Opportunistic Infections in HIV

- Illustrative case
- An update of things (PJP, Cryptococcus, Syphilis, latent tuberculosis)

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Occam's Razor vs Hickam' Dictum

- Occam's Razor:
  - Usually stated as "the simplest explanation is usually the correct one"
  - More accurately is "the explanation that requires the fewest assumptions is likely the correct one" or "Plurality should not be posited without necessity"
- Hickam's Dictum:
  - "A patient can have as many diseases as they damn well please"

Case Presentation

- Mr X
- 51 year old male
- Dual citizen China/Australia
- Splits time between Shanghai and Sydney
- New wife lives in Shanghai
- Son lives in Sydney
- Works as “bit of this and that”
- Current smoker

Referral to HIV Clinic

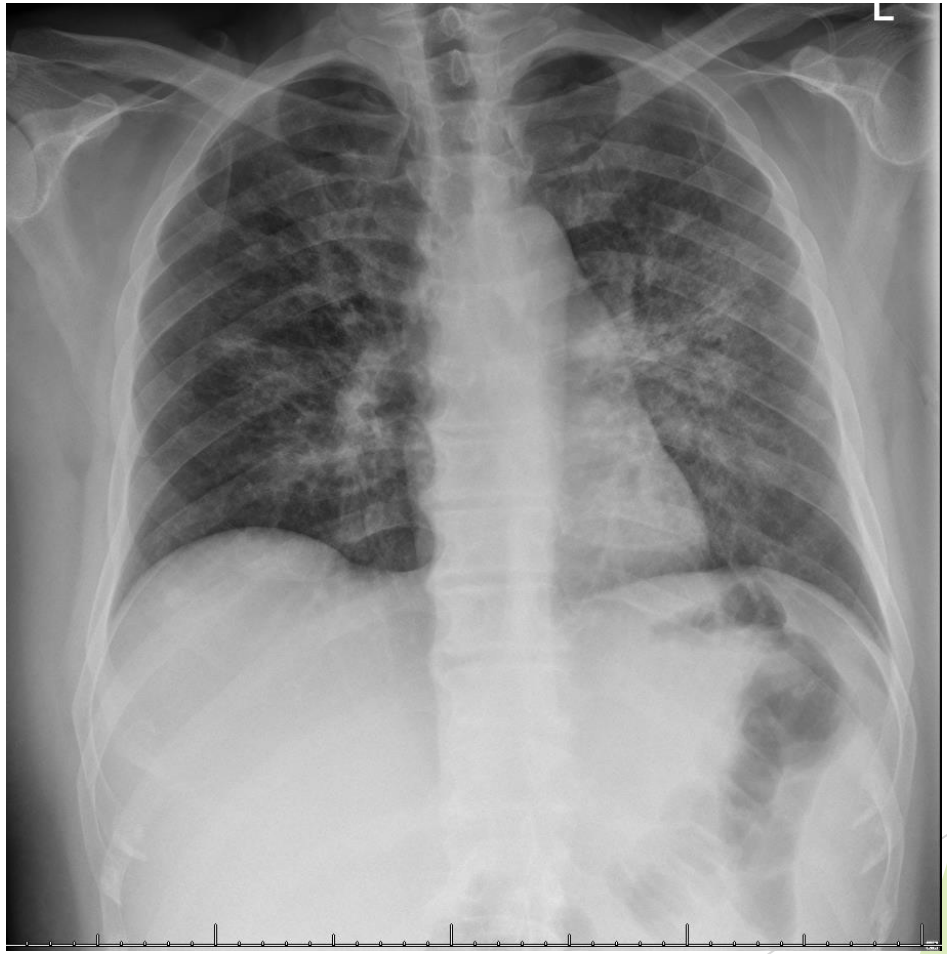
- “New HIV diagnosis”
- Phone call from GP
  - GP tested for HIV after noticing oral candida and fevers
  - Gave fluconazole and prednisone. Fevers are now gone.
  - Mentioned recent course ciprofloxacin for chest infection
  - Patient has non-settling chest infection for 2 months with several hospitalisations in Shanghai without improvement

Diverted to Emergency

- Further history
  - Current smoker
  - Heterosexual
  - Occasional uses sex workers in China
  - Unwell 2 months with fevers, SOB, cough
  - Several hospital admissions in Shanghai,
  - Prolonged oral and intravenous antibiotics without effect
  - Denies MSM
  - Denies IVDU

