

Ancient adversaries

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General outline

- This presentation content is biased toward the adult population and toward Mississippi although applicable to the Southeast region
- The presentation is intended to highlight these interrelated conditions at both a clinical/patient care level and a public health perspective
- To preserve this birds eye view, granular details of clinical practice have been deferred

Specific objectives

- Outline the historical context of Syphilis and Tuberculosis
- Describe how these diseases have affected, and still affect the immunocompetent population
- Compare the impact of these diseases in the Southeast region with the national epidemiology
- Compare these diseases effect on immunocompetent persons with the effect on Persons With HIV

Syphilis, what is it?

- Syphilis is a Sexually Transmitted Infection (STI) caused by *Treponema pallidum*
- There are other species within the same genus *T. pertenuis*, *T. carateum* and *T. pallidum endemicum*
- There is cross reactivity between members of the genus in testing but *T. pallidum* is the only STI of the group

Syphilis, when did it start?

- The origins are murky and there are a few hypotheses
- Either
 - the pre-Columbian hypothesis where it has always had a global distribution or
 - the Columbian hypothesis where it was brought back to the Old World by Columbus in the 1500's

Syphilis, when did it start?

- There is clear evidence supporting the existence of Syphilis in the American continent in the pre-Columbian period
- There is documentation of Italian physicians describing a pustular disease on soldiers bodies in 1495 that could be sexually transmitted and this has been identified as Syphilis

Syphilis, when did it start?

- War conditions in Europe represented a favorable field for the first outbreak of Syphilis
- Even at this early stage (in the 1500's) of documented spread and recognition as a disease, Syphilis was viewed as stigmatized and disgraceful
- The infection was blamed on neighboring countries and enemies during war

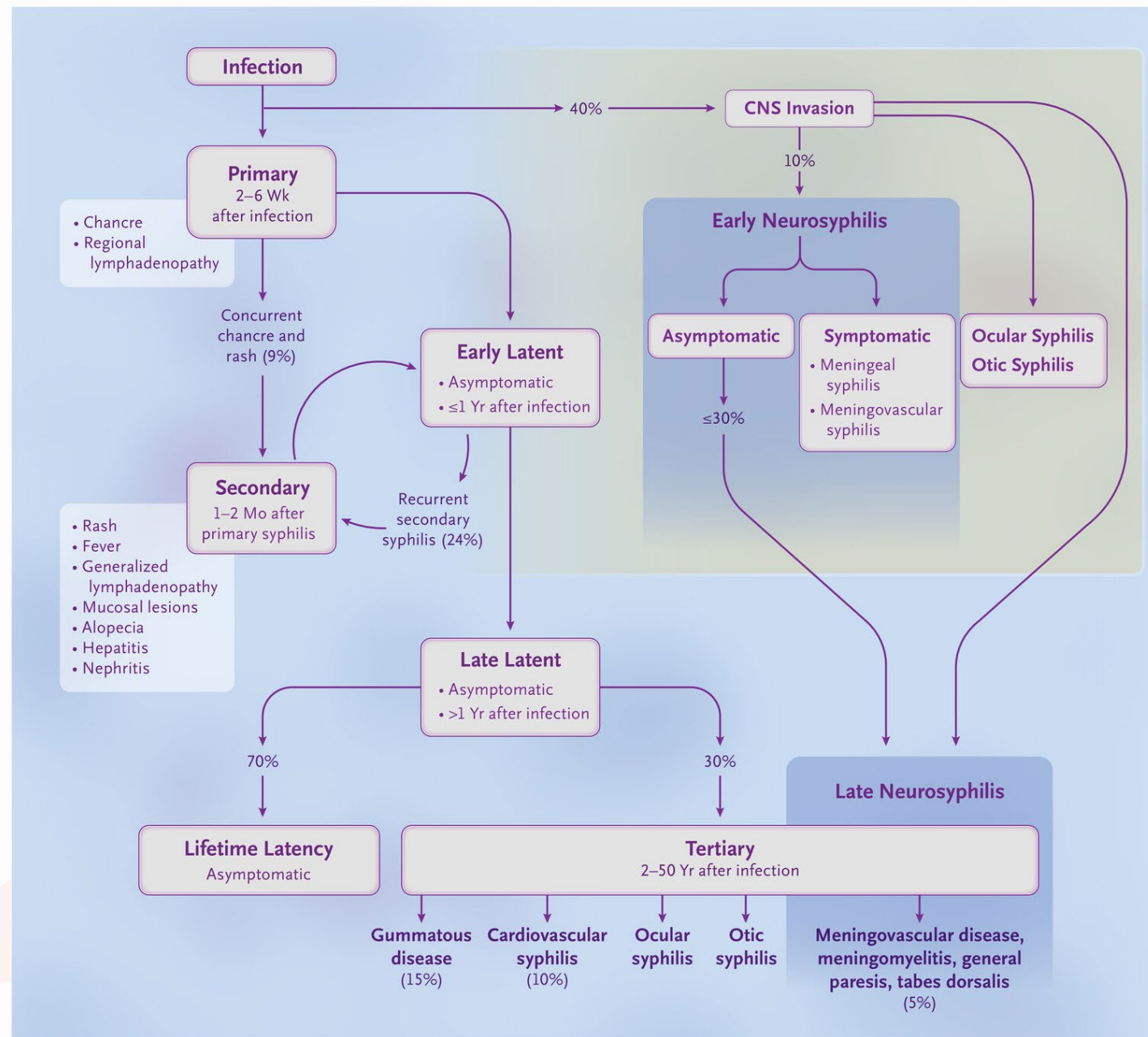
Syphilis, when did it start?

