Endemic (Nonvenereal) Treponematoses

The endemic, or nonvenereal, treponematoses are infections caused by bacteria that are closely related to Treponema pallidum pallidum, the etiologic agent of venereal syphilis.

- These include
  - Treponema carateum(pinta),
  - Treponema pallidum pertenue (yaws), and
  - Treponema pallidum endemicum (bejel or endemic syphilis).
- The diseases are distinguished from venereal syphilis by mode of transmission, age of acquisition, geographic distribution, and clinical features.
- Unlike syphilis, they are transmitted mostly among children living in tropical and subtropical climates, chiefly by casual contact rather than sexual contact, and congenital infection is unusual.
- Like venereal syphilis, the diseases progress through successive clinical early (primary and secondary) and late stages usually separated by periods of latency.
- Without treatment, patients remain potentially infectious indefinitely, although the skin lesions may become inconspicuous or subclinical.
- Patients do not develop lifelong immune resistance.
- Cross-immunity is absent in the early stages of endemic syphilis, yaws, and pinta but is variable in late stages.
- Notably, patients with late pinta are resistant to syphilis, but those with yaws or syphilis at any stage are susceptible to pinta.
- Untreated treponematoses are nonfatal but may cause cutaneous lesions and deformities of the bone and cartilage. This potentially leads to significant disfigurement, pain, disability, and social isolation.

PINTA (CARATE, MAL DE PINTA, AZUL)

EPIDEMIOLOGY AND ETIOLOGY

- Pinta is an ancient disease that was first described in the sixteenth century in Amerindians.
- The causative organism is T. carateum, which is the least antigenically related to the other human treponemes as it is a separate species from T. pallidum.
- The name of the organism derives from the Colombian word for the disease(“carate”), in reference to the color changes seen in persons having the disease.
- The organism can be propagated only in primates, and no isolates are known to exist. Consequently, much less is known about this treponeme than any of the others.

- The incidence of the disease has remarkably decreased over the last few decades. Today, pinta remains prevalent in scattered foci in rural areas of Central and South America (Southern Mexico, Brazil, Colombia, Venezuela, Peru, and Ecuador), where people still live in crowded, unhygienic conditions. People of all ages may be infected. However, half of all patients are younger than 15 years of age.
- The exact mechanism of disease transmission is not fully elucidated, but repeated direct lesion-to-skin contact is the most likely mode. Transmission through insects is unlikely.
- Because cell-mediated immunity is not completely effective against this organism, untreated infection persists indefinitely.

CLINICAL FINDINGS

- Pinta is the most benign of the endemic treponematoses with the skin being the only organ of involvement.
- As in syphilis, there are three distinct clinical stages. Lesions at different stages may be present in a single patient.
- Lymphadenopathy may develop during any stage.

PRIMARY STAGE.

- A small number (1–3) of erythematous macules or papules appear at the site(s) of inoculation after an incubation period of 1–8 weeks.
- Primary lesions are usually nonpruritic and do not ulcerate.
- Sites of predilection include exposed areas of the extremities in addition to the face and neck.
- The initial lesions expand or coalesce with other lesions over several weeks to months, forming irregular scaly lichenified plaques that can reach a diameter of up to 20 cm.
- Over time, the center of the lesions becomes hypochromic, grayish, light blue, or pale mauve.
- Eventually, lesions may heal spontaneously with residual depigmentation or may persist for years.

SECONDARY STAGE

- After several months and occasionally up to 10 years after the initial infection, secondary lesions (pintids) start to appear. These are highly infectious lesions teeming with spirochetes.
- Like the primary lesions, pintids start as erythematous scaly papules that enlarge and coalesce into psoriasiform plaques.
- However, they tend to be smaller and more extensive than the primary lesions.
- They may encircle the sites of the primary lesions or erupt generally on the body. Pintids may occur on the palms, soles, and groin.
- Some lesions may be circinate or annular with raised borders where the number of treponemes is highest
- Over time, lesions display remarkable variation in color ranging from copper colored to gray to slate blue.