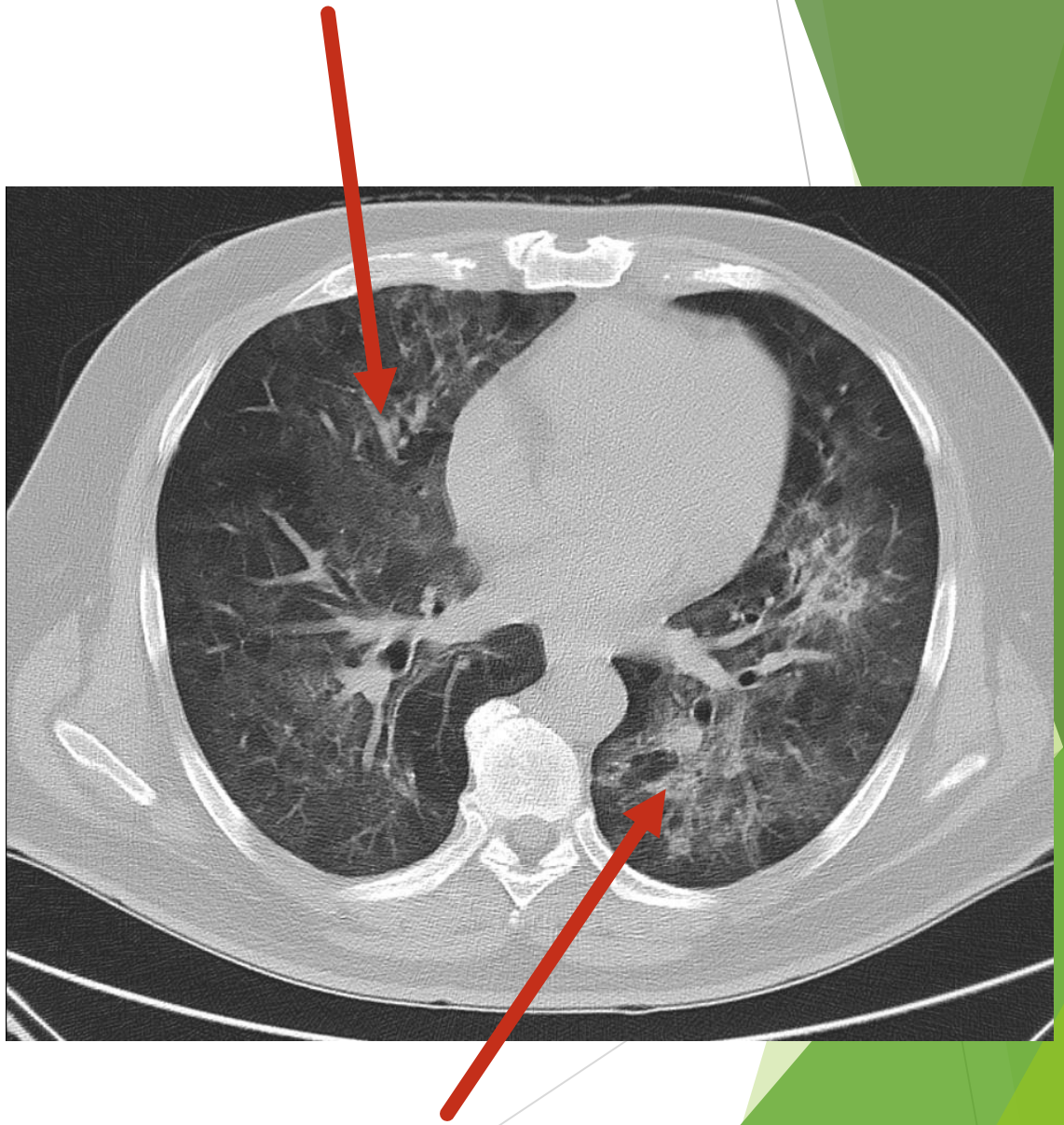
In Emergency

- Hypoxic
- Increased Respiratory rate
- Febrile



Management

- Commenced on high dose oral Bactrim
- Prednisolone
- Admitted to wards, but with ICU review
- CT Chest
- Negative pressure isolation pending sputum for AFB
- Ordered extensive pathology for advanced HIV
- Positive PCR for *Pneumocystis jirovecii*



HIV Results

- Wild-type virus

HIV Reference l

HIV DIAGNOSTIC SEROLOGY	19 5542	20 Jun 19 11:00 TC11531754	
RPT HIV Ag/Ab		Reactive *A	
Liaison XL HIV Ag/A		Reactive *A	
HIV Comment		Com'nt	
p24 Ag Qual		Not Tested	
HIV-1Proviral		Not Tested	
p18 HIV WB		3+ *A	
p24 HIV WB		3+ *A	
p34 HIV WB		3+ *A	
p40 HIV WB		3+ *A	
gp41-45 HIVWB		3+ *A	
p53 HIV WB		3+ *A	
p55 HIV WB		3+ *A	
p68 HIV WB		3+ *A	
gp120 HIV WB		3+ *A	
gp160 HIV WB		3+ *A	
Final Interp		Com'nt	

HIV MONITORING	42	20 Jun 19 11:00 TC11531754	Ra
Lymphocytes		640 *L	150(
CD3 T cells %		67	59
CD3 T cells		429 *L	780-
CD4 T cells %		3 *L	30
CD4 T cells		19 *L	500-
CD8 T cells %		62 *H	14
CD8 T cells		397	210-
CD4:CD8 ratio		0.0 *L	1.4-
Spec Type		Plasma	
HIV-1 RNA		Detected *A	
HIV-1 VL		4894830	20-1

