



UK National Guideline for the management of chancroid 2014

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Guideline development group membership

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New information in this guideline since the 2007 edition:

- Epidemiology
 - Latest data from GUM clinics reports in England [HPA 2013]
 - Chancroid is disappearing even from countries where *Haemophilus ducreyi* was once endemic. In some areas it may have disappeared already. Herpes simplex virus type 2 (HSV-2) is now the most common cause of genital ulceration in all countries.
- Management:
 - There have been no recent developments in the field of management.

Introduction and methodology

Objectives

The main purpose of this guideline is to offer recommendations on the diagnosis, treatment and health promotion principles for the effective management of chancroid. It is aimed primarily to assist in the management of people aged 16 years and older presenting to services offering Level 3 care in sexually transmitted infection (STI) management within the UK. However, the principles of the recommendations could be adopted at all levels.

Methods and rigour of development

This guideline was produced according to specifications set out in the Clinical Effectiveness Group's CEG 2010

document 'Framework for guideline development and assessment'.¹

The review has been updated by searching PubMed from 1999 to 2013 using the search terms/MeSH headings: "Chancroid", "Chancroid and diagnosis", "Chancroid and treatment", "*Haemophilus ducreyi* diagnosis", "*Haemophilus ducreyi* treatment" and "Chancroid and randomized trial". The Cochrane Library was searched to 2013 using the MeSH headings "chancroid" and "*Haemophilus ducreyi*" as were the CDC STD guidelines of 2010,² WHO STD guidelines³ and the 2011 European Guideline for the Management of Chancroid.⁴ In addition, abstracts and proceedings from the most recent International Conferences on AIDS, Meetings of the International Society for STD Research (ISSTD) and BASHH Spring Meeting were reviewed.

Piloting and feedback

The initial draft of the guideline, including a patient information leaflet was piloted for validation by the Clinical Effectiveness Group (CEG).

The final guideline was then reviewed by the CEG using the AGREE instrument before posting it on the BASHH website for external peer review for a two-month period. Comments received were collated by the CEG editor and sent to the guideline chair for review and action. The final guideline was approved by the CEG and a review date agreed before publication on the BASHH website.

The rare nature of this disease precluded the review of this guideline by a patient suffering from chancroid. However, the guideline was reviewed by the BASHH *Patient and Public Engagement* panel which includes members of the public, representatives of sexual

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NICE has accredited the process used by BASHH to produce its European guideline on the management of chancroid. Accreditation is valid for 5 years from 2014.
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health voluntary sector organisations, young people's groups and sexual health professionals.

Aetiology and epidemiology

H. ducreyi, the microbial causative agent of chancroid, is a Gram-negative facultative anaerobic coccobacillus and is placed in the family Pasteurellaceae.⁵ Chancroid was one of the most common causes of genital ulcer disease (GUD) in many parts of the world, but the incidence has now decreased markedly. It has been identified as the cause of up to 38% and 56% of genital ulcers in some countries of Asia and Africa, respectively.^{6,7}

Chancroid cases are now only diagnosed sporadically even in countries where there was a significant prevalence. In Durban⁸ in 2004, Lusaka⁹ in 2010 and Mozambique¹⁰ in 2005, the prevalences of chancroid infection were 1%, 0% and 4%, respectively. The decrease in chancroid occurred after GUD was identified as an important risk factor for female-to-male HIV transmission in the late 1980s.¹¹ Following this, more attention was paid to GUD control as a means of limiting the spread of HIV: the microbial aetiology of GUD subsequently changed so that herpes became by far the most common cause of GUD in developing countries.¹²

More specific reasons for the decrease in chancroid probably include a combination of the following:

- Use of more appropriate antibiotics – for a long time, tetracycline and trimethoprim-sulfamethoxazole (TMP-SMX) were used to treat genital ulcers in many African countries despite the emergence of widespread resistant strains of *H. ducreyi*. The decrease in chancroid coincided with the widespread use of erythromycin for GUD management.
- Behaviour change and increased condom use in high risk groups such as female sex workers and their clients.
- More widespread use of syndromic management coupled with increased serological testing for syphilis in many developing country settings.