TERTIARY STAGE

- Late lesions usually develop 3 months to 10 years after the appearance of the secondary lesions.
- Typically, patients have dyschromic patches that are hyperchromic, hypochromic, and achromic, which impart a mottled pattern with a variegated palette of white, brown, blue, red, and violet.
- The lesions have irregular borders and vary in size.
- The most commonly involved areas are the wrists, palms, ankles, and elbows as well as the skin around and within old lesions.
- It is common for periarticular lesions of pinta to exhibit scarring and atrophy ("cicatricial lesions of pinta"). This is in contrast to extensor surface plaques that tend to be hyperkeratotic.
- Patients with only late-stage lesions may appear to have vitiligo ("vitiligo of pinta").

DIFFERENTIAL DIAGNOSIS

- **Most Likely**; Leukodermas; Eczema (early lesions)
- **Consider**; Pityriasis alba; Pellagra and other vitamin deficiencies; Tineaversicolor; Melasma; Lichen planus (early lesions); Tuberculoid leprosy (early lesions); Tineacorporis; Psoriasis (early lesions); Lupus erythematosus (early lesions); Atrophic lichen planus; Yaws (early lesions); Syphilis; Leprosy
- **Always Rule Out**; Vitiligo (late depigmented stage); Erythema dyschromicum perstans

YAWS (FRAMBOESIA TROPICA, PIAN, BUBA, PARU, PARANGI)

EPIDEMIOLOGY AND ETIOLOGY

- Yaws is caused by T. pallidum pertenue.
- The infection affects rural populations along the tropical belt in areas with high humidity, heavy rain, and annual temperatures at and above 27°C.
- The spread of the spirochete is facilitated in the setting of poor hygiene, scanty clothing, and overcrowding.
- Yaws is the most prevalent nonvenereal treponematosis.
- Approximately 75% of new cases arise in children younger than 15 years of age. Currently, at least 100 million children are estimated to be at risk of becoming infected.
- The main route of transmission of yaws is direct skin-to-skin contact and via contact with open wounds, excoriations, or bites.

CLINICAL FINDINGS

- Yaws shares numerous clinical characteristics with venereal syphilis.
- In contrast to pinta, the disease is not skin-limited.
- Among the nonvenereal treponematoses, the disease is characterized by the most destructive and disfiguring skeletal involvement.

PRIMARY STAGE

- In the primary stage, skin lesions appear after an incubation period of 10–90 days (on average 3 weeks).
- Classically, the initial presentation is a single nontender but often pruritic erythematous infiltrated papule (mother yaw or buba madre) that often acquires a papillomatous surface.
- Its location often indicates the site where the spirochete penetrated the skin, usually the legs, feet, or buttocks.
- Over time, the mother yaw enlarges radially reaching up to 5 cm in diameter and occasionally merges with the smaller satellite lesions forming a larger plaque. It often ulcerates, forming the "chancre of yaws", and develops a yellow–brown crust which ultimately sloughs off, uncovering a moist soft base that is often likened to a raspberry, hence the synonym "framboesia". The ulcer is very rich in treponemes.
- Fever, regional lymphadenopathy, and arthralgias may accompany this stage
- The mother yaw heals over 3–6 months but sometimes remains through the secondary stage of the disease. It typically leaves a depigmented pitted scar with dark margins

SECONDARY STAGE

- The lesions of secondary yaws, known as "daughter yaws" or pianomas, may appear while the mother yaw is still present, but may take up to 2 years to develop. These lesions resemble the mother yaw but are smaller (up to 2 cm) and more disseminated.
- They are often accompanied by constitutional symptoms such as fever, malaise, and generalized lymphadenopathy.
- Over time, daughter yaws may ulcerate and secrete a fibrinous exudates teaming with infectious treponemes.
- The exudate attracts flies, which can cause great suffering to the affected person.
- Lesions usually favor periorificial locations, such as around the mouth and nose.
- In addition to the characteristic exudative papillomas, dry papulosquamous patches (pianides), comparable to those seen in venereal syphilis, may appear on anybody part.
- Occasionally, central clearing results in an annular morphology simulating a fungal infection and these have been called "tinea yaws."
- In the body folds, secondary lesions simulate condyloma lata.
- More rarely, the mucous membranes, especially the oral cavity, are involved in the form of hypertrophic mucous patches.
- Hyperkeratotic lesions, affecting mainly palms and soles, are characteristic. They are referred to as "crab yaws "because they get fissured and infected resulting in a painful "crablike" debilitating gait.
- Periungual hyperkeratosis results in a paronychia which is known as "pianic onychia."

