Infectious in Alaska: Alaskan Clinicians Battle Botulism, Tuberculosis and Syphilis

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Mycobacterium Tuberculosis

TB in Alaska: 62 cases in 2014 (8.4 per 100,000)
TB in Arizona: 184 cases of active TB in 2013 (2.8 per 100,000)
Incidence in the US overall: 3.0 per 100,000 in US

Stages of TB infection:
- Primary infection - Susceptible persons inhale airborn droplet nuclei containing viable tubercle bacilli. Granulomas are formed where the immune system walls off the bacteria. Viable organisms may remain in the granulomas.
- Latent TB – no active disease, not contagious. Occurs in an immune competent patient after primary infection – when the infection is walled off in granulomas.
- Reactivation TB – latent TB becomes active disease if there is a decrease in the immune health of the host. Occurs in 6% of individuals with latent TB if not given preventive treatment, usually within 2 years.
  - 90% of adult TB = reactivation of a formerly latent infection

Symptoms:
- Pulmonary: Chronic cough, dry at first then purulent, possibly blood streaked
- Constitutional: Malaise, anorexia, weight loss, fever, night sweats
- Children: can be failure to thrive in addition to the above

Exam findings:
- General: chronically ill in appearance, malnourished
- Lung: posttussive apical rales is CLASSIC for TB

At risk populations:
- Infections occur disproportionately among disadvantaged populations:
  - Malnourished
  - Homeless
  - Living in overcrowded, substandard housing
  - HIV positive
  - Diabetics
- Risk Factors for TB Specific to Arizona: Country of birth other than the US (Mexico 40%, Guatemala 5%, Philippines 5%, Honduras 4%, Vietnam 2%, Kenya 1%, India 2%, Other 15%), Residence in a correctional facility (23.9%), Diabetes Mellitus (19.6%), Homelessness (9.2%), HIV co-infection (5.4%)
Work up:
- Sputum Culture or Smear
- Chest xray - Cannot distinguish primary from reactivation TB on chest xray. However there are classic findings: upper lobe lesion or cavitary lesion.
  - Atypical findings more commonly found in immune deficient patients: lower lobe infiltrates, +/- pleural effusions
  - Seen in minority of chest xrays: Ghon (calcified primary complex) + calcified hilar lymph node = Ranke
- Tuberculin skin test in the Mantoux method – 0.1 mL solution with purified protein derivative (PPD), injected intradermally into the volar surface of the forearm with a 27 gauge needle, aka “tuberculin syringe”
  - After 48-72 hours, the transverse width is measured in mm of induration. The width required for a positive test varies with the patient’s likelihood of infection:
    - $\geq 5$ mm is positive if: HIV positive, recent contact with active TB, fibrotic changes on CXR consistent with previous TB, organ transplant patients or other immunosuppressed patients
    - $\geq 15$ mm = person at no risk for TB
    - $\geq 10$ mm = Recent immigrants from countries with high prevalence of TB, HIV negative injection drug abusers, Mycobacteriology lab personnel, Residents & employees of high risk congregate settings, Medical conditions that increase risk of TB, Children younger than 4 years old or infants, children and adolescents exposed to adults at high risk

Treatment:
- TB has a slow growth rate, so confirmatory studies may take a long time to process. Treatment should be provided early to improve outcome and limit spread.
- All suspected and confirmed cases of TB should be reported promptly to local and state public health authorities
- Goal of therapy – eliminate all tubercle bacilli from an infected individual while avoiding the emergence of clinically significant drug resistance. Basic principles:
  - Administer multiple medications to which the organisms are susceptible
  - Add at least two new antituberculous agents to a regimen when treatment failure is suspected
  - Provide the safest, most effective therapy in the shortest period of time
Ensure adherence to therapy – Directly Observed Therapy (DOT) – a healthcare worker physically observes the patient infesting antituberculous medications in the home, clinic, hospital or elsewhere.