Chancroid in the West

Chancroid has been a rare occurrence in industrialised countries since the mid-1960s. There were only between 50 and 80 reported cases of 'tropical genital ulcers' (combining chancroid, lymphogranuloma venereum [LGV] and donovanosis) in GUM clinics in England & Wales annually between 1996 and 2002. In the UK, separate reporting for chancroid was undertaken between 1975 until 1985.¹³ A peak of 125 cases was reported in 1982.¹⁴ From then until 2009 reporting

for the C1–C3 codes was undertaken. The Sexual Health & HIV Activity Property Type (SHHAPT) code that all clinics record and report to Public Health England for chancroid, LGV and donovanosis, respectively, was done jointly until 2009 when cases were diagnosed as separate disease entities again. The most recent data from the Health Protection Agency (HPA) report 79, 146, and 83 cases of chancroid in 2009–2011, respectively (HPA, personal communication). However, very few of these were confirmed and most are likely to be reporting errors. The majority of cases in the UK are either acquired abroad or from a partner who has been abroad.

Previously, a few sporadic outbreaks have been reported in Europe and the USA.^{15–20} In Sheffield UK, 46 cases were reported in 1982¹⁵ but a number of unusual features were apparent in that concomitant herpes infection was frequent and few partners of index cases were found to have chancroid.¹⁴ In Paris, chancroid accounted for 3% of genital ulcers in a STI clinic from 1995 to 2005 and all cases were observed before 2002.¹⁶ Other outbreaks have usually been associated with sex work and were brought under control using intensive partner notification schemes.

Clinical features

Chancroid is characterised by ano-genital ulceration and lymphadenitis with progression to bubo formation. A break in the skin during intercourse is usually required for sexual transmission to occur. The usual incubation period is 4–7 days. There are no prodromal symptoms. Lesions start as a tender papule that develops into a pustule and then an ulcer or soft sore. Classically, ulcers have a ragged undermined edge with a grey or yellow base that bleeds when touched. Lesions are painful and may be single or multiple.

The usual sites of infection are, in men, the prepuce, coronal sulcus, frenulum and glans and in women, the labia minora and fourchette. Ulcers of the vaginal wall and cervix are uncommon. Extragenital lesions are rare but have been reported on the fingers, breasts and inner thighs. *H. ducreyi* does not disseminate systemically. Asymptomatic carriage of *H. ducreyi* has been documented in the vagina and cervix.^{21,22}

Clinical variants can occur. These include giant phagedenic ulcers, dwarf chancroid similar to herpes, follicular chancroid similar to pyogenic infection, and single painless ulcers not unlike syphilis.

Painful inguinal lymphadenopathy is found in about half the male cases but less so in women. These lymph glands may develop into buboes that should be managed by aspiration rather than incision and drainage. Fluctuant buboes may rupture spontaneously causing delayed healing.

The differential diagnosis includes syphilis, genital herpes, LGV and donovanosis. Mixed infections with other causes of genital ulceration should always be considered.

Complications

Mostly seen in men, these may include phimosis and partial loss of tissue, particularly on the glans penis. Healed ulcers may result in tissue contraction and predispose to mucosal breaks and bleeding that might increase the risk of HIV transmission during sexual intercourse. Mild constitutional symptoms may occur.

A recent report from Papua New Guinea confirmed *H. ducreyi* infection as a cause of skin ulceration in children using 16S rDNA sequencing.²³

There appears to be little or no secondary protective immunity to *H. ducreyi* infection, as experimental studies of inoculation of *H. ducreyi* to human volunteers have shown.²⁴

Diagnosis

A number of papers have summarised the current approach to diagnosis. The main methods revolve around the identification of *H. ducreyi* by:

- Detection of nucleic acid (DNA) by amplification techniques such as polymerase chain reaction (PCR), using nested techniques.^{25–27} There are no commercial assays available, but a number of specialised or research laboratories have published their in-house methods.^{7,28}
- Culture of material obtained from the ulcer base, or the undermined edges of the ulcer, after removing superficial pus with a cotton-tipped swab, or from pus aspirated from the bubo. The material can be plated directly onto culture medium incubated at 33°C in high humidity with 5% carbon dioxide for a minimum of 48–72 h.

Culture media include²⁹:

- GC agar supplemented with 1–2% bovine haemoglobin, 5% fetal calf-serum.³⁰
- Mueller-Hinton agar enriched with 5% chocolatised horse blood (30). Both of these also require supplements of 1% IsoVitaleX, and 3 mg/L vancomycin to prevent overgrowth of Gram-positive organisms.
- Modification of these techniques by substitution of 0.2% activated charcoal instead of fetal calf serum has proven equally effective and is much cheaper.³¹