- In Europe it has been called the French disease, the Polish disease and the Castilian disease
- In Turkey it was called the Christian disease and in northern India Muslims and Hindus blamed each other for the affliction
- The etiologic agent took 4 centuries to be identified

Syphilis, the clinical manifestations

- The natural history of the disease is notoriously variable
- The organism disseminated within days after the infection and invades distant tissues
- It can be thought of affecting the Central Nervous System vs extra-CNS, being symptomatic vs asymptomatic and being early vs late

Syphilis, the clinical manifestations



Syphilis, the decline and resurgence

- Multiple medical therapies were tried with varying success
- The advent of Penicillin + Public Health measures led to an initial, marked decline
- And yet, this disease is not only with us, but its incidence seems to be increasing recently

Syphilis, the decline and resurgence

- The CDC reports that the number of cases has increased by 81% from 2014 to 2018
- A significant portion of those infected are Men, including those Men who have Sex with Men, and of that subset, those who have HIV
- And the stigmatization that it faced centuries ago is still present

Syphilis, the decline and resurgence

- A second, and alarming component of this rise affects women
- Between 2014 and 2018 syphilis cases rose by a factor of 6 among women who injected drugs or who had sex with a person who injected drugs
- This has translated into an increase in cases among women of childbearing age

Syphilis, the decline and resurgence

- And, as would be expected, this is mirrored by an increasing number of congenital Syphilis
- “In Mississippi, USA, infant hospitalization with congenital syphilis spiked by 1,000%, from 2016 to 2022” - Staneva, 2023

Syphilis, the decline and resurgence

- In Mississippi, this significant spike in congenital Syphilis mentioned parallels maternal substance use
- There are racial and socio-economic disparities identified as well
- And there is inadequate screening mandates and public health policies

Syphilis, the decline and resurgence

- “Mississippi has neither expanded Medicaid nor adopted presumptive eligibility for uninsured pregnant persons. Failure to pursue such policies created more structural barriers for early and effective prenatal care that enabled the syphilis problem to persist and grow” – Staneva, 2023

Tuberculosis, what is it and when did it start?

