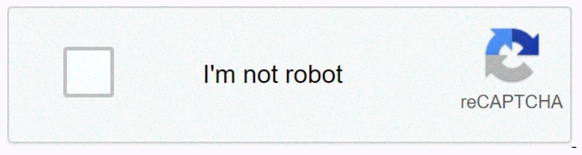

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Calymmatobacterium granulomatis pdf

Calymmataobacterium granulomatis is an intracellular organism that causes a ulcerative sexually transmitted infection, known as donovanose or granulominguinal (1). However, there is some debate about the classification of the causative organism. A link between C. granulomatis and Klebsiella species was suggested on evidence of antigen cross reactivity some time ago (40). A recent report has shown a close similarity between C. granulomatis and Klebsiella pneumoniae and K. rhinoscleromatis with the authors suggesting that the causative organism is reclassified as K. granulomatis comb Nov (4, 9). Epidemiology Transfer of C. granulomatis is usually sexual. Rare transmission during delivery and occasional non-sexual transmission are reported. The main endemic areas for donovanose have been in India, Brazil, South Africa, Papua New Guinea and among Australian Aboriginals. Over the past twenty years, the incidence of donovanosis has decreased significantly and few cases are reported today even in countries where prevalence was once high. Donovanosis has been associated with an increased risk of HIV infection. In Durban, where HIV infection had only been introduced recently, the proportion of men with donovanosis and HIV infection increased significantly as the duration of lesions increased, suggesting that HIV was achieved via sexual intercourse in the presence of ulcers (34). Clinical manifestations Donovanosis usually starts with ulceration in the ano-genital region. Spread to local lymph nodes is followed by ulceration of the skin that overlying lymph nodes. The wounds are characterized by slow growth, absence of pain and friability. Hypertrophic lesions that stand out from the surrounding skin are common. Primary oral lesions are described. In women, lesions can involve the cervix and upper reproductive ducts. Complications include tissue destruction, scarring, development of genital lymphoma, hematogenic spread to bones and viscera and squamous cell carcinoma. Laboratory diagnosis There are no established protocols for routine isolation and antibiotic sensitivity testing of C. granulomatis, although it is possible to culture C. granulomatis in human peripheral blood monocyte culture and in Hep 2 cells after decontamination of biopsy samples with appropriate antibiotics (10, 23). The diagnosis of donovanosis depends mainly on demonstrating the presence of intracellular organisms (called Donovan bodies) in large mononuclear cells such as Gram negative intracytoplasmic cysts filled with deep staining bodies that may have a safety hazard (33). Polymerase chain reaction (PCR) analysis using a colorimetric detection system can now be used in routine diagnostic laboratories and a genital ulcer multiplex PCR that includes C. granulomatis developed (11, 29). Pathogenesis C. granulomatis is an intracellular infection in which the organism is seen in the form of Donovan bodies within large histiocytes. It has been suggested that the inability of C. granulomatis to grow extracellularly is linked to the lack of sucrose transporter gene (scrA) found in other Klebsiella species. A granulomatous inflammatory response is seen leading to local tissue destruction and cutaneous ulceration. SENSITIVITY IN VITRO AND IN VIVO Only three articles report results of in vitro experiments with chemotherapeutic agents (6, 12, 39). Chen et al. (12) showed that streptomycin, penicillin, chlortetracycline and chloramphenicol have additive effects against C. granulomatis in vitro when administered in combination (Table 1). Numerous failed attempts have been made to find an animal model for donovanose. In 1931, DeMonbreun et al. Successful infection of the eyelids of macaques with tissues taken from human lesions of donovanosis, but these lesions resolved spontaneously (15). It has so far not been possible to assess antibiotic activity against C. granulomatis in an animal model. ANTIMICROBIAL TREATMENT C. granulomatis is found mainly within large histiocytes. The logical choice of therapy is thus an antibiotic with good activity against Gram negative bacteria, with good lipid solubility and able to achieve a high intracellular to extracellular concentration ratio. Relapse may occur if treatment is taken for a short time. Donovanosis may in the future prove an appropriate infection for treatment with liposome-encapsulated antibiotics. Drug of Choice Table 2 summarizes data from the main therapeutic studies. For an extensive bibliography of drug studies for donovanose up to 1991 readers are referred to a review paper (44). Drugs of the tetracycline group have been used widely in the treatment of donovanose for many years, in general with good results. Many published guidelines for the treatment of donovanosis (e.g. The World Health Organization, Centers for Disease Control) recommend the use of tetracyclines as first-choice therapy. Individual well-documented cases of tetracycline resistance have been reported (35) and the drug seemed ineffective in infections contracted in Vietnam (47). It can be assumed