The use of more than one medium increases sensitivity, which is still low (<80%).³⁰ Since *H. ducreyi* is a

fastidious organism, specimens should be plated out directly at the clinic or sent rapidly (within 4 h) to the laboratory; calcium alginate or plastic swabs should be used for sample collection; special transport medium may be helpful if culture media are not readily available.³² Confirmatory testing for oxidase, alkaline phosphatase, nitrate reduction and porphyrins can be used.³³

Microscopy of a Gram-stained smear (or other stains) of material from the ulcer base or of pus aspirate from the bubo may show characteristic Gram-negative coccobacilli, with occasional characteristic chaining. The test has low sensitivity and is not recommended as a diagnostic test.²⁹

Expert opinion has estimated that, in endemic areas, a positive *H. ducreyi* culture is achievable in 60–80% of patients considered to have chancroid on clinical grounds. Microscopy is only 50% sensitive compared to culture, and prone to multiple errors, given the polymicrobial flora of many ulcers. PCR is the most sensitive technique, and has been demonstrated to be 95% sensitive compared to culture; conversely culture may be only 75% sensitive relative to PCR. However, PCR may be negative in a number of culture-proven chancroid cases owing to the presence of Taq polymerase inhibitors in the DNA preparations extracted from genital ulcer specimens.³⁴ Multiple PCR assays have also been developed for the simultaneous amplification of DNA targets from *H. ducreyi*, *T. pallidum* and HSV types 1 and 2.^{7,28}

Other diagnostic methods

Other diagnostic tests have included various antigen-detection techniques involving immunofluorescence or radio-isotopic probes, but these are not used currently in the UK.

Serology

The detection of antibody to *H. ducreyi* as a marker of chancroid has been effective in a number of epidemiological studies with enzyme-linked immunoassays (EIAs) using either lysed whole cell, lipooligosaccharide (LOS) or outer membrane proteins (OMPs) as antigen sources.^{35,36} However, for the individual patient, the method lacks sensitivity, specificity (cross-reaction with other *Haemophilus* species) and cannot distinguish between remote and recent infection.

To circumvent the many problems of confirming a positive diagnosis of chancroid, the Centers for Disease Control and Prevention in the USA have proposed that a 'probable diagnosis' for both clinical and surveillance purposes be made if the patient has one or more painful genital ulcers, and (a) no evidence of

T. pallidum infection by dark field examination of ulcer exudate or by a serologic test for syphilis performed at least seven days after onset of ulcers, and (b) the clinical presentation, appearance of the genital ulcers and regional lymphadenopathy, if present, is typical for chancroid and a test for HSV performed on the ulcer exudate is negative.²

Clinical diagnosis

A number of studies have found that the clinical diagnosis of genital ulcers is often unreliable with an accuracy ranging from 33 to 80%, even in areas of high prevalence and good clinical expertise.^{37–39} However, the true accuracy may be higher. Some of these studies suffered because of the low sensitivity of culture methods used. In the past, this would not have mattered too much as syndromic management would cover the significant prevalence of mixed infections: co-infections of *H. ducreyi* with *T. pallidum* or HSV were frequent, occurring in over 10% of patients in many African studies.³ However, now that the prevalence of chancroid has decreased, it is likely that the use of syndromic management too will decrease and clinical diagnosis may assume increased importance.

Management

General advice

1. Patients should be advised to avoid sexual intercourse until they and their partner(s) have completed treatment and follow-up.
2. Patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications both for their health and that of their partner(s). This should be reinforced by giving them clear and accurate written information.

Further investigations

Screening for other possible causes of genital ulcerative disease should be undertaken, particularly for syphilis, genital herpes, LGV or donovanosis. Full STI screening should be offered. Biopsy of lymph nodes may be required to exclude neoplasia, if lymphadenopathy does not resolve following treatment.

Treatment

Successful treatment of chancroid should cure infection, resolve clinical symptoms and prevent transmission to sexual partners.

It should be noted that no comparative treatments have been published since 1999 in which chancroid has been confirmed by culture or PCR.⁴⁰ The main treatment options are presented in Table 1 (summarised below) and most are similar to the 2010 CDC guidelines from the USA. Evidence of their clinical efficacy has been obtained in randomised controlled trials for some (level of evidence Ib). However, grading of recommendation also takes account of ease of administration, side effects and compliance.

Recommended regimens

- Azithromycin 1 g orally in a single dose (Ib, grading A)
or
- Ceftriaxone 250 mg intramuscularly (IM) in a single dose (Ib, B)
or
- Ciprofloxacin 500 mg orally two times a day for three days (Ib, B/A) or
- Erythromycin base 500 mg orally four times a day for seven days (Ib, B/A).

