from at least one RCT;

IIa: Evidence obtained from at least one well-designed study without randomization;

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 RCT as part of the body of literature of overall good quality and consistency addressing the specific recommendation.

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

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