- Of special interest is the influence of the climate on the clinical expression of yaws. During wet seasons, lesions tend to be more florid and diffuse whereas they are less exudative and confined to them moist intertriginous areas in the setting of a dry climate.
- Bone and joint manifestations may already occur during this early stage of the disease. These consist of painful osteoperiostitis of the forearm or leg, in addition to the proximal phalanges of the hands or feet. The characteristic "ghoul (monster) hands" appearance reflects swelling of the proximal two phalanges. Some of the early bone changes can be seen on radiographs. Periosteal thickening can often be palpable
- Lesions of secondary yaws tend to resolve spontaneously without scarring over weeks to months.
- The disease then enters a latent stage during which relapses, usually one or two, are common. In relapsing yaws, lesions tend to be confined to the perioral, perianal, and periaxillary areas.
- Recurrences are possible for as long as5 years after the initial infection. This is followed by either elimination of the organisms or in most cases a lifelong latency period.

TERTIARY STAGE

- Tertiary yaws is estimated to develop in approximately 10% of cases around 5–10 years after inoculation
- This stage is characterized by irreversible soft tissue and skeletal deformities
- Gummatous suppurative nodules may involve the skin and subcutaneous tissues (gumma framboesiodes).
- These often break down and coalesce into serpiginous ulcers characterized by significant necrosis.
- Eventually, keloidal scarring and debilitating contractures ensue
- Hyperkeratotic lesions on the palms and soles, similar to those occurring in early yaws, are another common cutaneous manifestation of this stage and may lead to palmoplantar keratoderma.
- Mottled depigmentation of the hands, over the wrists, and along the shins has-been described in older adults

DIFFERENTIAL DIAGNOSIS

Most Likely; Frambesiformleishmaniasis (pianomas, gangosa); Paracoccidioidomycosis (pianomas)

Consider; Psoriasis (pianides); Impetiginized eczema (pianides); Pyodermavegetans (pianomas); Arthropod bites (pianides); Myiasis (pianides); Scabies (pianides); Dermatophytosis (pianides); Pyoderma (pianomas); Lupus vulgaris (gangosa); Atypical mycobacterial infection; Deep fungal infections (gangosa); Tuberculoid leprosy (pianides); Ecthyma (pianomas); Vitiligo (late dyschromic stage); Pinta (late dyschromic stage); Keratodermas; Plantar Verrucae; Rhinosporidiosis (gangosa); Rhinoscleroma (gangosa); South American Blastomycosis (gangosa); Bacterial osteomyelitis (bone lesions); Sickle cell anemia (bone lesions)

Always Rule Out; Frambesiform syphilis (pianides, pianomas)

ENDEMIC SYPHILIS (BEJEL, FIRJAL, LOATH, BISHEL, BELESH, NJOVERA)

EPIDEMIOLOGY AND ETIOLOGY

- Bejel is the name given by the Arab Bedouins of Syria and Iraq to endemic syphilis
- The causative organismis T. pallidum endemicum.
- It is prevalent among rural communities in dry and arid climates, under conditions of crowding and poor hygiene. it is mostly prevalent among nomads and semi-nomads in the Arab Peninsula (Iraq, Syria, and Saudi Arabia), and along the Sahel (Southern border of the Sahara desert).
- In endemic areas, children under15 years of age represent around 80% of all cases and serve as an important disease reservoir.
- Transmission occurs via direct contact with infectious lesions on the skin and mucous membranes. One study demonstrated the presence of treponemes on a drinking flask, supporting indirect transmission through sharing food and fomites.