- Noncorrectional completion rates in Arizona: 12 mo completion: 90.9%, Overall completion: 97.4%
- Correctional facility completion rates in Arizona: 2013: 73.2%, versus 2010: 59.1%
  - 2011: 64 correctional TB cases diagnosed, 45.3% Lost to Follow Up (due to repatriation, transferring to a facility out of Arizona or community release)

- Treatment in HIV negative, nonpregnant patients with active TB:
  - 6 or 9 months in duration (6 months preferred, with addition of extra 3 months beyond documentation of sputum culture conversion to negative for TB). Three options:
    - First two months: daily isoniazid, rifampin, pyrazinamide and ethambutol
      - Once susceptibility to isoniazid and rifampin are confirmed, d/c pyrazinamide and ethambutol
    - Two weeks of daily isoniazid, rifampin, pyrazinamide and ethambutol, then the same agents twice a week for six weeks.
      - Once susceptibility to isoniazid and rifampin are confirmed, d/c pyrazinamide and ethambutol and continue isoniazid and rifampin twice weekly for 4 months.
    - For the entire six months: daily isoniazid, rifampin, pyrazinamide and ethambutol

- In HIV positive persons with active TB:
  - Complex, involve experts
  - Duration of treatment will be longer, and there is the potential for interaction between rifamycin derivatives and anti-HIV medications

- In pregnant patients with active TB:
  - Isoniazid, rifampin and ethambutol for 2 months followed by 7 additional months of isoniazid and rifampin.
    - Pyrazinamide not recommended in pregnancy

- Treating patients with latent TB:
  - Reduces the risk that the infection will reactivate.
  - Treat patients with a positive PPD who are at increased risk of disease or exposure
  - Treatment regimens once latent infection is confirmed (and Active disease should be excluded):
    - Isoniazid oral for 9 months, or 270 doses within 12 months
      - To prevent isoniazid-associated peripheral neuropathy, give pyridoxine (vitamin B6) to those at risk
- Rifampin and pyrazinamide both oral daily for 2 months (60 doses within 3 months)
  - This regimen associated with significant hepatotoxicity, liver function must be carefully monitored
- Rifampin only for 4 months if patients unable to tolerate isoniazid or pyrazinamide.

A word on drug resistant TB: Drug resistant TB important worldwide, but is relatively rare in the US (<1%)
- Risk factors for drug resistant TB: nonadherence to therapy, unsuccessful preventive therapy, immigration from countries with high prevalence of drug-resistant TB, close and prolonged contact with individuals with drug-resistant TB
- Definitions:
  - Drug resistant: resistant to 1st line drug (rifampin or isoniazid)
  - Multi-drug resistant: resistant to rifampin and isoniazid +/- others.
  - Extensively drug resistant: resistant to isoniazid, rifampin, fluoroquinolones and either aminoglycosides or capreomycin or both.
    - In the United States, extensively drug resistant strains kill HIV positive patients more frequently than HIV negative (10% and 68% respectively)
- Drug resistance in Arizona 2013: 11.1% were Isoniazid resistant (7.9% 2012).
  - 1 case was multi-drug resistant.
Botulism

- Clostridium botulinum is a ubiquitous anaerobic spore-forming bacillus found in soil.
- C. botulinum produces botulinum toxin (4 types – A, B, E & F produce disease in humans), which is extremely potent. It blocks release of acetylcholine.
- 3 naturally occurring forms:
  - Food-borne – occurs after ingestion of preformed toxin found in canned, smoked or vacuum packed foods (home-canned veggies, home smoked meats, vacuum packed fish, etc...)
  - Infant – associated with honey ingestion, toxin produced in the gut rather than being preformed.
  - Wound – in conjunction with IVDA, toxin produced in the wound itself rather than being preformed.

At risk populations:
- Infants eating honey < 1 year old
- Populations eating home canned/smoked/fermented foods regularly – aka Alaska Native
- Prison inmates drinking prison-made illicit alcohol

Clinical presentation:
- Symptom onset 12-36 hours following ingestion
- Pentad: sudden onset diplopia, dry mouth, dysphagia, dysphonia, muscle weakness
- Early: visual disturbances (esp diplopia, loss of accommodation), along with ptosis, cranial nerve palsies, impairment of EOMs with fixed & dilated pupils.
- Paralysis progresses to respiratory failure and death without mechanical ventilatory support.
- Nausea & vomiting if toxin type E.
- Normal temperature and sensorium.

