

Yaws

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Continuing Education Activity

Yaws, a treponemal disease caused by the spirochete *Treponema pertenue*, causes disease in 3 stages with the last being most specific and manifesting as destructive osteitis. Antibiotic resistance is a concern with yaws and optimizing antibiotic stewardship is important to prevent worsening of this problem. This activity reviews the evaluation and management of yaws and highlights the role of the interprofessional team in the care of affected patients.

Objectives:

- Describe the common presentation of a patient with yaws.
- Identify treatment considerations for patients with yaws.
- Explain why antibiotic resistance is a concern with yaws.
- Explain the importance of improving coordination amongst the interprofessional team to enhance care for patients affected by yaws.

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Introduction

Yaws is a non-venereal tropical infectious disease caused by the organism *Treponema pertenue*.^[1] This organism is closely related to the syphilitic spirochete, *Treponema pallidum*. Yaws is most commonly seen among children in tropical regions and is spread by skin-to-skin contact. The disease is characterized by an acute phase followed by a chronic, relapsing course in a minority of patients. Clinically, the disease is comprised of distinct stages similar to venereal syphilis with cutaneous findings in early stages, and after a latent period, late yaws may manifest as gummatous nodules, scarring, and destructive bone lesions. Treatment was traditionally benzathine penicillin-G,^[2] but as a single dose of azithromycin has been found to equally effective^[3] for primary and secondary stages, the latter has become the cornerstone of therapy. The World Health Organization (WHO) proposes possible eradication of Yaws by 2020.^[4]

Etiology

The genus *Treponema* includes several uncultivable spirochete pathogens notably including but not limited to *T. pallidum*, the causative agent of syphilis, *Treponema endemicum*, the causative agent of bejel, related *Treponema carateum*, the causative agent of pinta, and *Treponema pertenue*, the causative agent of yaws. The first genome mapping of *T. pallidum* in 1998 led to the further genomic sequencing of twelve treponemal pathogens and this notably revealed minimal variability between sub-species.^[5] Despite this *T. pertenue* and its associated disease, yaws presents with a distinct history and clinical features. Unlike syphilis, yaws is neither sexually transmitted nor transmitted from mother to baby. Disease is most commonly seen in children and is transmitted from skin to skin contact.^[2] In 1954 the WHO and the United Nations Children's Fund put forth a dramatic effort to address yaws in endemic areas. Over the next 20 years, the annual incidence fell from 140.85 to 1.25 per 100,000.^[6] As the disease continues to decline and efforts to treat all cases reported is hoped disease can be eradicated.^[4]

Epidemiology

Yaws is found in tropical regions with warm and humid environments. The disease mostly affects children between the age of 2 to 15 who also serve as reservoirs for the spirochete. Infection is spread by direct skin to skin contact, and there has been a consideration for fly vectors although the latter is unproven.^[2] And though primate species also carry treponemal infections closely related no evidence of zoonotic transmission exists.^[7]

Treponema pertenue is found to cause disease in Africa, Asia, and the South Pacific. Between 2008 and 2012 over 300,000 cases were reported to the WHO. 12 endemic countries exist and include Benin, Cameroon, Central African Republic, Republic of the Congo, Cote d'Ivoire, the Democratic Republic of the Congo, Ghana, Togo, Indonesia, Papua New Guinea, Solomon Islands, and Vanuatu. Two countries that used to harbor disease now boast eradication and those are India and Ecuador.^[8] These reports and other systematic reviews evaluating epidemiology show slight progress since 1992, but now notably the vast majority, up to 84% of all cases, are from only 3 countries: Papua New Guinea, Solomon Islands, and Ghana.^[1]

Pathophysiology

*Treponema pertenu*e are spirochetes that cannot be cultured in vitro. All subspecies are morphology and serologically indistinguishable. These organisms reproduce every 30 hours and with corkscrew motility these move through connective tissue. These spirochetes are fragile outside of their host vectors and are rapidly killed by exposure to heat, oxygen, and drying.[2] As yaws is contracted, most commonly from skin-to-skin contact poor hygiene has been a risk factor for transmission. Poverty, crowding, rural settings, and a climate of heavy rainfall and high humidity are also linked to increased prevalence.[9]

Histopathology

T. pallidum, as a group, are not viable *ex vivo*, and therefore, diagnostic methods are limited. Darkfield microscopy does allow direct visualization of spirochetes; however, equipment is often not available in endemic areas. Combinations of serologic assays and nucleic acid amplification tests have been used as the primary mode of identification.[2]

History and Physical

The disease is characterized by primary, secondary, and tertiary stages.

The initial lesion typifying primary yaws infection are solitary nodules[2] or multiple ulcerative non-tender papules.[9] They classically are yellow, 2 to 5 cm in diameter, and have a distinct red base of granulation tissue with elevated borders.[10] This occurs at the site of inoculation on average 21 days after exposure. Time to onset ranges from 9 to 90 days. This lesion is termed the “Mother Yaw” and is an exudative papillomatous lesion that may degenerate into a single crusted non-tender ulcer. The most common location is the lower extremity, but any site of exposure may be involved. Untreated lesions heal spontaneously over 3 to 6 months leaving hyperpigmentation.[2]

Dissemination of the organism through lymphatic or hematogenous spread is responsible for the progression of the disease.[11] Arthralgias manifest during this period, and the primary and secondary stages may overlap. Secondary lesions can occur in the presence of primary findings. One to 2 months after inoculation, (up to 2 years), patients develop disseminated papillomatous or ulcerative lesions with macular or hyperkeratotic palmoplantar involvement. A term “crab-yaws” describes a crab-like gait change secondary to painful fissuring of hyperkeratotic pedal plaques and secondary infection.[2][11] Generalized lymphadenopathy and constitutional malaise are present during this stage. During the secondary stage of yaws, the specific bony disease begins to manifest.[2] Osteoperiostitis presents as a bilateral polyostotic disorder with an average of 3 bones involved. Radius, ulna, and phalanges are the most frequent. Radiologic abnormalities reveal dactylitis and osteoperiostitis.