- Tuberculosis (Tb) is caused by Mycobacterium tuberculosis, one of many species in the Mycobacterium genus
- Tb, unlike Syphilis has a better documented origin story
- Archaeological evidence of Egyptian mummies, from 5000 years ago, reveals typical skeletal deformities of Tb
- The first written documentation is from India and China about 2000-3000 years ago

Tuberculosis, when did it start?

- The famous scientist Koch was able to isolate the Tubercle bacillus in the 1800's
- But unfortunately the discovery of the bacillus by Koch in the 1800's had no significant consequences for medical practice for > 60 years

Tuberculosis, clinical manifestations

- Multiple clinical manifestations are possible
- The lung is the most common organ involved as in Pulmonary Tb
- But extrapulmonary Tb occurs as well
 - Lymph nodes
 - Bone/joints
 - Intraabdominal
 - CNS

Tuberculosis, clinical manifestations

- Primary pulmonary Tb is usually asymptomatic and can become latent (Latent Tb Infection, LTbI)
- 13 million persons in the USA are estimated to have Latent Tb
- Post primary pulmonary Tb (reactivation, active Tb) may follow primary Tb, but reactivation may be delayed until many years after the initial infection

Tuberculosis, clinical manifestations

- This manifestation often presents with the classic clinical features of productive cough/hemoptysis, anorexia, weight loss, fever, chest discomfort and night sweats
- Reactivation may be provoked by temporary or permanent immunological impairment
- In immunocompetent patients the lifetime chance of reactivation (developing post primary Tb) is 5-10%

Tuberculosis, initial attempts disease control

- Since the identification of the etiology in the 1800's there have been multiple modalities of treatment attempted
- Included immunizations with related non-tuberculous mycobacteria
- Sanatoria were created to isolate infected persons and protect the general population
- Therapeutic pneumothoraces were performed

Tuberculosis, initial attempts disease control

- Streptomycin was the first effective anti-Tb drug and arrived in 1943
- “The enthusiasm for the success of anti-tuberculosis therapy stifled the alarm bells” Armocida, 2020

Tuberculosis, going but not gone

- These alarm bells toll for multiple reasons
- One is the emerging of Tb drug resistance to antimicrobials
- But primarily, Tb no longer made headlines because many social determinants of Tb became the exception rather than the norm

Tuberculosis, going but not gone

- These public health determinants included absolute poverty, malnutrition and overcrowding
- Due to these becoming rarer in some societies, Public Health experts declared the virtual elimination of Tb was in sight
- Was it really?

Tuberculosis, going but not gone

- Despite progress in care and prevention, tuberculosis remains one of the world's leading causes of ill-health and death and the top cause of death from an infectious disease globally
- Globalization is creating circulation of microbial agents which may find favorable habitats
- Individuals with immune deficiencies represent an ever-increasing population at higher risk of contracting tuberculosis

Tuberculosis, going but not gone

- Specifically, co-infection with HIV is a relatively new scenario
- And lastly, ageing affects the effectiveness of Tb therapy by increasing difficulty in tolerating side effects of anti-tuberculosis drugs

Tuberculosis, going but not gone

Persons at high risk of progressing from latent to active TB

Recent contact with a TB case

Persons with fibrotic changes on chest radiograph consistent with old TB

HIV-infected persons

Organ transplant recipients

Persons immunosuppressed for other reasons (e.g., taking the equivalent of 15 mg/d of prednisone for >1 mo or taking tumor necrosis factor- α inhibitors)

Recent immigrants (<5 yr) from high prevalence countries

Persons with the following clinical conditions:

Diabetes mellitus

Chronic renal failure

Some hematologic disorders (e.g., leukemia and lymphomas)

Other specific malignancies (e.g., carcinoma of the head or neck and lung)

Gastrectomy and jejunioileal bypass

Silicosis

Injection drug users

Tobacco smokers

Residents and employees of high-risk congregate living facilities (e.g., correctional facilities, nursing homes, homeless shelters, hospitals, and other health-care facilities)

Mycobacteriology laboratory personnel

Data modified from Diel et al. 2013.

