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1071 8.6.14 Haemophilus ducreyi and chancroid 8.6.14 Haemophilus ducreyi and chancroid Nigel O'Farrell ESSENTIALS Haemophilus ducreyi is a Gram-negative, facultative anaerobic bacillus that is the cause of chancroid. The condition was endemic in sub- Saharan Africa and the Caribbean, but the overall global incidence of the condition has decreased dramatically since the mid-1990s. More recently the organism has been identified as a cause of paediatric skin disease in some South Pacific islands and Ghana. Clinical features—after an incubation period of 4 to 10 days, pres- entation is with a tender genital papule that develops into a pustule and then an ulcer with a ragged undermined edge and a yellow base that bleeds readily. The usual sites of infection in men are the prepuce and coronal sulcus, and in women the labia minora and fourchette. Inguinal lymphadenopathy is found in about half the male cases. Chancroid is an important risk factor for the transmission of HIV infec- tion. HIV infection may result in atypical manifestations of chancroid. Diagnosis and treatment—nucleic acid amplification tests are the optimal method of diagnosing H. ducreyi. Treatment is with either ciprofloxacin, erythromycin, azithromycin, or ceftriaxone. Introduction The causative organism is Haemophilus ducreyi, a Gram-negative fac- ultative anaerobic bacillus. Chancroid has also been known as soft sore (ulcus molle) and was first differentiated from syphilis by Ricord in 1838 in France. In 1889 in Naples, Ducrey inoculated the forearms of patients with material from their own genital ulcers and main- tained serial ulcers through multiple generations. The first successful culture was undertaken by Lenglet in 1898. The Ito-Reenstierna test was developed subsequently using a commercial antigen for intra- dermal testing and proved positive in 90% of true cases. Aetiology Recent phylogenetic studies suggest that the causative organism should be reclassified as an actinobacillus of the Pasteurellaceae. Traditional phylogenies divide genital strains into class 1 and II clades. The organism is a small, nonmotile, and non-spore-forming Gram- negative rod that requires enriched media for growth. Colonies can be seen after 48 h incubation in 5% CO_2 and are greyish in colour. These colonies are cohesive and can be pushed across culture media with a thin wire. Microscopic examination using Gram's stain shows streptobacillary chaining. Epidemiology Overall, the global incidence of chancroid has decreased dramatic- ally since the mid-1990s when it accounted for 30–50% of genital ulcers in southern Africa. Chancroid was endemic in eastern and southern Africa

and the Caribbean. In Asia, cases in India and Thailand used to be fairly common, but are now only sporadic. The decrease in chancroid may reflect changes in sexual behaviour, the increased use of and adherence to syndromic management for genital ulcers that included effective antibiotic cover for chancroid, or some other unknown factors. Sporadic outbreaks have been reported in the West. These have usually been associated with sex work and have been brought under control using intensive partner notification schemes. The male to female ratio is about 5:1. Chancroid is more common in uncircumcised than circumcised men. This may reflect inferior standards of genital hygiene and a tendency for small microabrasions to develop in the subpreputial space that might provide a portal of entry for infection. Asymptomatic carriage has been identified in women but is uncommon. Recently H. ducreyi has been implicated as a cause of skin ulceration mainly involving the legs of children in some South Pacific islands. Pathology and pathogenesis The pathogenesis of chancroid is incompletely understood. Bacterial adherence to susceptible cells appears to involve interaction be- tween a protein mediator and liopoligosaccharide with fibronectin contained in the extracellular matrix, followed by the elaboration of a heat shock protein (GroEL). A cytotoxin, similar to cytolethal distending toxin, appears to play an important role in epithelial in- jury and ulcer formation. The histological features include a superficial purulent exudate in the epidermis and a perivascular and interstitial mononuclear cell infiltrate, containing CD4+ T-lymphocytes, in the dermis. This may partly explain the increased risk of HIV transmission among people with chancroid. H. ducreyi cutaneous ulcer strains may arise from Class I and II Clades. Clinical features The usual incubation period is 4 to 10 days (range 1–5 days) and there are no prodromal symptoms. Lesions start as a tender papule that develops into a pustule and then an ulcer. Classically, ulcers have a ragged undermined edge with a grey or yellow base that bleeds when touched. Lesions may be single or multiple. The usual sites of infection are the prepuce, coronal sulcus, frenulum, and glans in men, and the labia minora and fourchette in women. 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. Clinical variants can occur. These include giant phagedenic ul- cers, 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 one-half the male cases but less so in women. These lymph glands may develop into buboes that should be managed by aspiration rather than in- cision and drainage. Fluctuant buboes may rupture spontaneously causing delayed healing.

