

## 2007 National Guideline for the Management of Chancroid

Clinical Effectiveness Group (British Association for Sexual Health and HIV, BASSH)

### New information in this guideline since 2001 revisions

- *Aetiology and Epidemiology:*
  - latest data from GUM clinics reports in England [HPA 2006]
  - chancroid is increasingly disappearing even from countries where *H ducreyi* was once endemic; this is replaced by an epidemic of HSV-2; reasons for this epidemiological shift are provided
- *Diagnosis:* a review of chancroid diagnostic methods has been added [Lewis & Ison, 2006]
  - details of the culture media components given
  - successful use of multiplex PCR (to detect simultaneously *H ducreyi*, *T pallidum*, and HSV) has been reported in several studies
- *Management:*
  - There have been no recent development in the field of management.

## **Aetiology and Epidemiology**

*Haemophilus ducreyi*, the microbial agent of chancroid, used to be probably the most common cause of genital ulcers in many parts of the world, particularly in the developing countries of Africa and Asia, where it was isolated from 20-60% of patients with genital ulcerations until the early 1990's [Plummer, 1983; Piot & Holmes, 1990]. The pattern of genital ulcer disease (GUD) is changing, however, and recent studies [Chen, 2000; Htun, 1998; Malonza, 1999; Lai, 2003; O'Farrell, 1999; Paz-Bailey, 2005; Riedner, 2007; Wawer, 1999] have found that, while GUD attributable to *Herpes simplex virus* type-2 (HSV-2) infection is increasing, *H ducreyi* is decreasing in many areas. In repeated cross-sectional studies of gold miners in South Africa, the proportion of genital ulcers caused by HSV-2 increased from 1% in 1986, to 17% in 1994, and 36% in 1998, while the corresponding decline in *H ducreyi* isolation was observed from 70% to 50% [Lai, 2003]. Similar findings were reported from Botswana [Paz-Bailey 2005]. Possible explanations include (i) diagnostic advances for HSV detection using nucleic acid amplification tests (NAATs); (ii) increasing HIV epidemic which would be expected to facilitate clinical recurrences of HSV-2 with advancing immunosuppression, and may have led to excess mortality among core groups such as sex workers and their partners, who traditionally experience high rates of *H ducreyi* infection; and (iii) possible success of the widespread use of syndromic management coupled with increased serological testing for syphilis in many developing country settings. As evidence of this, one study among a cohort of sex workers in Tanzania showed that regular STI screening and treatment of STI over an extended period could effectively reduce bacterial STI and led to the relative emergence of HSV-2 [Riedner, 2007].

*H ducreyi* is also known to be an important cofactor in the transmission of HIV infection [Plummer, 1991; Fleming & Wasserheit, 1999], its diagnosis and treatment assuming therefore even greater importance. Chancroid has been a rare occurrence in industrialised countries since the mid-1960's. There had been only between 50 and 80 reported cases of 'tropical genital ulcers' (combining chancroid, LGV and donovanosis) in GUM clinics in England & Wales annually between 1996 and 2002, and the recent

increase to 300 cases is mainly due to the recent epidemic of LGV [HPA, 2006]. Most cases are acquired abroad or with a partner who has been abroad. A few outbreaks have occurred in recent years in Canada and in some of the US Southern states. Aggressive control methods have been employed successfully [Hammond, 1980; Ernst, 1995].

Co-infections of *H ducreyi* with *Treponema pallidum* or *Herpes simplex virus* (HSV) are frequent and occur in over 10% of patients in many African studies. Differential clinical diagnosis is often unreliable with an accuracy ranging from 33-80%, even in areas of high prevalence and good clinical expertise [Dangor, 1990; O'Farrell, 1994; Ndinya-Achola, 1996; Chen, 2000]. Two alternatives can be considered and even combined: laboratory testing to rule out the presence of other GUD-causing pathogens such as syphilis, and where possible HSV-2, or the use of syndromic treatment, a strategy that combines antimicrobials to cover all possible treatable aetiologies of GUD. This approach has been advocated by the World Health Organisation (WHO) in places where diagnostic facilities are not readily available [WHO 2003].