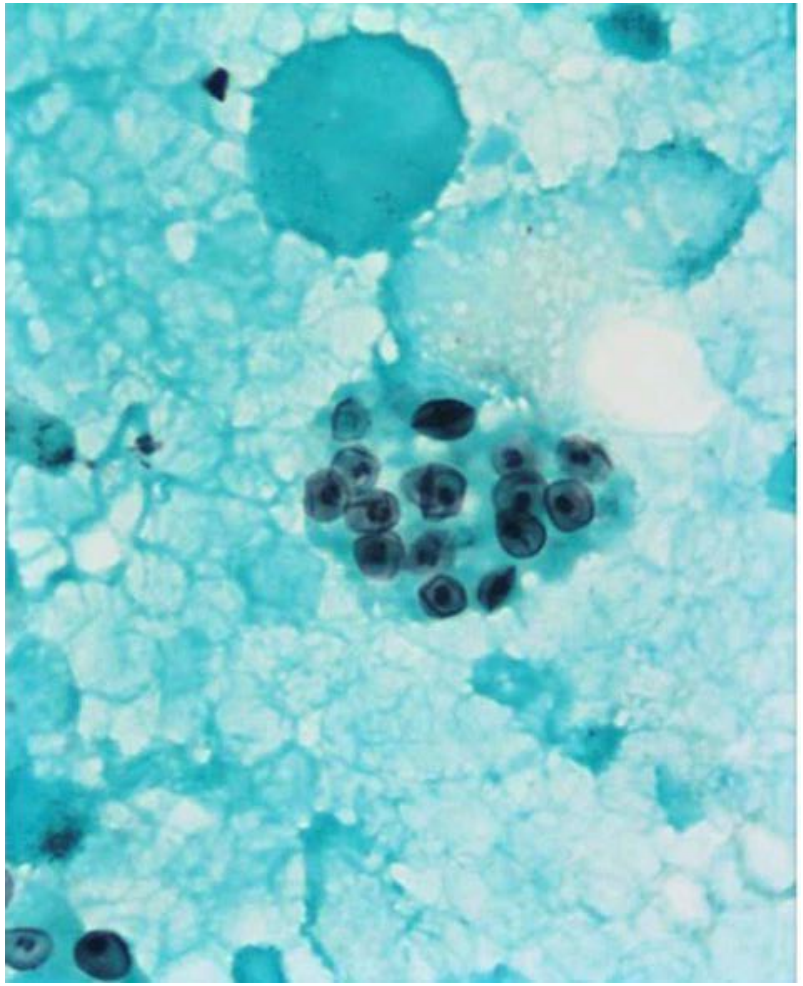
Opportunistic Infections and HIV/AIDS

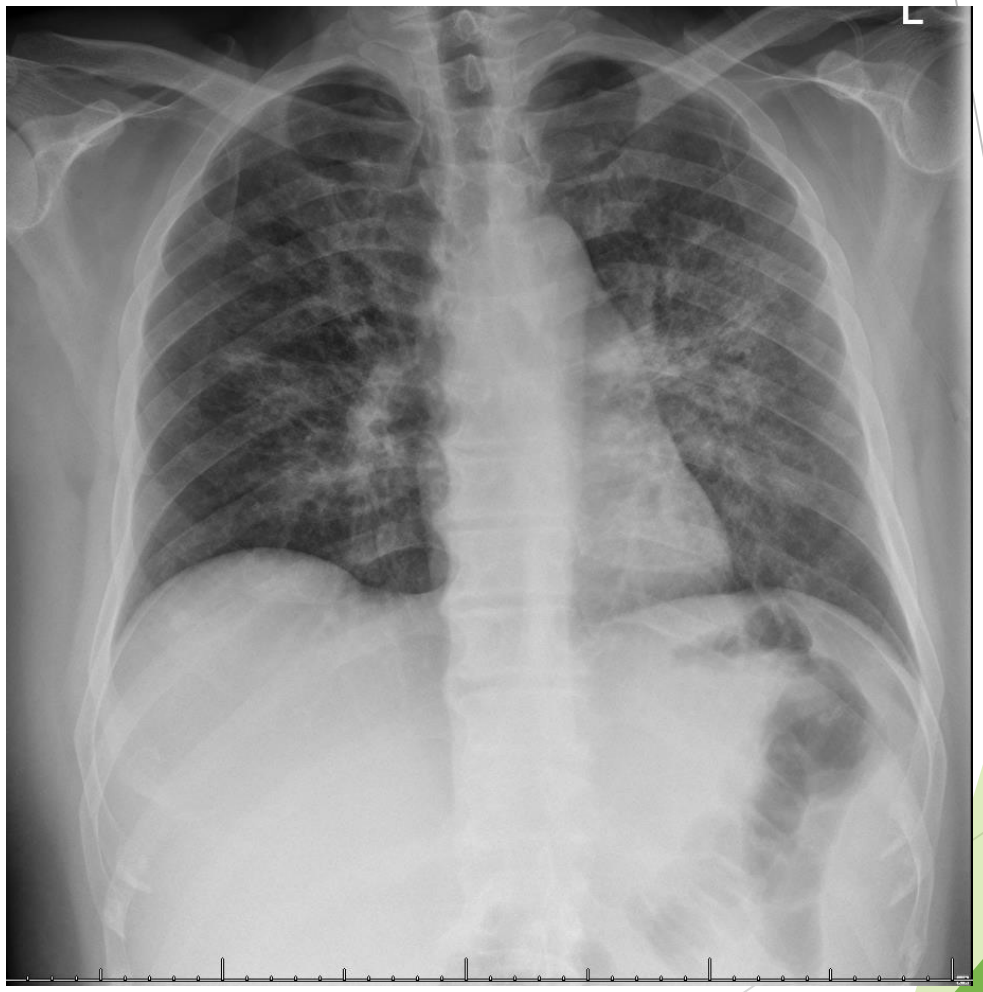
- Opportunistic pathogens only cause disease under certain circumstances, whereas obligate pathogens cause disease for general population
- AIDS: CD4<200cells/microL
- AIDS Defining Illnesses
  - Pneumocystis jirovecii pneumonia (PJP)
  - Oesophageal Candididasis
  - CMV retinitis
  - Kaposi's sarcoma
  - Lymphoma
  - *Mycobacterium avium complex (MAC)* or *Mycobacterium kansasii*
  - *Mycobacterium tuberculosis reactivation*
  - *Cerebral Toxoplasmosis*
  - *HIV wasting syndrome*
  - *Chronic Crypotosporidiosis*

Pneumocystis jirovecii (PJP) - The artist formerly known as PCP

- Fungal infection that was originally thought to be a Protozoan parasite
- Widespread environmental organisms that you can have colonisation with. Immunucompetent people don't develop a clinical illness
- Clinical suspicion: subacute onset. Fever, breathlessness, fatigue. Disproportionate hypoxia, dry cough.
- Radiography: Diffuse ground-glass changes. Peri-hilar predominance (Bat Wings). Pleural effusions are rare
- Not able to culture so diagnosis historically was made through immunoflourescent techniques but these were insensitive
- Standard diagnosis now PCR, lower tract sampling preferred (Bronchoscopy or induced sputum)

PJP





Use of PCR in PJP Diagnosis

- PCR has become standard of care in diagnostics because of the low sensitivity of fluorescent microscopy, however more prone to detect colonisation
- Should always interpret a positive test by ensuring patients have a consistent clinical disease
- Research done shows that there is a quantitative difference between those with clinical PJP and those who are asymptomatic. HIV-positive patients tend to have higher levels of organism than HIV-negative patients.
  - Detection of Pneumocystis jirovecii by Quantitative PCR to Differentiate Colonization and Pneumonia in Immunocompromised HIV-positive and HIV-negative Patients. J Clin Micorbiol 206 June;54(6):1487-1495
- You may see this reported as “Positive” and “Low Positive”. Some laboratories may do this but complicated as won’t be specific to HIV status.
  - Still incorporate clinical assessment to reach diagnosis.