In between primary and secondary or secondary and tertiary stages, a latent period occurs. The latent period is defined as a positive serology with no clinical signs. This is due to the host immune response against the organism. During this relapse of clinical disease can occur and characteristically manifests around axillae, anus, and mouth.[2]

Tertiary disease historically occurred in 10% of untreated patients; however, due to surveillance and available antibiotics, it is now rarely seen. Late lesions may occur 5 to 10 years after inoculation. Cutaneous manifestations are the most common and are typically near joints with ulcerative necrotic nodules. Facial destruction historically has been a marked manifestation[2] with other classic late findings including juxta-articular nodules (gummas), bowed tibia (saber shins), nasal cartilage destruction (gangosa), or exostosis of the paranasal maxilla (gondou).[12]

Evaluation

Diagnosis is based on the combined clinical picture and serologic testing. The latter requires the presence of antibodies with one being a non-treponemal antigen and the other a treponemal antigen. The non-treponemal antibodies are the same as used in syphilitic disease: the venereal disease research laboratory (VDRL) and rapid plasma reagin (RPR). These have a chance of false-positive results but good sensitivity and are useful as markers to confirm cure with falling titers following treatment. The treponema-specific antibodies include *Treponema pallidum* particle agglutination (TPPA) and haemagglutination (TPHA) assays. Once positive, these latter 2 tests are positive for life.[2]

Additionally, as the treponemes are indistinguishable serologically and early clinical features may overlap accurate diagnosis may be difficult. A combination of epidemiology, clinical signs and symptoms, direct visualization, and serologic data are required to establish the diagnosis.[2]

Treatment / Management

Treatment in the 1950s, during the initial eradication of *T. pertenu*e and yaws, began with penicillin aluminum monostearate. Benzathine penicillin subsequently supplanted this as it was found to have prolonged treponemicidal levels and convenient dosing. Treatment dosing was

determined by age with 600,000 units for age younger than 6 years old, 1.2 million units for children 6 to 14 years,[9] and some sources reporting similar dosing of 1.2 million units for adults. This dosing is lower than used in venereal syphilis.[2]

Prolonged oral penicillin and tetracyclines may be effective; however, azithromycin 30 mg/kg became the primary alternative after it was shown to be non-inferior when compared to penicillins maintaining a 96% cure rate at 6 months.[3] In 2012, the WHO re-duplicated efforts for eradication and implemented single mass dosing of oral azithromycin in endemic areas and case detection monitoring with subsequent treatment. It is through this they hope to eradicate the disease by the target date of 2020, as stated above.[4]

Resistance to macrolides is a concern, however, as *T. pallidum* is notoriously resistant, and concerns about the similar organism of yaws have been discussed.[9]

Differential Diagnosis

Yaws is often distinguished by its late feature of destructive bony disease. However, cutaneous manifestations of other diseases may have significant overlap.

Other Treponemal Diseases

T. pallidum (Syphilis): Features that distinguish it from yaws include worldwide distribution, disease primarily of adults with a history of sexual contact, initial lesions primarily on genitals, congenital transmission, prominent neurologic late complications, and prominent cardiovascular late complications.

T. endemicum (Bejel): Although this is also a disease of children, it has many features distinguishing it from yaws, for example, a presence in hot, dry areas including deserts of Africa and Saudi Arabia, transmission from salivary contact, rare to have initial cutaneous lesions, and if present on oral mucosa, limited dissemination, destruction of nose and palate are late complications.

T. carateum (Pinta): Although transmitted by skin to skin contact, initial lesions are on lower extremities, and it is also prevalent in hot and humid climates such as South America and Central America. There are many features that distinguish it from Yaws: a disease of adults, disseminated disease restricted to skin, late complication of local skin hyponatremia.[2][13]

Tropical Ulcerative Lesions

Leishmaniasis, *Fusobacterium*, or pyoderma may be indistinguishable in the initial papular/ulcerative stages.[13] Most notable is the infectious chancroid caused by *Haemophilus ducreyi*. This painful skin lesion from sexual contact that may cause genital and non-genital lesions in areas where endemic. Lesions are also responsive to azithromycin.[2]

Prognosis

Prognosis with treatment is very good if caught during primary or secondary stages.[12] With treatment, the tertiary disease has become nearly non-existent. Primary and secondary lesions heal spontaneously after 3 to 6 months with or without treatment, but when untreated a minority of patients develop the late-stage disease.[2][13] If tertiary yaws develops, morbidity can be devastating with bony destruction causing severe facial disfigurement and bowing of the tibias with resultant gait difficulty.[12]

Pearls and Other Issues

Yaws, a treponemal disease caused by the spirochete *Treponema pertenue*, causes disease in 3 stages with the last being most specific and manifesting as destructive osteitis. Although once common in endemic areas, global efforts to eradicate the disease through penicillin and azithromycin have made the tertiary disease a rarity and significantly decreased global prevalence.

Enhancing Healthcare Team Outcomes

Yaws has required global coordination, as endemic areas often are under-equipped for diagnosis or treatment. WHO has helped orchestrate the delivery of healthcare to these areas. The most notable studies in this field included an open-label, small, randomized, controlled trial proving the efficacy of azithromycin when compared to benzathine benzylpenicillin.[3] (Level 2) Otherwise, most studies are retrospective cohorts and epidemiological (Level 3), assessing the incidence, prevalence, genetic heterogeneity,[1][2][5][7] or case series.[12] (Level 5)

Review Questions

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