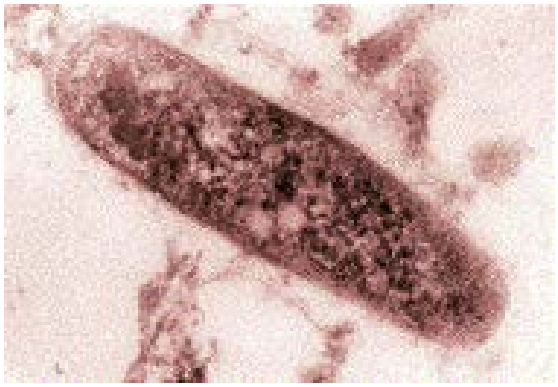
Australian Tuberculosis Review

October 2017



M. tuberculosis EM Photo

Forthcoming Meetings

International course on the clinical management of drug-resistant tuberculosis

20-24 November 2017, Bangkok, Thailand

Contact: Secretariat The Union

Editorial Group

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Editorial: That the surgical treatment of spinal tuberculosis remains controversial is illustrated by yet another study, this time from Urumqi in western China. Here young children with deformed spines of 32 degrees or more were subjected to mostly very effective surgery. Yet in other studies surgery + chemotherapy has shown no superiority in outcome to chemotherapy alone. This is the case now in most western countries where the disease is rare and the diagnosis made before cord damage or more than a little kyphosis has occurred. It is possible that in Xingjiang, where spinal TB is more common, the Region's vast spaces could make early diagnosis difficult, and severe spinal deformity and/or neurological damage far more common than in Australia. Surgery, particularly where an

anterior approach is difficult and can result in morbidity. From the literature, it seems that there is consensus among orthopedic surgeons with the most experience.

1 Patients with a < 30 degree deformity should receive anti-tuberculosis chemotherapy as outpatients and be followed up by means of X-Ray images to detect progression

2) Chemotherapy for 9-12 months

3) Surgery is indicated for those younger than 15 years with > 30 degree deformity

4) Deformity progression despite chemotherapy

5) No neurological improvement despite chemo-therapy.

6) X-ray shows signs of continued spinal instability

7) The surgeon has some experience in performing the procedure.

Diagnosis

Evaluation of the GeneXpert MTB/RIF assay on extra-pulmonary and respiratory samples other than sputum: a low burden country experience.

Pandey et al Brisbane, Qld, Australia

Pathology 2017; 49: 70

Abstract: The aim of this study was to assess the performance of the GeneXpert MTB/RIF assay on extrapulmonary (EP) and respiratory (non-sputum) clinical samples suspected of having tuberculosis (TB) from Queensland, Australia. A total of 269 EP and respiratory (non-sputum) collected from Qld patients who were suspected of having TB were subjected to the GeneXpert MTB analysis, Ziehl-Neelsen (ZN) staining, Mycobacterium tuberculosis (Mtb) culture and drug susceptibility testing. Phenotypic and genotypic data were compared. The overall performance analysis of the GeneXpert MTB/RIF assay for detection of MTB complex demonstrated sensitivity 89%, specificity of 95%. PPV of 89% and NPV of 95% using culture as a reference standard. The GeneXpert MTB/RIF analysis of acid-fast bacilli (AFB) smear positive samples and AFB smear negative samples showed sensitivities of 100% and 77%, respectively. Looking at individual EP and respiratory (non-sputum) sample types, the sensitivity ranged from 60% to 100% although the specificity ranged from 32.3% to 100% with the specificity of lymph node tissue biopsy being the lowest. The GeneXpert MTB/RIF assay detected 11% more TB cases than culture and 27% more cases than ZN microscopy. Due to insufficient numbers, performance analysis of the GeneXpert MTB/RIF assay on rifampicin resistance could not be carried out. The GeneXpert MTB/RIF assay is potentially valuable for TB diagnosis in the majority of the EP and respiratory (other than sputum) samples in our setting. Although the GeneXpert MTB/RIF assay provides rapid diagnostic results. The overall sensitivity to rule out the disease is suboptimal for some specimen types. Performance varied according to specimen type and AFB smear status. The sensitivity and specificity of lymph node tissue was 63% and 33%. Care must be taken when using the GeneXpert MTB/RIF assay in lymph node tissue samples. All samples should be cultured regardless of the GeneXpert MTB/RIF assay result.

Comment: In Australia, if AFB are seen on smear, and the patient does not come from a country where MDR-TB is prevalent, then an GeneXpert MTB/RIF assay may not be necessary.

Diagnostic accuracy of the Xpert MTB/RIF cycle threshold level to predict smear positivity.

Lange et al Freiburg, Gautang, Germany; London, UK; Bishkek, Kyrgyzstan; Kuala Lumpur, Malaysia; Dunedin, NZ; Newark, NJ, Chapel Hill, NC,USA; Cape Town, South Africa; Santiago, Chile; Geneva, Switzerland; Lille, France; Dar es Salaam, Tanzania;

Manisa, Turkey; Oviedo, Lleida, Spain; Singapore.

Int J Tuberc Lung Dis 2017; 21: 493

Setting: Xpert MTB/RIF is the most widely used molecular assay for rapid diagnosis or tuberculosis (TB). The number of polymerase chain reaction cycles after which detectable product is generated (cycle threshold value, CT) correlates with the bacillary burden.

Objective: To investigate the association between Xpert CT values and smear status through a systematic review and individual–level data meta-analysis.

Design: Studies on the association between CT and smear status were included in a descriptive systematic review. Authors of studies including smear, culture and Xpert results were asked for individual-level data and receiver operating characteristic curves were calculated.