(1,3)-Beta-D-glucan – future possibilities

- Cell wall component of many fungi including Candida, Aspergillus, and Pneumocystis
- Test is a serum antigen, values >=80pg/mL are significant
- Sensitivity for PJP up to 92%, and specificity is 86%, possibly more sensitive in HIV
- Benefits: High negative predictive value, not a respiratory tract specimen so sampling easy
- Problems: Not yet widely available, interacts with other fungal infections so diagnosis still needs confirmation
- Ethical concerns about sourcing material…….

Treatment of PJP

- Trimethoprim/Sulfamethoxazole remains treatment of choice
  - Bactrim DS (160/800mg) 2 tablets tds
  - Fever and rash more common in HIV
  - Monitor LFTs and K
  - Duration is 21 days treatment then prophylaxis
- Alternatives are clindamycin+primaquine, dapsone, atovaquone, pentamidine. Would not use without infectious diseases advice
- Corticosteroids in PJP:
  - Well established that there is a benefit for treatment in patients with substantial hypoxaemia.
  - Adjunctive corticosteroids for Pneumocystis jirovecii pneumonia in patients with HIV infection. Cochrane Database Syst Rev 2015 Apr;2015(4)
- Initiation of HAART
  - Presence of PJP does not preclude starting HAART even with risks of IRIS
  - Early treatment (<2 weeks) associated with reduced HIV progression/death and better virologic control without worse adverse events
  - Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: A multi center randomized strategy trial. PLOS ONE 2009 May

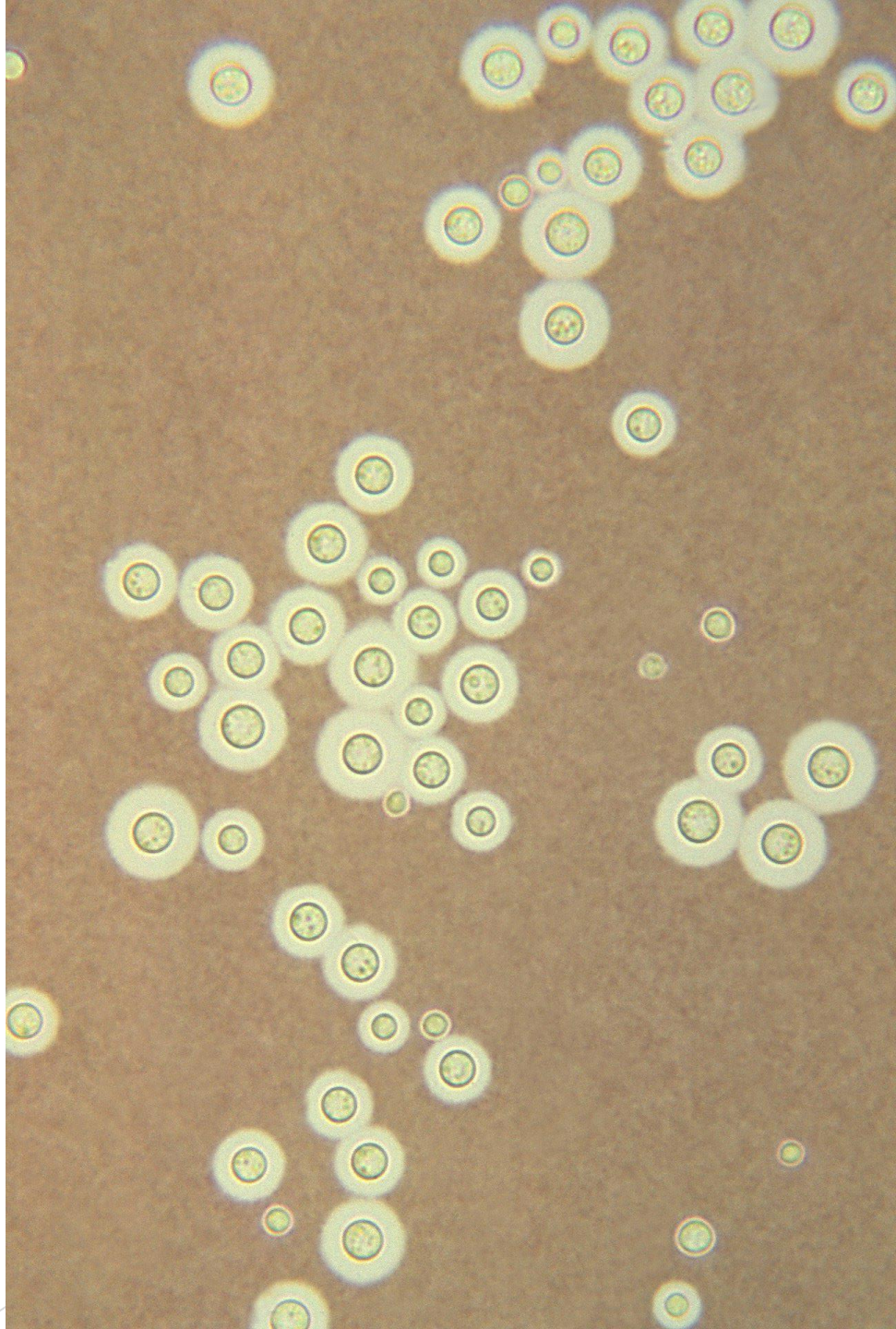
Where does Hickam's Dictum Fit?