Work up:
- Toxin identified in patient’s serum, wound, stool and in suspected foods

Treatment:
- Equine serum heptavalent botulism antitoxin – administer as soon as diagnosis is suspected, do not wait for confirmatory lab studies!
  - Consult state health department authorities or CDC to obtain antitoxin and help with assay testing of serum, wound, stool and suspected foods.
  - Perform skin testing before antitoxin administration in order to avoid hypersensitivity reaction.
- Respiratory failure: intubate, mechanical ventilation
- Swallowing difficulties: IV fluids or alimentation
- Find all persons who may have eaten infected food and monitor closely for onset of infection.

Prevention:
- Adhere to proper canning, smoking and vacuum packing techniques
- Avoid feeding honey to infants < 1 year old.
Syphilis
- Caused by *Treponema pallidum*, a spirochete
- Transmission occurs most commonly during sexual contact
- 30-50% risk of acquiring syphilis after unprotected sex with an individual with infectious syphilis
- May also be transmitted through non-sexual contact, blood transfusion, or via placenta from mother to fetus (congenital syphilis)
- Public health efforts focus on early recognition and treatment of infectious individuals and their partners

In Alaska:
- Incidence of primary or secondary syphilis in 2009 - 0/100,000
- Incidence of primary or secondary syphilis in 2013 - 3.1/100,000
- Alaska ranks 32nd in rates of primary and secondary syphilis in the 50 states
- 2 cases of congenital syphilis from 2009-2013

In Arizona:
- Incidence of primary or secondary syphilis in 2009 - 3.5/100,000
- Incidence of primary or secondary syphilis in 2013 - 4.4/100,000
- Arizona ranks 17th in rates of primary and secondary syphilis in the 50 states
- 86 cases of congenital syphilis between 2009 and 2013

Stages:
- Early (Infectious syphilis)
  - Primary lesions – chancre, regional lymphadenopathy
  - Secondary lesions – can involve skin, mucous membranes, occasionally bone,
  - CNS or liver (secondary syphilis); relapsing lesions, or congenital lesions
  - Marked by an abundance of spirochetes
  - Lesions are self-limiting
- Late
  - Benign gummatous lesions of skin, bone, and viscera; CV disease, CNS and ocular syndromes
  - Non-infections
  - Lesions are highly destructive may be disabling and lead to death

Symptoms/Exam Findings:
- Primary
  - Chancre – typical lesions found on penis, labia, cervix, anorectal region, lip, tongue, tonsil, breast, or finger – classically described as non-tender, non-purulent, and indurated
  - Only 31% of patients have this classic triad
  - Appears as small erosion on average 3-4 weeks after inoculation
- Rapidly develops into a painless superficial ulcer with a clean base and firm, indurated margins
- Enlarged regional lymph nodes described as rubbery discrete and non-tender
- May develop secondary bacterial infection
- Resolves without treatment, often unnoticed, may scar especially in cases of secondary bacterial infection

**Secondary**
- Seen a few weeks up to 6 months after chancre
- Systemic signs and symptoms secondary to disseminated infection
- Fever, lymphadenopathy, or infections lesions
- Skin and mucosal lesions most common
  - Lesions are non-pruritic, macular, popular, pustular, or follicular; or may be a combination of any of these types – often mistaken for non-infectious rash
  - Lesions are generally NOT vesicular
  - Palms and soles involved in 80% of cases
  - Condylomata lata – fused weeping papules on the moist areas of the skin and mucous membranes – often mistaken for genital warts, highly infectious
- Meningeal, hepatic, renal, bone, and joint invasion may occur