### **Clinical features**

Chancroid is characterized by ano-genital ulceration and lymphadenitis with progression to bubo formation. The incubation period ranges between 3 and 10 days, and the initial lesion may progress rapidly to form an open sore. There are no prodromal symptoms.

#### **AT THE SITE OF PRIMARY INOCULATION**

The ulcer is classically described as:

- Single or (often) multiple
- Not indurated (“soft sore”)
- With a necrotic base and purulent exudate
- Bordered by ragged undermined edges
- Bleeding easily on contact
- Painful: a distinctive feature, more common in men than in women, depending on the site of inoculation

In males, most ulcers are found on the prepuce near the frenulum or in the coronal sulcus. In females, most lesions are found at the entrance of the vagina, particularly the fourchette. Several lesions may merge to form gigantic ulcers.

#### REGIONAL LYMPH NODES

Painful inguinal adenitis is also a characteristic feature of chancroid and may be present in 50% of cases. The adenitis is unilateral in most patients. Bubo forms and can become fluctuant and rupture, releasing thick pus, resulting sometimes in extensive ulceration.

#### COMPLICATIONS

Mostly seen in men, these may include phimosis and partial loss of tissue, particularly on the glans penis (so called “phagedenic” ulcers).

There can be mild constitutional symptoms but *H ducreyi* has not been shown to cause systemic infection or to spread to distant sites.

There appears to be little or no immunity to *H ducreyi* infection, as experimental studies of inoculation of *H ducreyi* to human volunteers have shown [Al-Tawfiq, 1999].

#### **Diagnosis**

A number of excellent recent reviews have summarized the approach to diagnosis. The main methods revolve around the identification of *H ducreyi* [Van Dyck & Piot, 1992; Ronald & Albritton, 1999; Lewis, 2000; Lewis & Ison 2006] by:

- (i) *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 hours.

Culture media include [Lewis & Ison, 2006]:

- GC agar supplemented with 1-2% bovine haemoglobin, 5% fetal calf-serum, 1% IsoVitaleX, and 3mg/L vancomycin [Dangor, 1992]
- Mueller-Hinton agar enriched with 5% chocolatised horse blood, IsoVitaleX and 3mg/L vancomycin [Dangor 1992]
- modification of these techniques by substitution of 0.2% activated charcoal instead of fetal calf serum has proven equally effective and is much cheaper [Lockett, 1991]

The use of more than one medium increases sensitivity, which is however low (<80%) [Dangor, 1992]. Since *H ducreyi* is a fastidious organism, patients' specimens should be plated out directly at the clinic or sent rapidly (within 4 hours) to the laboratory; calcium alginate or plastic swabs should be used for sample collection; unfortunately, special, not widely available, transport medium needs to be used.

- (ii) *Detection of nucleic acid (DNA)* by amplification techniques such as polymerase chain reaction (PCR), using nested techniques [Trees & Morse S, 1995; West, 1995; Webb, 1996]. There are unfortunately no commercial assays available, but a number of specialized or research laboratories have published their in-house methods [Orle, 1996; Morse, 1997].
- (iii) *Microscopy* of a Gram stained smear (or other stains) of material from the ulcer base or of pus aspirate from the bubo: demonstration of characteristic gram-negative coccobacilli, with occasional characteristic chaining. The test has low sensitivity and is not recommended as a diagnostic test [Lewis & Ison, 2006].

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. Yet, 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 [Lewis, 2000]. 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 [Orle, 1996; Morse, 1997].

#### OTHER DIAGNOSTIC METHODS

Other diagnostic tests have included various antigen-detection techniques involving immunofluorescence or radio-isotopic probes.

##### *Serology*

The detection of antibody to *H ducreyi* as a marker of chancroid has been useful in a number of epidemiological studies, using enzyme-linked immunoassays (EIAs) using either lysed whole cell, lipo-oligosaccharide (LOS) or outer membrane proteins (OMPs) as antigen sources [Museyi, 1988; Alfa, 1993]. However, for the individual patient, the method lacks sensitivity, specificity (cross-reaction with other *Haemophilus* species) and cannot distinguish between remote and recent infection, so serology should not be used for management.