- Serum Cryptococcal Antigen Positive
  - Titre 16
- MRI Brain showed small amount peri vascular enhancement
- Commenced on Liposomal amphotericin and flucytosine
- Proceeded to LP

WCC	0
RCC	1
Prot	825
Gluc	3.7
Gram	Negative
CrAg	Negative
AFB	Negative

Cryptococcosis

- Fungal infection caused by an environmental yeast
- Generally acquired by inhalation
- *Cryptococcus neoformans*
  - Worldwide distribution
  - Associated with immune deficiency (HIV/AIDS, prolonged steroids, transplantation, liver disease)
  - Found in soil where pigeons frequent
- *Cryptococcus gattii*
  - Australia, PNG, British Colombia (Canada) and various places in USA
  - Often occurs in immunocompetent hosts
  - Found in eucalypt trees and certain other species in geographic areas where endemic disease observed

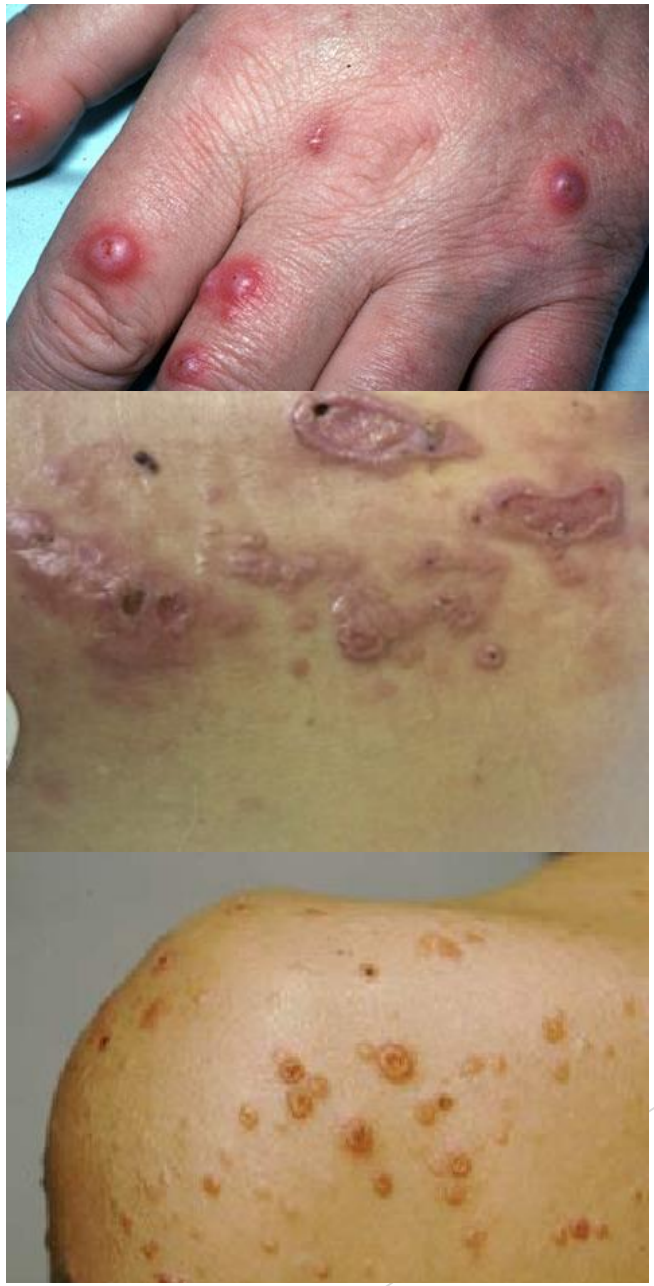


Manifestations

- Pulmonary Disease
  - Focal pneumonitis
  - Non-calcified nodules
  - Dissemination and severe disease rare in immunocompetent
  - Dissemination, ARDS, haemoptysis more common in immune compromise
- Meningitis
  - Almost all immune compromised
  - Subacute (usually 2-4 weeks)
  - Fevers variable
  - Intracranial pressure can be significantly elevated
  - CSF usually monocyte predominant

Manifestations

- Cutaneous
  - Part of disseminated disease
  - Usually nodules or abscesses
- Other:
  - Liver
  - Lymph nodes
  - Eyes
  - Skeletal system



Diagnosis

- Cryptococcal Antigen
  - Rapid test
  - Detects *C. neoformans* and *C. gattii*
  - RF can cause false positive but has been improved over the years
  - More sensitive for meningitis and dissemination than pneumonia
  - Titre >160 in asymptomatic HIV + patients predicts meningitis
    - High Cryptococcal Antigen Titres in Blood are Predictive of Subclinical Cryptococcal Meningitis among Human Immunodeficiency Virus-Infected Patients. Clin Infect Dis 2018
  - Titre decreases slowly so not good for monitoring progress in early treatment
- Culture
  - Samples: Blood, CSF, lower respiratory tract, tissue biopsy
  - Relatively slow growing

Treatment (General Principles)

- Susceptible to amphotericin, fluconazole, flucytosine routinely
- Resistant to echinocandins (micafungin, caspofungin, anidulafungin) intrinsically
- Immunocompetent patient with isolated pulmonary disease can go onto fluconazole
- Disseminated disease, meningitis, and pulmonary infection in immunocompromised should be treated with amphotericin and flucytosine, and once improved can move to fluconazole
- Immunocompromised patient should be assumed to have meningitis and must always have a lumbar puncture with CSF opening pressure recorded
  - If opening pressure >20mmH20 need therapeutic removal of CSF and ongoing LPs
- Treatment is for at least 6 months in immunocompetent patients and usually 12 + months in immunocompromised