The latter two regimens are recommended for HIV-positive patients rather than the single dose treatments.

Azithromycin and ceftriaxone offer the advantage of single-dose therapy. They have excellent in vitro activity against *H. ducreyi* with no reported resistance.¹⁸ However, a study comparing single dose treatment of chancroid using thiamphenicol versus azithromycin found that all four HIV-positive cases treated with azithromycin failed therapy.⁴¹ Moreover, in this study chancroid was diagnosed after exclusion of syphilis by clinical characterisation of genital necrotic and painful sores and positive Gram stains and not by culture or PCR.

Erythromycin given at high doses for seven days is one WHO-recommended first line treatment for chancroid.³ Although efficacious (with cure rates of 93% noted in Kenya⁴² and India⁴³), poor compliance and gastrointestinal intolerance make alternative therapy desirable (Ib, B). Lower dosage and simpler regimens of erythromycin have been evaluated in two separate trials in Kenya. Cure rates of 91% were achieved in a randomised double blind trial of erythromycin 500 mg three times daily for seven days (versus a single dose of ciprofloxacin)⁴⁴ (Ib, B). The efficacy of an even shorter regimen (250 mg three times daily for five days) was reportedly high in a small trial conducted by the same team, but this was not a randomised comparative trial⁴⁵ (III, C).

Table 1. Drugs shown to be effective in the treatment of Chancroid.

Drug	Dose	Route	Cost	Grading of recommendation	Level of evidence	References
Azithromycin*	1 g STAT	O	£7.16	A	Ib	42 56
Ceftriaxone*	250 mg STAT	IM	£2.40	B	Ib	41 57 50 56
Ciprofloxacin*	500 mg twice daily for three days ^a	O	£7.50	B/A	Ib	58 43
Erythromycin*	Or 500 mg STAT	O	£1.25	B	Ib	44
	500 mg four times daily for seven days ^a	O	£11.22	B/A	Ib	42 ^b 43
	or 500 mg three times daily for seven days	O	£8.73	A	Ib	44
	Or 250 mg three times daily for five days	O	£3.00	C	III	45

Note: Costs from British National Formulary Sept 2012.

^aCurrently recommended by CDC.

^bProposed for HIV +ve patients.⁴¹

Worldwide, several isolates with intermediate resistance to either ciprofloxacin or erythromycin have been reported; thus single dose ciprofloxacin and the shorter (five days) regimen of erythromycin may not be effective, as has been reported by teams in Rwanda and Malawi.^{46,47} However, a double-blind randomised controlled trial conducted in Nairobi showed comparable cure rates for single dose ciprofloxacin (92%) and the standard seven-day course of erythromycin (91%).⁴⁴

Widespread resistance to TMP-SMX renders this cheap and once effective alternative^{48,49} virtually useless.

Allergy

Patients allergic to quinolones or cephalosporins should be treated with the erythromycin regimen.

Special considerations

Treatment for pregnant or lactating mothers and treatment for children

The safety of azithromycin for pregnant and lactating women has not been established. Ciprofloxacin is contraindicated for pregnant and lactating women,

children and adolescents less than 18 years of age in which case erythromycin or ceftriaxone regimens should be used. No adverse effects of chancroid on pregnancy outcome or on the fetus have been reported.

HIV infection

- Probable increased incidence of delayed healing and treatment failures though evidence is conflicting.
- Treatment of choice is erythromycin 500 mg qds for seven days or ciprofloxacin 500 mg bd for three days.

Patients co-infected with HIV should be closely monitored. There have been concerns that healing may be slower among HIV-infected people^{45,47} and treatment failures have been frequently recorded in Kenya using azithromycin,⁴² ceftriaxone,⁵⁰ and in Malawi using low-dose erythromycin or ciprofloxacin.⁴⁷ However, delayed healing of coexistent HSV infection may have contributed to these findings. A higher treatment failure rate among HIV-infected patients has, however, not been observed by the same Kenyan team in a study using low-dose erythromycin or single-dose ciprofloxacin.⁴⁴ In Rwanda, Bogaerts

et al. found that HIV and the degree of immunosuppression as measured by CD4 counts had no effect on bacteriologic and clinical outcomes, and that treatment failures were entirely attributable to resistance of *H. ducreyi* to TMP-SMX.⁴⁶ CDC recommends that “since data on therapeutic efficacy with the recommended ceftriaxone and azithromycin regimens among patients infected with HIV are limited, those regimens should be used among persons known to be infected with HIV only if follow-up can be assured”.² Others have concluded that azithromycin should be avoided in co-infected patients.⁴¹ The case for using erythromycin was borne out by the acceptable response to syndromic management that was not related to HIV-1 infection when this drug was used in a study in Durban.⁵¹