CLINICAL FINDINGS

Like yaws, the clinical features of bejel resemble those of venereal syphilis, except that mucosal involvement tends to predominate. Although joint pain and bone changes are common, they tend to be less severe than the skeletal manifestations seen in yaws.

PRIMARY STAGE

- Early lesions of endemic syphilis start to appear after an incubation period of 2–4 weeks.
- In contrast to other nonvenereal treponematoses, primary lesions often go unnoticed because they usually involve the oral and nasopharyngeal mucosa.
- These present as painless, small papules that may become eroded and ulcerated. Lesions on the nipples of breastfeeding women can also be seen. Primary lesions usually resolve in 1–6 weeks

SECONDARY STAGE

- This stage develops around 6 months postinoculation.
- It is characterized by both mucocutaneous and skeletal manifestations
- Painless, often macerated and eroded mucous patches develop on mucosal membranes of the oral cavity, nasopharynx, and might even reach the larynx. Angular stomatitis(also known as split papules) appear at the labial commissures
- Skin lesions include vegetating condyloma lata in the moist intertriginous areas of the axillae and groin. These are comparable to those seen in yaws and venereal syphilis
- In up to 15% of cases, a diffuse skin rash with generalized lymphadenopathy may develop. As in secondary syphilis, the rash can assume different morphologies such as macular, papular, or annular lesions.

- Painful periostitis of the long bones and hands, as in yaws, may occur at this stage leading to nocturnal lower extremity pain
- Untreated, secondary lesions continue to appear for up to 9 months postinoculation. This is followed by a latent stage of variable length (up to 15 years). Occasionally, it may last for only few months leading to the development of the tertiary stage at a very young age

TERTIARY STAGE

- Tertiary bejel is characterized by mucocutaneous and skeletal manifestations in the form of deforming gummas that tend to be generally less mutilating than those of yaws.
- In the skin, destructive ulcers result eventually in the formation of depigmented scars with hyperpigmented borders.
- Mucosal involvement may eventuate in disfiguring complications such as saddle-nose deformity, palate perforation, and gangosa. The larynx has been reported to be solitarily involved
- Although joint pain and bone changes are common, they tend to be less severe than the skeletal manifestations seen in yaws.

DIFFERENTIAL DIAGNOSIS

Most Likely; Condylomataacuminate**;** Molluscumcontagiosum**;** Oral herpes simplex**;** Aphthous ulcers**;** Angular cheilitis

Consider; Seborrheic dermatitis (papulocircinated lesions)**;** Psoriasis (papulocircinated lesions)**;** Dermatophytosis (papulocircinated lesions)**;** Deep fungal infection (gummas)**;** Leishmaniasis (gummas)**;** Mycobacterial infection (gummas)**;** Lymphomas and sarcomas (gummas)**;** Granulomatous diseases (gummas)

Always Rule Out; Venereal syphilis

Nonvenereal Treponematoses—Clinical Manifestations

	Pinta	Yaws	Endemic Syphilis
Causative organism	Treponema carateum	Treponema pallidum pertenue	Treponema pallidum endemicum
Transmission	Skin-to-skin contact	Skin-to-skin contact, via eye flies (?)	Skin or mucosal contact, via drinking flasks (?)
Peak ages	1–15 years	1–15 years	Months–15 years
Incubation	7–60 days	10–90 days	15–30 days
Primary lesions	Erythematous papules become psoriasiform plaques	Vegetating, soft, ulcerating papule (mother yaws) with satellites	Small eroded mucosal papule (often overlooked)
Secondary lesions	Erythematous scaly and psoriasiform plaques (pintids); dyschromia	Warty or frambesiform Nodules (pianomas), papulosquamous plaques(pianides), palmoplantar plaques, pianiconychia	Mucous patches (split papules), condylomata lata, syphilis-like eruptions
Tertiary lesions	Dyschromic, hypochromic, achromic, and polychromic patches	Serpiginous gummas, pintoid dyschromia, juxta-articular nodes, gangosa, goundou, keratoderma	Gummas, gangosa, juxtaarticular nodes on elbows only
Reactive serologic test result	2–3 months after primary lesion	2–3 weeks after primary lesion	2–3 weeks after primary lesion
Treatment	Penicillin	Penicillin	Penicillin