Prognosis

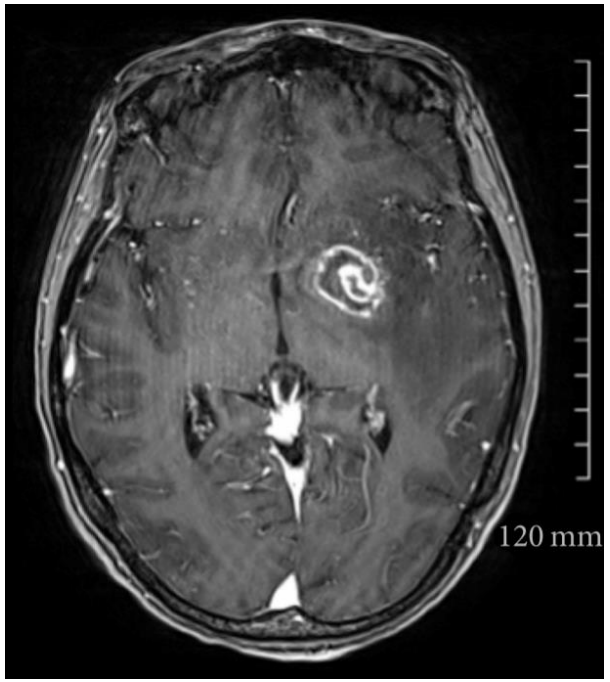
- Variable depending on site (meningitis vs pulmonary) and patient factors
- Poor prognostic factors
  - Cirrhosis
  - Malignancy
  - Positive staining of CSF
  - Low CSF white cell count
  - Cryptococcal antigen titre >32 (CSF or serum)
  - High opening pressure on LP

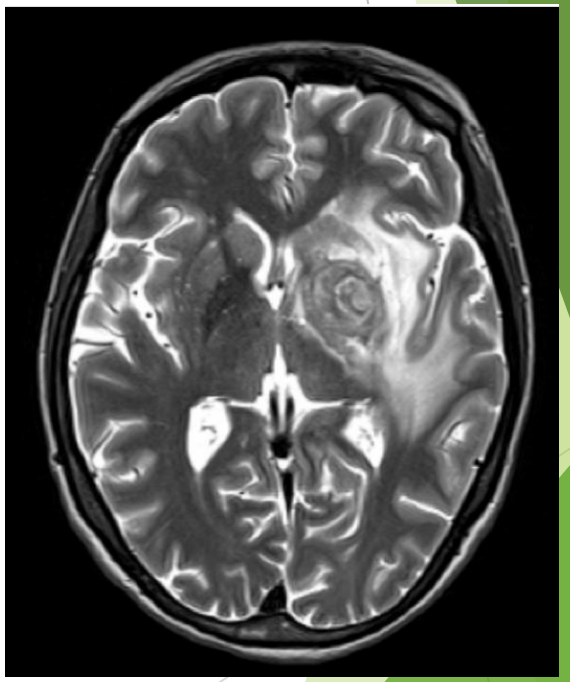
Doesn’t have Cryptococcal Meningitis - Does seem to have CNS abnormality

- 3276 copies HIV in CSF
- Subtle MRI changes
- Elevated CSF Proteins

Differential:

- HIV related
- Cryptococcus
- Tuberculosis
- CNS Lymphoma
- Toxoplasmosis
- Syphilis





Investigating CNS Disease in HIV

- Toxoplasma: Serum IgG, PCR on CSF, classic radiology
- Syphilis: Peripheral serology, PCR and VDRL on CSF. Low threshold to treat.
- Cryptococcus: Cryptococcal antigen on CSF
- Primary CNS Lymphoma: Cytology on CSF (need white cells). MRI to look for leptomeningeal changes
- Tuberculosis: AFB culture and PCR on CSF, CSF white cells, evidence of peripheral disease
- HIV: viral load on CSF. Consider in neurological signs despite suppressed peripheral viral load

- Our patient
  - Syphilis EIA positive
  - RPR 64
  - VDRL positive on CSF

Neurosyphilis

- Really challenging area, particularly in HIV
- Asymptomatic neurosyphilis is fairly common
- Can develop symptomatic meningitis particularly early disease
- Other clinical manifestations:
  - Ocular syphilis
  - Otosyphilis (hearing loss, tinnitus)
  - Meningovascular syphilis (infarcts)
- Late neurosyphilis:
  - Tabes dorsalis
  - General paresis (dementing illness)
  - Nerve palsies

HIV and Neurosyphilis

- Neurosyphilis including early forms are more common in HIV+
- Risks:
  - CD4<350
  - RPR >128
- Early signs to watch for
  - Vision changes (ocular syphilis reported more frequently in HIV)
    - Often present as part of secondary phenomenon
    - 10% had permanent vision loss
  - Hearing loss (I don't have data on this but bilateral neurosensory hearing loss has been a common referral for me)
  - Cranial nerve palsy
- Consider routine LP in HIV and syphilis if low CD4 or high RPR
- Consider treating if high white cells, high protein, or consistent clinical syndrome

Diagnosis of Neurosyphilis

- Clinical suspicion and positive serology are first step
  - RPR does not have to be elevated in late disease
- Anyone (particularly HIV+) with ocular, otologic, or neurological symptoms with positive syphilis serology should ideally undergo lumbar puncture
- Cell count and protein
  - High protein suggestive. Note HIV+ patients may have elevated protein as part of HIV infection
  - Raised WCC. Early symptomatic disease has higher white cell count than asymptomatic and late disease
- Syphilis specific testing
  - PCR is uncommonly done
  - VDRL is most commonly used. Positive confirms diagnosis (in absence of blood stained sample). Negative does not exclude
  - FTA-ABS is more sensitive but less specific.

Treatment of Neurosyphilis

- Recommended in Australia is 15 days of IV benzylpenicillin 1.8g q4 hourly
  - 10.8g per day via infusers
- Consider corticosteroids at commencement to mitigate JH reactions (evidence for this is limited)
- Penicillin allergic patients
  - 1st line is desensitisation
  - Second would be Ceftriaxone daily
  - Third would be 28 days doxycycline (high dose 200mg bd)
- Monitoring after treatment:
  - Follow RPR until at least 4 fold reduction from baseline. Establish nadir
  - Repeat LP at 6 months to ensure normal isolation of CSF (can take up to 2 years)
  - Some evidence that normalization of RPR predicts CSF normalization.
    - Applies to HIV infected and uninfected, but may be less reliable if not on HAART