that the various forms of tetracycline have a similar effect. Doxycycline is now generally preferred over options for easy administration (twice daily). Good results with co-trimoxazole have been reported from India (26) and Africa (28). Two co-trimoxazole treatment failures have been reported in South America (38). Chloramphenicol is widely used to treat donovanose in Papua New Guinea (30), usually with good results. Long experience with the use of chloramphenicol for a number of infections in Papua New Guinea has shown that haematological toxicity is rare in this population. While chloramphenicol may be considered a treatment of choice in Melanesians, concerns about potential toxicity would limit its use elsewhere. Recent work from South America suggests thiampfenicol, a congens of chloramphenicol, which has the convenience of once daily administration and reportedly does not carry the risk of haematological toxicity, is of comparable effect (5). Ceftriaxone can produce good results in chronic relapse cases that have not responded to a number of other antibiotics (32). Weekly or daily azithromycin has useful activity that can make it a valuable drug for use in poorly compatible patients (7). Good results with azithromycin have also been reported in patients who have failed on other treatments (31). In India, an initial study of norfloxacin showed good results (43). Erythromycin and lincomycin both produce good results in donovanosis although only a few studies have been conducted and experience is limited. Streptomycin was for many years the main drug used for the treatment of donovanose. It continued in use in India until 1971 (27) and more recently it has been evaluated in combination with tetracycline (28). Most clinicians now prefer to choose antibiotics with less toxicity and greater administration. Gentamicin also shows useful activity, but has not been used much (30). Ampicillin produced good results when used in U.S. troops in Vietnam (8), but the results in other trials have been poor. A treatment failure with ampicillin was reported by Johnson in 1991 (22). On the strength of available evidence ampicillin can not be recommended as first line treatment. Combination therapy Only one study has been reported to compare monotherapy with combination therapy in the treatment of donovanose (28). In this study, streptomycin with tetracycline was compared to co-trimoxazole and no significant difference in outcome was noted in the two groups. Good results in the treatment of pregnant women taking combined erythromycin and lincomycin have been reported from Australia (3). A small number of patients have been treated with combinations of streptomycin plus penicillin or chloramphenicol and with chloramphenicol plus tetracycline. The effect of antibiotics in the treatment of donovanose has largely been considered in small-scale open studies. No randomised comparisons of treatment have been reported, and the study of streptomycin and tetracycline compared to concomitant trimoxazole described above (28) is one of a very small number of non-randomised comparisons published. Published guidelines for treatment tend to favor antibiotics in the tetracycline group over alternatives, but they do not offer explicit reasons for adopting this choice. Based on the published data indicated in Table 2 and known adverse reaction profiles, the following antibiotics should be considered as first-line treatment for donovanosis: azithromycin, erythromycin, fluorinated quinolones, doxycycline. The dosage used in reported studies is indicated in Table 2. In general, most antibiotics are given at conventional dosage. Most clinicians continue treatment until and some further prolong the treatment period in the hope of Relapse. One or two weeks of treatment is often sufficient for small early lesions, but therapy may need to continue for 2-3 months for female patients with extensive pelvic infection. Special situations disseminated infection Hematogenous spread spread is a life-threatening complication of donovanosis. In a case report and review of 18 previously published reports, 7 of the 19 cases died, including the subject of the case report (37). Among the cured were five cured with tetracycline, two with streptomycin and one with chloramphenicol. Two authors have reported successful treatment of disseminated disease with combined streptomycin and tetracycline (13, 14). Paterson suggests that the effect of azithromycin in other forms of the disease makes it the most promising choice for patients with spread infection, although its use in this rare situation has not yet been reported (37). He advocates the first daily therapy for a week followed by weekly dosing for 4-6 weeks. Pregnancy Donovanosis tends to stretch rapidly during pregnancy and to show a reduced response to antibiotic therapy. Many of the reported cases of hematogenous spread have been linked to tearing during the delivery of an infected cervical lesion. Cordero has described such a patient who responded well to combination therapy with streptomycin and minocycline (14). Many first-line antibiotics are contraindicated in pregnancy. Erythromycin is considered