Tuberculosis, going but not gone

- In the US, the national incidence of reported Tb cases was 2.16 per 100,000 in 2020 and 2.37 per 100K in 2021
- Mississippi as a whole had a case rate of 2.2 per 100,000 in 2019 which is lower than the US average, but Hinds county had a rate of 5.6 per 100K in that year

Tuberculosis, going but not gone

- As often happens in the management of infectious diseases eradication requires
 - comprehensive approaches that aim to tackle social determinants of tuberculosis
 - scientific progress in diagnostic and therapeutic management of patients with tuberculosis

The syndemic

- A syndemic is defined as the convergence of two or more diseases that act synergistically to magnify the burden of disease
- HIV is synergistic with multiple other infectious diseases because
 - Risk factors are shared (mass incarceration, homelessness, substance use, transactional sex)
 - HIV leads to immunosuppression which may affect disease progress of co-existing infections

The syndemic

- HIV increases risk of Tb infection and disease progression (PWH are 18 times more likely to develop active Tb) and Tb slows CD4 recovery
- Without adequate control of the TB-HIV syndemic, the long-term TB elimination target set for 2050 (US Agency for International Development) will not be reached

The syndemic

- Not only is Syphilis incidence in PWH several fold greater than the general population but the presentation of Syphilis can be more severe
- Syphilis progresses to tertiary Syphilis 3.5 times more quickly in PWH vs persons without HIV

Solutions, general

- Integrated HIV/Tb programs improve health outcomes for both conditions
- Among Persons Who Inject Drugs, integrating services for addiction+HIV+Tb demonstrate improved outcomes

Solutions, general

- Suggestions from Staneva, 2023
 - To address the evolving Congenital Syphilis crisis in Mississippi effectively state agencies and political leaders should be encouraged to adopt all available tools to support early comprehensive prenatal care
 - Public health structures should receive adequate resources to diagnose and treat the most vulnerable populations, including underserved and uninsured/underinsured infected mothers
 - Enhancing sexual health literacy, including providing comprehensive sex education for youth, would further empower Mississippi residents to prevent or seek treatment for reemerging syphilis infection

Solutions, specific

- At every new patient encounter prioritize these interrelated conditions
- Orient history taking toward assessing risk and need for screening
- Screen where appropriate
- Discuss preventative measures

Solutions, specific

- Syphilis screening
 - USPSTF recs screening for Syphilis infection in persons at increased risk
 - The risk groups are not specifically defined nor are screening intervals

Solutions, specific

- However, USPSTF mentions reasonable to screen for Syphilis
 - men who have sex with men
 - persons with HIV infection
 - persons with a history of incarceration
 - Transactional sex
 - PWID
 - Already diagnosed with another STI
 - Annual screening is reasonable

Solutions, specific

- There are multiple approaches to Syphilis testing in the context of screening
 - One well accepted approach is to use the serum Syphilis Antibody test followed by reflex testing of the Rapid Plasma Reagin (RPR)
 - This can then reflex to a third tier of *Treponema pallidum* Particle Agglutination if initial results are equivocal

Solutions, specific

- The USPSTF recommends screening for Latent Tb Infection in populations at increased risk
 - Persons born in, or are former residents of, countries with high tuberculosis prevalence
 - Persons who live in, or have lived in, high-risk congregate settings such as homeless shelters or correctional facilities
 - Persons who have immunosuppression such as those persons living with HIV

Solutions, specific

- CDC suggests either the Tuberculin skin Test or an Interferon Gamma Releasing Assay (such as Quantiferon) for LTBI screening
- There are practical considerations and cost considerations to each