Mycobacterium Disease and HIV

- From an endemic region for *Mycobacterium tuberculosis*
  - Need to actively exclude active or latent TB
  - Golden rule:
    - If you diagnose HIV you have to look for TB
    - If you diagnose TB you have to look for HIV
- Atypical Mycobacteria
  - CD4 count <50, at risk of *Mycobacterium avium* complex
  - Prophylaxis indicated.
  - Avoid starting MAC prophylaxis until comfortable patient does not have active disease
- Patients quantiferon gold was positive
- Sputum culture was smear negative
  - Late growth of Acid Fast Bacilli (AFB)
  - TB PCR negative, Mycobacterium kansasii

Latent Tuberculosis an HIV

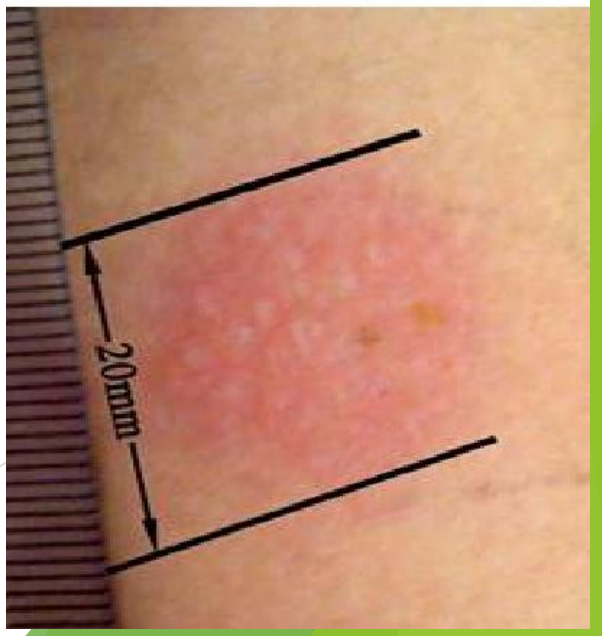
- Latent tuberculosis is most common form of TB
- Non-infectious but risk of reactivation
- Aim investigation and treatment at
  - Healthcare workers
  - High prevalence countries
  - Recently infected
  - Most likely to reactivate
    - Immune compromised
    - Recently infected
    - HIV
    - Diabetes
    - Younger than 35 (lifetime risk is high)

Approach to Latent TB

- Clinical Detail:
  - Age, country of birth/childhood, age moved to Australia, BCG vaccination
  - Smoking history, diabetes, HIV, cancer, immune suppression
- Screening test
  - Tuberculin skin test TST (Mantoux)
  - Interferon Gamma Release Assay IGRA (Quantiferon gold)
- Chest X-Ray
  - Central lymphadenopathy, upper lobe changes, granuloma
- Deciding on which patients to intervene with
  - Tools to calculate yearly and lifetime reactivation risk
- Choosing treatment option

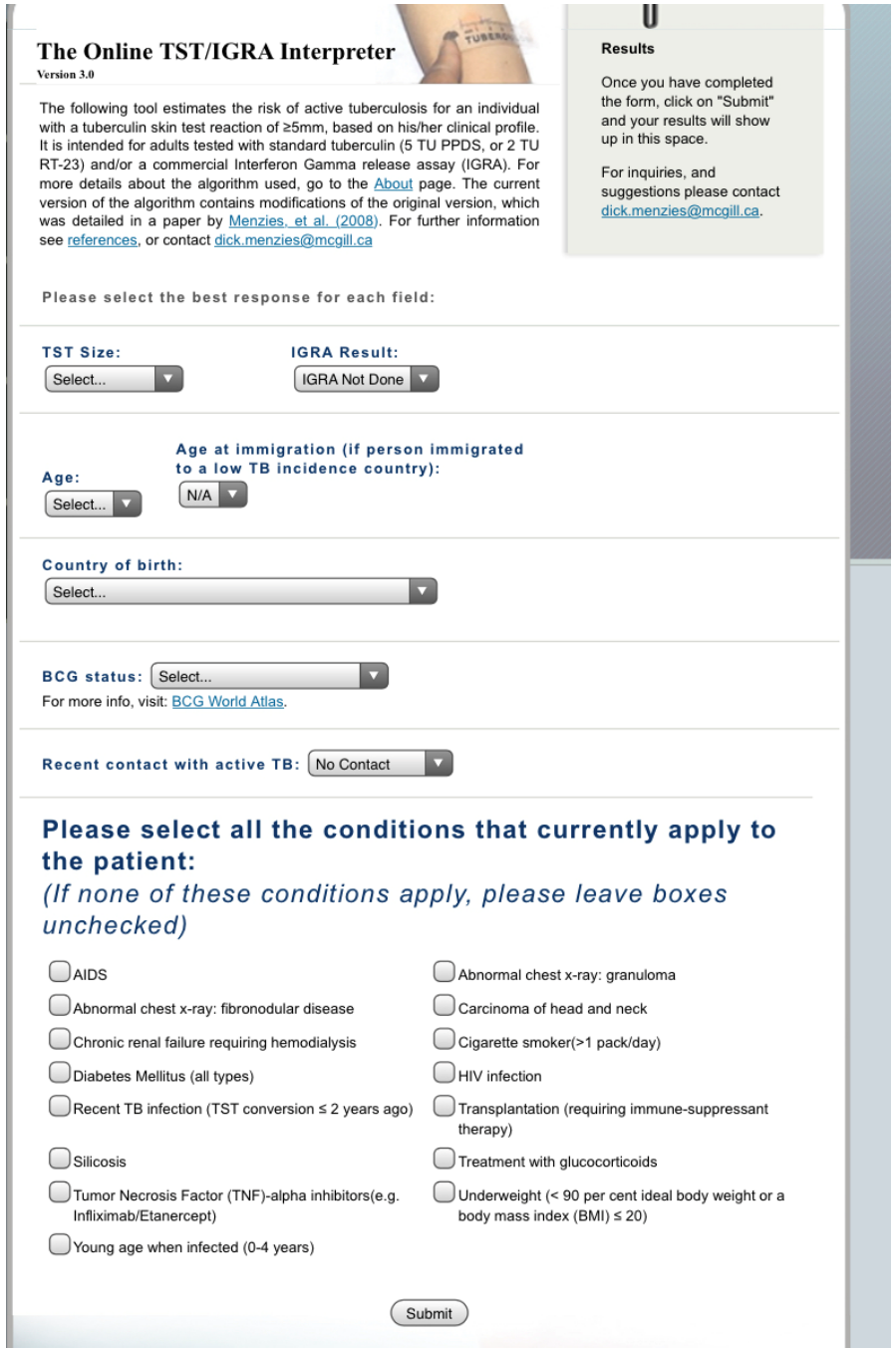
Performance of screening tests in HIV positive patients