section 8 Infectious diseases 1072 The differential diagnosis includes syphilis, genital herpes, lymphogranuloma venereum, and donovanosis. Mixed infections with other causes of genital ulceration should always be considered as coinfection with syphilis has been documented. The presence of HIV infection may result in atypical manifest- ations, for example, numerous lesions, extragenital involvement, or slow resolution after treatment. H. ducreyi lesions affecting the lower extremities in children in some South Pacific Islands can be mistaken for yaws. Laboratory diagnosis Nucleic acid amplification tests are now the optimal method of diagnosing H. ducreyi but their availability remains limited in areas where chancroid is found. Primers have been developed to amp- lify sequences from the H. ducreyi 16S ribosomal RNA gene, the rrs (16S) to rrl (23S) ribosomal intergenic spacer region, and the groEL gene. Multiplex polymerase chain reaction tests have been developed that can identify infection with H. ducreyi, Treponema pallidum, and Herpes simplex virus types 1 and 2 from genital ulcers. Whole-genomic sequencing has helped to better define the phylo- genetic tree of H.ducreyi and has shown that the cutaneous strains in children arise from class I and II clades. Antigen detection using fluorescence techniques may be useful but is expensive. Serological tests are unable to differentiate between old and new infections and have

limited application. Culture was the usual method of diagnosis of chancroid until rela- tively recently but has now been overtaken by nucleic acid amplifica- tion tests. Culture media must be fresh and may need fine adjustment depending on the characteristics of local strains of H. ducreyi. Two culture media are required to achieve a reasonable sensitivity of 50– 80%. Media used include gonococcal agar base and Mueller–Hinton with various additives and supplements. Vancomycin may be used to inhibit Gram-positive bacteria. Cultures should be incubated at 33°C with 5% carbon dioxide in a humid atmosphere. Thioglycolate haemin-based transport medium may allow storage of viable organ- isms at 4°C for 24 h or possibly longer. Most strains are β-lactamase producers. H. ducreyi reduces nitrate to nitrite and all strains are oxi- dase positive and catalase negative. Gram-stained smears of material from ulcers may show characteristic Gram-negative coccobacilli in a 'school of fish' or 'railroad track' appearance. Histology shows superficial necrosis with large numbers of neu- trophils, endothelial proliferation, and infiltration with plasma cells, lymphocytes, and fibroblasts. Treatment Current treatment of chancroid comprises one of the following re- gimens: ciprofloxacin (500 mg twice daily for 3 days), erythromycin (500 mg three times daily for 7 days; can be used in pregnant women), azithromycin (a single oral dose of 1 g), or ceftriaxone (a single dose of 250 mg intramuscularly). Trimethoprim/sulphamethoxazole is no longer recommended. Healing of ulcers is usually achieved after 7 to 14 days. Longer courses of treatment are sometimes required in HIV-positive patients who should be followed up until healing is complete. Single-dose treatment should probably not be given to HIV-positive patients. In the preantibiotic era, circumcision, saline soaks, and improved hygiene were recommended. Initially organisms were sensitive to penicillin, but resistance emerged fairly rapidly. Trimethoprim/ sulphamethoxazole then became the mainstay of treatment but re- sistance to this antibiotic emerged in the early 1990s. Chancroid and HIV Chancroid has been identified as an important risk factor for the bidirectional transmission of HIV, particularly in eastern and southern Africa. In some high-risk groups it was undoubtedly an important factor in driving the initial spread of HIV. At the bio- logical level, the mechanism for this is likely to be that chancroid ulcers allow a route of entry and exit for HIV and are likely to bleed when subject to trauma. In addition, subpreputial lesions in men that subsequently heal might result in partial phimosis with thin- ning of the superficial mucosa. This mucosa would then be more susceptible to trauma during sexual intercourse thereby increasing the potential risk of HIV transmission through microulcerations. There are some reports that HIV-positive men have increased num- bers of ulcers that heal slowly, although this may be related to low CD4 counts. Prevention and control In developed countries intensive partner notification and epi- demiological treatment of sexual contacts have formed the basis for managing outbreaks. In most developing countries, genital ulcers have been managed by the syndromic approach. This involves treating for the most likely causes of ulceration that in the past have been syphilis and chancroid. However, the prevalence of chancroid in previously en- demic countries has reduced considerably leaving genital herpes as the most frequent cause of genital ulceration. With this emergence of genital herpes, the case for treating empirically for chancroid has weakened and it may be that new epidemics of chancroid will emerge as treatment regimens change. FURTHER READING Bong CT, Bauer M, Spinola SM (2002). Haemophilus ducreyi: clinical features, epidemiology, and prospects for disease control. Microbes Infect, 4, 1141–8. Gonzalez-Beiras C, et al. (2016). Epidemiology of Haemophilus ducreyi infections. Emerg Infect Dis, 22, 1–8. Marks M, et al. (2018). Direct whole-genome sequencing of cutaneous strains of Haemophilus ducreyi. Emerg Infect Dis, 24, 786–9. Mitja, O, et al. (2014). Haemophilus ducreyi as a cause of skin ulcers in children from a yaws-endemic area of Papua New Guinea. Lancet Global Health, 2, e235–41. Spinola S (2008). Chancroid. In: Holmes KK, et al. (eds) Sexually trans- mitted diseases. McGraw-Hill, New York, NY. Spinola SM, Bauer ME, Munson RS (2002). Immunopathogenesis of Haemophilus

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