DIAGNOSIS OF THE NONVENEREAL TREPONEMATOSES

- A presumptive diagnosis of pinta, yaws, or endemic syphilis in a given patient should be suspected on the basis of the clinical findings in the setting of an endemic area
- The diagnosis is confirmed by detection of the treponemes under dark field microscopic examination or with a direct fluorescent antibody (DFA) test, by serology, or by histologic examination.
- The same serological tests used in the diagnosis of venereal syphilis are used to diagnose the endemic treponematoses; however, no single test is yet available that can differentiate endemic treponematoses from each others or from venereal syphilis.
- Nontreponemal serological tests are usually used for screening, whereas treponemal tests are used for diagnosis confirmation. Nontreponemal tests,

including the Venereal Disease Research Laboratory test and the Rapid Plasma Regain test, use a nonspecific cardiolipin antigen that is cross-reactive among the various treponemes. Positivity indicates either a recent or a current infection.

- ❖ In yaws and endemic syphilis, nontreponemal tests yield reactive results in 2–3 weeks after the onset of the primary lesion
- ❖ In pinta, these tests give reactive results in 80% of cases within 3 months after the appearance of primary lesions and in essentially all patients with the late stage of the disease
- ❖ After treatment, serological titers of the nontreponemal tests decrease, which makes them valuable in monitoring patients post-therapy

- The specific treponemal tests, which use T. pallidum as an antigen, include the fluorescent treponemal antibody absorption (FTA-ABS) and the microagglutination assays for antibodies to T. pallidum (MHA-TP) tests.
  - ❖ They are important in excluding false-positive nonspecific tests
  - ❖ In contrast to the nontreponemal tests, they may not only indicate a current or recent infection, but would remain reactive even after adequate treatment, indicating as such a past infection ("serological scar")

Although serological tests are still the most practical diagnostic tool, they are not subspecies specific. Recent identification, by molecular testing, of reliable genetic signatures for the different treponemal subspecies, may prove in the near future to be a valuable tool not only for research but also for diagnostic purposes.

TREATMENT AND PREVENTION OF THE NONVENEREAL TREPONEMATOSES

- The WHO recommends a single intramuscular injection of benzathine penicillin for the treatment of early and late stages of the endemic treponematoses
- With proper penicillin therapy, cure rates up to 97% are possible and lesions become noninfectious within 24 hours. In addition, the titers of the nontreponemal serological tests show a gradual decline and eventually become negative
- In pinta, the a chromic patches persist for life.
- Erythromycin is indicated for the treatment of infections in those who are allergic to penicillin. Other macrolide antibiotics are also probably effective, despite a scarcity of reported experience
- In persons allergic to penicillin, other alternatives may include tetracycline and doxycycline
- Close contacts should also receive therapy.
- Recommendations for prophylactic treatment depend on the number of seropositive children younger than 6 years of age and are as follows:
  1. If the prevalence is more than 50%, treatment is given to the entire population.
  2. If the prevalence ranges between 10% and 50%,treatment is given to patients, their contacts, and all children under the age of 15 years.

3. If the prevalence is less than 10%, then treatments administered only to patients and their close contacts

Treatment of the NonvenerealTreponematoses

First Line	Benzathine penicillinG	>10 years <10 years	1.2 million units IM 0.6 million units IM	Single dose Single dose
Second Line	Oral erythromycin	Adults Children <8 years	500 mg qid 8–10 mg/kg qid	15 days 15 days
	Oral doxycycline	Adults	100 mg bid	15 days
	Oral tetracycline	Adults Children >8 years	500 mg qid 250 mg qid or 25 mg/kg/day	15 days 15 days

Eradication campaigns have been effective using a 7- to 10-day course of oral penicillin, at a dose of 50 mg/kg per day in four divided doses up to 1,200 mg daily. However, experience has shown that mass treatment campaigns alone are insufficient. Treatment of those infected and those at risk must be followed by periodic clinical follow up, serosurveillance, and screening campaigns

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