- TST:
  - Inject tuberculin into skin and have a delayed hypersensitivity reaction by T cells if have previously had mycobacterial disease
  - False negative in heavy immune suppression, advanced HIV, very recent or very distant infection
  - False positive in BCG vaccination, non-tuberculous mycobacterial infection
- IGRA: (Preferred in HIV)
  - Serology test. Measure the amount of interferon gamma released from T cells when stimulated with TB antigens.
  - Indeterminate results in heavy immune suppression or advanced HIV.
  - Do not have false positives in BCG vaccine or non-tuberculous mycobacteria
  - Can have a false negative in highly active TB
- Both of these are ONLY to be used to diagnose latent TB.



Risk Stratification

- People with HIV are far more likely to progress to active TB (by an order of magnitude
  - HAART does reduce this risk
  - Significant reactivation rate in first year of HIV acquisition
  - Yearly reactivation rates are high
- TB outcomes are worse in HIV infected people
- In general all HIV patients with Latent TB should be treated
- For both HIV infected an uninfected patients there is a useful tool
- TSTin3: http://tstin3d.com/en/calc.html
  - I use this for virtually every latent TB patient
  - Gives you firm numbers to make decision on, individualized for patient



The Online TST/IGRA Interpreter

Version 3.0

The following tool estimates the risk of active tuberculosis for an individual with a tuberculin skin test reaction of ≥5mm, based on his/her clinical profile. It is intended for adults tested with standard tuberculin (5 TU PPDS, or 2 TU RT-23) and/or a commercial Interferon Gamma release assay (IGRA). For more details about the algorithm used, go to the About page. The current version of the algorithm contains modifications of the original version, which was detailed in a paper by Menzies, et al. (2008). For further information see references, or contact dick.menzies@mcgill.ca

Results

Once you have completed the form, click on "Submit" and your results will show up in this space.

For inquiries, and suggestions please contact dick.menzies@mcgill.ca.

Please select the best response for each field:

TST Size: Select...

IGRA Result: IGRA Not Done

Age: Select...

Age at immigration (if person immigrated to a low TB incidence country): N/A

Country of birth: Select...

BCG status: Select...

For more info, visit: BCG World Atlas.

Recent contact with active TB: No Contact

Please select all the conditions that currently apply to the patient:

(If none of these conditions apply, please leave boxes unchecked)

- AIDS
- Abnormal chest x-ray: fibronodular disease
- Chronic renal failure requiring hemodialysis
- Diabetes Mellitus (all types)
- Recent TB infection (TST conversion ≤ 2 years ago)
- Silicosis
- Tumor Necrosis Factor (TNF)-alpha inhibitors(e.g. Infliximab/Etanercept)
- Young age when infected (0-4 years)
- Abnormal chest x-ray: granuloma
- Carcinoma of head and neck
- Cigarette smoker(>1 pack/day)
- HIV infection
- Transplantation (requiring immune-suppressant therapy)
- Treatment with glucocorticoids
- Underweight (< 90 per cent ideal body weight or a body mass index (BMI) ≤ 20)

Submit

Below are the results for a patient with a **Positive** QFT Test, who is **52** years old, born in **China, Shanghai**, **immigrated at age 52**, whose BCG status is **Never vaccinated or unknown**, who has had **no contact** with active TB, and who can be characterized by:

- **Cigarette smoker(>1 pack/day)**
- **HIV infection**

The likelihood that this is a true positive test (PPV) is: **98%**

The annual risk of development of active tuberculosis disease is estimated to be **8.09%**.

The cumulative risk of active tuberculosis disease, up to the age of 80, is: **100%**

If treated with INH, the probability of clinically significant drug-induced hepatitis is **2.3%**, and the associated probability of hospitalization related to drug-induced hepatitis is **0.6%**.

How to Treat Latent TB

- Isoniazid 300mg daily for 9 months (very common in HIV+)
  - Long treatment course
  - Can cause hepatitis
  - Risk of peripheral neuropathy, consider pyridoxine
  - Isoniazid resistance is 7.4% minimum globally, higher in Eastern Europe and Western Pacific
- Rifampicin 600mg daily for 4 months (normal weight range)
  - Short course
  - Less common resistance
  - Drug/Drug interactions
- Rifampicin + Isoniazid for 3 months
- Rifapentine
- Yearly monitoring with Chest X-ray
  - What to do if unsuitable for treatment

Rifampicin in HIV

- Inducer of cytochrome P450
- Reduces activity of corticosteroids, OCP
- Interactions with HAART
  - Reduces bictegravir (Biktarvy)
    - Raltegravir and Dolutegravir probably ok
  - Affects TAF but not TDF to same extent
  - Reduces all PIs
- Alternative drug is Rifabutin
  - No evidence for use in latent TB

Hickam's Dictum…..

- Opportunistic Infections in 51yo male with HIV/AIDS
  - PJP
  - Oesophageal Candidiasis
  - Cryptococcosis
  - Mycobacterium kansasii
  - Latent tuberculosis
  - Neurosyphilis
  - Reactivated Hepatitis B
  - Lymphoma
  - CMV viraemia

Other OI updates of interest

- CMV Resistance in retinitis
  - Letermovir
  - Maribavir
- Fluconazole resistance in Candidiasis
  - Increasing rates of resistance to fluconazole
  - Echinocandins may have a role, rezafungin of interest
  - Ibrexafungerp is promising oral agent for future

The End