To circumvent the many problems of positive diagnosis of chancroid, the Centers for Disease Control and Prevention (CDC [CDC, 2007]) proposes 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 7 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 is negative.

#### **Management**

##### General advice

- (1) Patients should be advised to avoid unprotected 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 for the health of themselves and 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 arranged, particularly the diagnosis of *T pallidum* and genital herpes, but also sometimes the diagnosis of lymphogranuloma venereum (LGV) or donovanosis (see specific guidelines). In addition serological screening for syphilis and HIV should be offered. Biopsy of lymph nodes may be required to exclude neoplasia.

#### Treatment

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

The main treatment options are presented in Table 1 (summarised below) and most are similar to the 2006 CDC guidelines. Evidence of their clinical efficacy has been obtained in randomized controlled trials for most (level of evidence Ib), however grading of recommendation will also take 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 in a single dose (Ib, B)  
*or*
- Ciprofloxacin 500 mg orally two times a day for 3 days (Ib, B/A)  
*or*

- Erythromycin base 500 mg orally four times a day for 7 days (Ib, B/A)

Azithromycin and ceftriaxone offer the advantage of single-dose therapy. They have excellent in vitro activity against *H ducreyi* with no reported resistance to date [Ronald & Albritton, 1999].

Erythromycin given at high doses for 7 days is the WHO-recommended first line treatment for chancroid [WHO, 2003]. Although efficacious (with cure rates of 93% noted in Kenya [Tyndall, 1994] and India [D'Souza, 1998]), 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 7 days (versus a single dose of ciprofloxacin) [Malonza, 1999] (Ib, B). The efficacy of an even shorter regimen (250 mg three times daily for 5 days) was reportedly high in a small trial conducted by the same team, but this was not a randomized comparative trial [Kimani, 1995] (III, C).

Worldwide, several isolates with intermediate resistance to either ciprofloxacin or erythromycin have been reported, thus single dose ciprofloxacin and the shorter (5-day) regimen of erythromycin may not be effective, as has been reported by teams in Rwanda and Malawi [Bogaerts, 1995, Behets, 1995]. However, a double-blind randomised-controlled trial conducted in Nairobi showed comparable cure rates for single dose ciprofloxacin (92%) and the standard 7-day course of erythromycin (91%) [Malonza, 1999]. The single dose nature and relatively lower cost of the ciprofloxacin regimen makes it an attractive option for many low-income countries.

Widespread resistance to trimethoprim-sulfamethoxazole (TMP-SMX) renders this cheap and once effective alternative [Knapp, 1993; Van Dyck, 1994] virtually useless.

#### Alternative regimens:

- Oral single dose fluoroquinolones such as fleroxacin 400mg [Plourde, 1992; Tyndall, 1993b], or norfloxacin 800mg [Schmid, 1989] (Ib, B);
- Single dose aminoglycoside such as spectinomycin 2g intramuscularly [Fransen, 1987; Guzman, 1992] (IIa, B).

#### Allergy

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

#### Treatment for pregnant or lactating mothers and 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. The erythromycin or ceftriaxone regimens should be used. No adverse effects of chancroid on pregnancy outcome or on the fetus have been reported.

#### Special considerations

##### HIV INFECTION

Patients co-infected with HIV should be closely monitored. There have been concerns that healing may be slower among HIV-infected people [Behets 1995, Kimani, 1995] and treatment failures have been frequently recorded in Kenya using azithromycin [Tyndall, 1994], ceftriaxone [Tyndall, 1993a], or single dose fleroxacin [Tyndall, 1993b], or in Malawi using low dose erythromycin or ciprofloxacin [Behets, 1995]. 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 [Malonza, 1999]. 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 [Bogaerts,

1995]. Dosage and duration of the fleroxacin regimen also needed to be increased to treat HIV-infected patients in Nairobi [Plourde, 1992]. 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" [CDC, 2006]. Some experts suggest using the full-dose erythromycin 7-day regimen for treating HIV-infected persons.

#### 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 randomized study conducted during an outbreak of chancroid in the USA [Ernst, 1995] 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 3 days and substantial re-epithelization occurs within 7 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 2 weeks.