A Cochrane review⁵² done to investigate whether genital ulcer disease treatment reduced sexual acquisition of HIV identified three studies, two of which involved treatment of chancroid in Nairobi involving HIV-negative men.^{53,54} The former trial compared fleroxacin to TMP-SMX and the latter investigated two different doses of fleroxacin. The cure rates for chancroid were both very high. Not surprisingly, HIV acquisition was not reduced given the short follow up – presumably seroconverters would have acquired chancroid and HIV from an untreated HIV-positive contact at the same time prior to any treatment. However, the conclusion of the Cochrane review was that there was insufficient evidence that treatment of genital ulcer disease reduces sexual acquisition of HIV infection. The results of this review once again demonstrate both the difficulties in designing trials that might be capable of investigating the link between STIs and HIV transmission amongst casual sex acts – one of the main determinants in the spread of HIV,⁵⁵ and the need to undertake reviews in areas where there is significant biological plausibility in the question asked.

Management of fluctuant buboes

The classic strategy has been to needle-aspirate fluctuant buboes from adjacent healthy skin. The procedure is simpler and safer than incision, which is prone to complications (sinus formations). A randomised study conducted during an outbreak of chancroid in the USA²⁰ has shown that careful incision and drainage was also an effective and safe method for treating fluctuant buboes and avoided frequent needle re-aspirations. This procedure should always be performed under effective antibiotic cover.

Follow-up. Patients should be re-examined 3–7 days after initiation of therapy. If treatment is successful, ulcers

improve symptomatically within three days and substantial re-epithelisation occurs within seven days after onset of therapy. The time required for complete healing is related to the size of the ulcer (and perhaps HIV-related immunosuppression; large ulcers may require more than two weeks). Clinical resolution of fluctuant lymphadenopathy is slower than that of ulcers and may require frequent needle aspiration (or drainage).

A test of cure is not recommended.²⁹

Treatment failures should warrant: (i) investigation of possible coinfections with *T. pallidum* or HSV; or (ii) determination of possible resistance by isolation of *H. ducreyi* and susceptibility testing by the agar dilution technique to determine minimal inhibitory concentrations but this requires a specialised laboratory.³³

Sexual partner(s) management

Persons who have had sexual contact with a patient who has chancroid within the 10 days before onset of the patient’s symptoms should be examined and treated even in the absence of symptoms, as asymptomatic carriage of *H. ducreyi* has been proven to occur,^{21,22} but screening is not recommended.

Intended audience

Clinicians working in Genito-Urinary Medicine/Level 3 Sexual Health clinics in the UK.

Applicability

Suggestions for diagnostic approaches made in this guideline should be tailored to local resources. This guideline recommends the use of NAAT and culture tests to diagnose *H. ducreyi* infection. However, these tests may not be routinely available except in specialised laboratories.

In the UK, specimens should be sent to the Sexually Transmitted Bacteria Reference Unit (STBRU) at Public Health England (stbru@phe.gov.uk). For PCR testing, a dry swab should be taken and stored at 4°C. This is an in-house realtime multiplex PCR that also tests for syphilis and HSV in addition to *H. ducreyi*.

Antimicrobials recommended are widely available in the UK, but depending on costs, choices can be made. The costs of therapy based on recent British National Formulary costs are indicated in Table 1.

Auditable outcome measures

All cases of suspected chancroid should be subjected to laboratory investigations. Target 100%. Sexual partners should be traced and treated.

H. ducreyi should be isolated from genital ulcer swabs in 40% of clinically diagnosed chancroid cases.²⁹

The SHHAPT code "C1" should be submitted to the Genito-Urinary Medicine Clinic Activity Dataset (GUMCAD) for each case with a diagnosis of chancroid. (England and Wales). Standard: 97%.

A plan for HIV testing, that included HIV testing and repeat testing to account for early HIV infection, should be documented. Standard: 100%.

A plan for syphilis testing, that included testing and retesting after three months to account for early syphilis infection, should be documented. Standard: 100%.

Editorial independence

This guideline was commissioned, edited and endorsed by the BASHH CEG without external funding being sought or obtained. All members of the guideline writing committee completed the BASHH conflict of interest declaration at the time the guideline's final draft was submitted to the CEG.

Conflict of interest

The authors declare no conflict of interest.

Membership of the Clinical Effectiveness Group

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