**Latent**
- Dormant period
- Absence of primary or secondary lesions
- Divided into early (first year after primary infection) and late (one year after entering latent phase) stages
- Early latent syphilis may relapse into secondary syphilis
  - Diagnosis:
    - No active clinical manifestation (infectious lesions)
    - Documented seroconversion or fourfold rise in non-treponemal titers in the past 12 months
    - Patient can recall symptoms of primary and/or secondary syphilis
    - Patient had partner with documented primary, secondary, or early latent syphilis
- Late latent syphilis considered non-infectious to sex partners
  - Diagnosis:
    - History and physical examination show no evidence for tertiary disease or neurosyphilis
- Probable transmission to fetus at any stage
- This stage can last for months to a lifetime

**Late (tertiary) syphilis**
- Occurs anytime after secondary syphilis
- Rarely seen in developed countries
May present in multiple organ systems

- Skin- cutaneous lesions
  - Multiple nodular lesions
  - Solitary gummas
- Mucous membranes
  - nodular gummas
  - leukoplakia
- Skeletal system
  - Periostitis
  - Osteitis
  - Arthritis
- Eyes
  - Gummatous iritis
  - Chorioretinitis
  - Optic atrophy
  - Cranial Nerve palsy
- Respiratory System
  - Gummatous infiltrates in the larynx, trachea and pulmonary parenchyma
- Gastrointestinal
  - Liver lesions
  - Gastric lesions
- Cardiovascular
  - Arteritis supra cardiac portion of aorta
- Nervous
  - Neurosyphilis
    - Can present at any stage of infection
    - Meningovascular
    - Tabes dorsalis

Lesions divided into 2 types

- Localized gummatous reaction
  - Rapid onset, responds to therapy
- Diffuse inflammation
  - Insidious in onset, involves CNS and large arteries
  - Fatal if untreated
  - At best treatment will halt progression

At risk populations:
- Most US cases occur in men who have sex with men

Work Up:
- Serologic tests
  - Non-treponemal antigen tests
    - VRDL, RPR
    - Commonly used for routine screening
Establishes diagnosis and also measures efficacy of treatment
Positive 4-6 weeks after infection or 1-3 weeks after appearance of primary lesion
Almost always positive in second stage
Lower titers in late stage
Non-specific, must be correlated with clinical findings
False positives seen with a wide variety of other conditions
Distinguish false positive from true positives by performing treponemal specific antibody test
False negatives when titers are high, lab can dilute the specimen

- Treponemal antibody tests
  - Specific
  - Positive in primary syphilis, and most cases of secondary syphilis
  - Usually remains reactive throughout a patient’s life, however, with appropriate treatment it may revert to non-reactive
  - TPHA, TPPA, FTA-ABS
    - Confirm the diagnosis of syphilis following a non-treponemal test
  - EIA, CIA
    - Used to screen instead of non-treponemal tests

- Rapid tests
  - Single rapid treponemal test is approved in the United States

- CSF examination
  - Not routinely performed unless clinical signs and symptoms of neurosyphilis or ophthalmologic involvement are present
  - In classic cases CSF has elevated protein, lymphocytic pleocytosis, and a positive CSF reagin test (VRDL)
    - Positive reagin test confirms the diagnosis
    - Negative reagin test does not exclude neurosyphilis as CSF VRDL may be negative 30-70% of cases of neurosyphilis

Treatment:
- Penicillin remains the preferred treatment for syphilis
  - Benzathine penicillin G
    - Primary 2.4 million units IM x 1 dose
    - Secondary 2.4 million units IM weekly x 3 weeks
    - Tertiary without neurosyphilis as for secondary
  - Aqueous penicillin G 18-24 million units IV daily divided every 3-4 hours or given as continuous infusion x 10-14 days; followed by benzathine penicillin G 2.4 million units IM weekly x up to 3 weeks
• No reported cases of penicillin resistance
• For pregnant women penicillin is the only antibiotic to reliably treat the fetus
• For non-pregnant women, and men other antibiotic options include:
  o Doxycycline
  o Ceftriaxone
  o Azithromycin – documented resistance in MSM
  o All patients treated with non-penicillin regimen need close clinical and serologic follow-up

Public Health Measures:
• No sex for 7-10 days after treatment
• Cases must be reported to local public health facility
• Partner notification, and treatment
• HIV test at time of diagnosis
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