Clinical resolution of fluctuant lymphadenopathy is slower than that of ulcers and may require frequent needle aspiration (or drainage).

#### Recommendation for a test of cure

A test of cure is not recommended [Lewis & Ison, 2006].

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 or the equally effective but simpler E-test [Lewis, 2000].

#### 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 [Plummer, 1989; Hawkes, 1995], but screening is not recommended.

#### **Intended Audience**

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

#### **Applicability**

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

In the United Kingdom, specimens should be sent to the Sexually Transmitted Bacteria Reference Laboratory (STBRL) at the Health Protection Agency (Stbrl@hpa.org.uk) . Antimicrobials recommended are widely available in the UK, but depending on costs, choices can be made. 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. Serological syphilis and HIV testing should be offered to all patients.

*H ducreyi* should be isolated from genital ulcer swabs in 40% of clinically diagnosed chancroid cases [Lewis & Ison, 2006].

### **Stakeholder involvement**

Microbiologists, clinicians and epidemiologists at the Health Protection Agency in Colindale, London, the Regional Microbiology Laboratory, Plymouth, Devon, the HIV/STI Centre at University College London Medical School (UCLMS), and the London School of Hygiene & Tropical Medicine (LSHTM) had been consulted during the original development of these guidelines. Recommendations from a recent review on diagnostic methods by David Lewis (STI Reference Centre, National Institute for Communicable Diseases, Johannesburg) and Catherine Ison (HPA) have been incorporated.

The guidelines will be posted for three months for general consultation on the BASHH website ([www.bashh.org](http://www.bashh.org)) before finalization by the CEG.

The rare nature of this disease precluded patient's consultation.

### **Authors and Centre**

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### **Membership of the CEG**

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### **Conflict of interest**

None.

### **Rigour of Development**

The previous guidelines (1998) were largely based on several extensive reviews of the treatment of chancroid published in the late 1980's [Schmid, 1986; Schmid 1989], forming the basis of the

1993 and 1997 CDC recommendations [Schulte & Schmid, 1995; CDC, 1997], and on a Medline search spanning the years 1966-1998. The review has been updated by searching PubMed from 1999-2007 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 from 1957-2007 using the MeSH headings "chancroid" and "*Haemophilus ducreyi*". CDC STD guidelines of 2006 [CDC, 2006], and the European Guideline for the Management of Tropical Genito-Ulcerative Diseases [Roest , 2001] were consulted. Key review papers have been referenced [Ronald & Albritton, 1999; Lewis, 2000; Lewis & Ison, 2006]

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

Drug	Dose	Route	Cost <sup>1</sup>	Grading of recommendation	Level of evidence	References
Azithromycin *	1 g STAT	O	£ 8.95	A	Ib	Tyndall, 1994 Martin, 1995
Ceftriaxone *	250 mg STAT	IM	£ 2.74	B	Ib	Taylor, 1985 Tyndall, 1993a Martin , 1995
Ciprofloxacin *	500 mg twice daily for 3 days *	O	£ 8.52	B/A	Ib	Naamara, 1987 D'Souza, 1998
	<i>or</i> 500mg STAT	O	£ 1.42	B	Ib	Malonza, 1999
Erythromycin*	500mg four times daily for 7 days *	O	£ 6.16	B/A	Ib	Tyndall, 1994 D'Souza, 1998
	<i>or</i> 500mg three times daily for 7 days	O	£ 4.62	A	Ib	Malonza, 1999
	<i>or</i> 250 mg three times	O	£1.65	C	III	Kimani, 1995

Comment [I1]: Need updating with 2007 prices!!

<sup>1</sup> Costs from British National Formulary Number XX (XXX 2007);\* Currently recommended by CDC; \*\* proposed for HIV +ve patients (references Plourde, 1992; Tyndall,1993)

	daily for 5 days					
Fleroxacin	400 mg STAT	O		B	Ib	Plourde, 1992
	<i>or</i>		(not in BNF 2007)			Tyndall, 1993
	400 mg once daily	O		C	III	(same as above)
	for 5 days **					
Spectinomycin	2g STAT	IM	£ 8.95	B	IIa	Fransen, 1987
			(not in BNF 2007)			Guzman, 1992

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