safe for use during pregnancy and satisfactory results among pregnant erythromycin alone (20) or in combination with lincomycin (3). Donovanose in patients with HIV Jardim has described two patients with HIV infection who did not respond to extended treatment with combinations of co-trimoxazole, tetracycline and thiampfenicol (21). This would suggest that some patients may require vigorous, high-dose, parenteral, combination regimens. In a recent study from South Africa, 18 pregnant women with HIV and donovanose were not significantly different in terms of outcomes compared to women without HIV (20). Alternative therapy Second line drugs that can be considered for patients who do not respond to, or intolerant of the first-line drugs mentioned above include ampicillin, chloramphenicol, thiampfenikol, lincomycin, streptomycin, co-trimoxazole and gentamicin. Before the introduction of antibiotics, the following treatments were used successfully for the treatment of donovanosis: intravenous potassium antimonic tartrate and other trivalent antimonials, surgical excision of lesions, diathermic fulguration, local treatment with podopyllin, ultraviolet radiation and radiation therapy (44). ADDITIONAL TREATMENT Additional surgical measures are required for patients with complications such as abscess formation, fistulas, strictures and elephantiasis (36). Surgery carries the risk of spreading active infections if performed without antibiotic cover. Patients with extensive Ulcers benefit from the addition of penicillin to treatment regimens and by bathing wounds in solutions of diluted potassium permanganate. END POINTS OF MONITORING TREATMENT Patients can be clinically monitored by observing the healing and reepittelization of wounds. Repeat smears can be done from lesions to monitor the disappearance of Donovan organs, although this is rarely conducted outside the framework of clinical trials. Follow-up should ideally be extended up to 18 months, as late relapse can occur after healing. In prolonged cases, a biopsy should be done to exclude malignant change. PREVENTION As donovanose is transmitted sexually, management should always address the problems of partner management, health education and screening for other sexually transmitted infections, especially syphilis that often accompanies donovanosis. Exposed sexual partners should be offered examination and treated if lesions are found. Epidemiological treatment may be offered asymptomatically exposed individuals who are worried about becoming infected. CONTROVERSIES, WARNINGS, COMMENTS The debate continues about the best nomenclature for the causative organism. Aragao and Vianna originally cultivated a pleomorphic bacterium from wound lesions and identified it as C. granulomatis (2), but a number of studies suggested a link to klebsiella species. After using PCR, DNA sequencing of 16SrRNA and phoE genes showed that C. granulomatis had a greater than 99% similarity to Klebsiella pneumoniae and K. rhinoscleromatis and a proposal was put forward to reclassify the causative organism as K. granulomatis comb Nov (4, 9). However, Kharsany et al performed a phylogenetic analysis of C. granulomatis based on 16S rRNA gene sequences and found that strains had similarities of only 95% and 94% respectively to the genus Klebsiella and Enterobacter (24). REFERENCES 1. Anderson K. The cultivation from the granulominguinal of a microorganism that has the properties of Donovan bodies in the egg yolk secretion of chicken embryos. Science 1943;97:560-1. 2. Aragao HD, Vianna G. Pesquizas sobre o granuloma venereo. Memn Inst Oswaldo Cruz 1913;5:211-238. 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Key Trials of Antibiotics for Treatment of Granuloma Inguinale Drug Dose Route Duration M:F Total patients Smear positive Relapse Days to smear negative Days to heal Ref Ampicillin 500 mg qid O 2-4wk 31 67% 8 Chloramphenicol 500mg-1g 6h O 5-20d 0/23 23 2 2-4 days 18 2-4g every 3-4 days IM 8-12d 20/23 43 43 5 1-7 days 7-30d 19 500mg qid O 10-55d 50 1 av. 7 days av.17d 30 Thiamphenicol 2.5g stat, then 1Gram/day O 2 wk 10/0 10 10 2 15 days 15-30d 5 Co-trimoxazole 160/800mg, bid O Mean 12.5d 84/32 116 116 2 5 days 7-22d 26 160/800mg, bid O 20-49d 19/1 20 16 2-5wk 46 160/800mg, bid O 14d 12/6 18 18 7-21d 28 Erythromycin 1-300mg 6h O 16-37d 5/4 9 9 1 9-30d 45 Lincomycin 500mg qid O 14d 5 8 Streptomycin 0.3-1g 4h IM 6-46d 23 23 3 5-9 days 17 0.3-4g/d IM 5-62d 32/16 48 48 3 2-11 days av. 3wk 25 1g bid IM 3-70d 146/81 227 219 1 av. 6 days 41 1g bid IM av.12.5d 83/39 122 27 Gentamicin 1mg/kg tds IM mean 22d 9 mean 12 days mean 22d 30 Tetracyclines Minocycline 200mg stat, then 100mg bid O 15-45d 5/1 6 6 15-90d 48 Oxytetracycline 2-3g/d O 2-29d 32 32 2 4-5 days 16 Tetracycline hydrochloride 1g/d O 20d 14/6 20 20 5-7 days 25-45d 42 Norfloxacin 400mg bid O 2-11d 10/0 10 10 8 by 3 days mean 7.3d 43 Ceftriaxone 1g od IM/IV 10d 4/8 12 8 5 32 Azithromycin 1g per week or 500mg daily O 1-4 wk 4/7 11 9 0 7 Antibiotic Combinations Streptomycin with 1g/d IM 14d 7/6 13 13 7-21d 28 tetracycline 500mg 6h O 14d Erythromycin with 500mg qid O 10-14d 0/4 4 4 rapid 3 Lincomycin 500mg qid O 10-14d 10-14d