Solutions, specific

- For HIV screening CDC guidelines recommend
 - All people between the ages of 13 and 64 should be tested for HIV at least once as part of routine health care, and those at ongoing risk should be tested more frequently
 - How frequently? Health-care providers should subsequently test all persons likely to be at high risk for HIV at least annually.
 - Who are high risk persons? Transactional sex, PWID (persons who inject drugs), having an STD and/or multiple partners with unknown HIV status, MSM

Solutions, specific

- Which test to use for HIV screening?
- Once you have identified that HIV screening is indicated, HIV Antigen Antibody test is the test of choice
- Sometimes called the “4th generation” HIV test
- This test utility assumes that the patient is asymptomatic and has not had a recent high risk encounter (injection drug use, sexual encounter)

Solutions, specific

- Pharmacological prevention for Syphilis
 - A study looking at MSM and Trans Gender Women who had bacterial STIs in the past year and who were either PWH or taking HIV PrEP were assigned to either receive a single dose of 200mg po Doxycycline ideally within 24hrs but up to 72 hours of unprotected intercourse vs no PEP

Solutions, specific

- Pharmacological prevention for Syphilis cont'd
 - STI testing was performed quarterly
 - They were followed for 1 year
 - The combined incidence of Gonorrhea, Chlamydia and Syphilis were lower by 2/3 in the intervention group
 - The CDC has put out draft guidelines about this but has not yet published it as part of their standard STI Treatment Guidelines (last published in 2021)

Solutions, specific

- If Latent Tb testing is positive, and there is no clinical suspicion for active Tb
- There are several regimens for the treatment of Latent Tb Infection
- “3HP” is one of several regimens, its well accepted and simple
- These regimens prevent patients from progressing to active Tb in future

Solutions, specific

12-DOSE REGIMEN (3HP) for Latent Tuberculosis Infection Treatment

CDC continues to recommend the use of the short-course combination regimen of once-weekly isoniazid-rifapentine for 12 weeks (3HP) for treatment of latent tuberculosis infection (LTBI) in adults.

CDC now also recommends use of 3HP:

- by directly observed therapy (DOT) **or self-administered therapy (SAT)***
- in persons aged **2–11 years**
- in persons with LTBI who are **living with HIV infection** including AIDS and taking antiretroviral medications with acceptable drug-drug interactions with rifapentine

Shorter treatment regimens, like 3HP, **have higher treatment completion rates** and **lower costs**.

* Healthcare providers should choose the mode of administration (DOT vs. SAT) based on local practice, individual patient attributes and preferences, and other considerations, including risk of progression to severe forms of tuberculosis disease.



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Solutions, specific

- Pharmacological prevention for HIV
 - Pre Exposure Prophylaxis is well established
 - The data on PrEP started with the iPrEx study in 2010 where ~ 2500 MSM and transgender women received FTC/TDF (Truvada) vs placebo and were followed, those in the FTC/TDF (Truvada) group had a 44% reduction in HIV incidence

Solutions, specific

- What options are there for PrEP?
 - **Oral daily doses of FTC/TDF (Truvada), ≤90-day supply for all gender categories and practices**
 - Oral daily FTC/TAF (Descovy), for cisgender men and transgender women at risk as an alternative to FTC/TDF (Truvada)
 - Oral non-daily Truvada (“2-1-1 regimen”, “event driven” or “on demand”) for MSM according to IAS-USA, not FDA recommended
 - Injectable Cabotegravir (Apretude) every 2 months* for all gender categories at risk of sexually acquired HIV

Take home (or take back to office) messages

- In summary, for the ancient adversaries Tb and Syphilis which have now coincided with the relatively new epidemic, HIV
 - Aim for simple measures and “low hanging fruit”
 - Adopt a comprehensive and unbiased approach to determining risk
 - Screen for multiple co-existing conditions simultaneously if indicated
 - Advise patients that disease prevention options exist which are pharmaceutical and non-pharmaceutical
 - Prescribing pharmaceutical prevention is not confined to Infectious Disease specialists

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Thank You!

Questions?