Results: Of 918 citations, 10 were included in the descriptive systematic review. Fifteen data sets from studies potentially relevant for individual-level data meta-analysis provided individual-level data (7511 samples from 4447 patients); 1212 patients had positive Xpert results for at least one respiratory sample (1859 samples overall). ROC analysis revealed an area under the curve (AUC) of 0.85 (95% CI 0.82-0.87). Cut-off CT values of 27.7 and 31.8 yielded sensitivities of 85% (95% CI 83-87) and 95% (95% CI 94-96) and specificities of 67% (95% CI 66-77) and 35% (95% CI 30-41) for smear positive samples.

Conclusion: Xpert CT values and smear status were strongly associated. However, diagnostic accuracy at set cut-off values of 27.7 or 31.8 would not replace smear microscopy. How CT values compare with smear microscopy in predicting infectiousness remains to be seen.

Comment: Can we find a place for Xpert MTB.RIF tests except in those from countries where MDR-TB is common?

JT

New synthetic lipid antigens for rapid serological diagnosis of tuberculosis.

Jones et al Bangor, St Andrews, UK; Geneva, Switzerland; Rome, Italy

PLoS One 2017Aug 14

Background: During pulmonary tuberculosis (PTB) antibodies are generated to trehalose esters of mycolic acids which are cell wall lipids of Mycobacterium tuberculosis (Mtb). Attempts have been made to use these complex natural mixtures for PTB diagnosis.

Aim: The aim of this work was to determine whether a serological tests based on a panel of defined individual trehalose esters of characteristic synthetic mycolic acids has improved diagnostic accuracy in distinguishing patients with culture positive PTB from individuals who were Mtb culture negative.

Method: One hundred serum samples from well-characterized patients with presumptive tuberculosis and diagnosed as having pulmonary smear and culture positive TB or being culture and smear negative were evaluated by ELISA using different combinations of synthetic antigens and secondary antibodies. Using cut-off values determined from these samples we validated study blind in samples from a further 249 presumptive TB patients.

Results: With the first 100 samples, detailed responses depended both on the precise structure of the antigen and on the secondary antibody. Using a single antigen, a sensitivity/specificity combination for smear and culture PTB detection of 85 and 88% respectively was achieved; this increased to 96% and 95% respectively by a statistical combination of the results with seven antigens. In the blind study a sensitivity /specificity of 87% and 83% was reached with a single antigen. With some synthetic antigens, the responses from all 349 samples were significantly better than those with the natural mixture. Combining the results for seven antigens allowed a distinction between culture positive and negative with an ROC AUC of 0.95.

Conclusion: We have identified promising antigen candidates for serological assays that could be used to diagnose PTB and which could be the basis of a much-needed, simple, rapid diagnostic test that would bring care closer to communities;

Comment: Watch this space.

JT

The utility of immunohistochemistry in Mycobacterial infection: a proposal for multimodality testing.

Solomon et al Boston, MA, Chicago, IL, USA

Am J Surg Pathol 2017 Aug 8

Abstract: Mycobacterium species are slow growing bacteria that cause significant morbidity and mortality worldwide. Because of the relative rarity of mycobacterial infections, potential for detection of nonpathogenic environmental contaminants and substantial costs associated with molecular diagnostics, effective screening methods are needed to identify samples most suitable for

molecular testing. While anatomic pathology specimens can be utilized to identify characteristic inflammatory patterns and to directly visualize mycobacteria through histochemical (acid fast bacilli [AFB]) stains), the utility of immunohistochemistry (IHC) in this setting is unknown. A cohort of 121 cases previously referred for mycobacterial sequencing, including 12 Mycobacterium tuberculosis (MTB), 42 no tuberculosis mycobacteria (NTM) , and 67 cases negative for mycobacteria by polymerase chain reaction (PCR), were stained with an antimycobacterial antigen, and the results were compared with histology, AFB stains, PCR and cultures. IHC was positive in 50% MTB, 81% NTM and 49% of cases negative for mycobacteria by sequencing, with excellent concordance (>90%) with AFB stains. Organisms were identifiable by IHC using a 10* objective in the majority of cases. Negative PCR with positive IHC was attributed to paucity of organisms in 30/33 cases, and positive PCR with negative IHC was most often associated with MTB. IHC is highly sensitive for NTM but has a lower sensitivity for MTB, suggesting that cases a high clinical and histologic suspicion for MTB should be sent for PCR even when AFB and IHC are negative. Incorporation of IHC into a screening algorithm for molecular testing has the potential for significant savings of cost and time.

Comment: Particularly when looking at lymph node biopsies to distinguish between NTM and MTB.

JT

High detection rates of urine mycobacterium tuberculosis in patients with suspected miliary tuberculosis.

Yokoyama et Kurume, Kyushu, Nagata, Japan

Intern Med 2917; 56: 895

Objective: The utility of detecting Mycobacterium tuberculosis in urine samples from patients with pulmonary tuberculosis with diffuse small nodular shadows (suspected miliary tuberculosis (MTB)) is still unclear in Japan. A retrospective cross-sectional study was conducted to investigate the detection rates of M. tuberculosis in urine of patients with suspected MTB.

Methods: among 687 hospitalised patients with tuberculosis, 45 with culture-confirmed suspected MTB and the data of culture and polymerase chain reaction (PCR) for M tuberculosis in urine and sputum cultured were investigated. The detection rates of M.tuberculosis using cultures and PCR were calculated. The detection rate of urine was then compared with that from bone marrow aspiration.

Results: Fourteen patients with suspected MTB were ultimately analyzed. A diagnosis of miliary tuberculosis was suspected in all patients before anti tuberculosis chemotherapy. Positive results by PCR (11[78.8%] cases)

and culture 8 [57.1]) were obtained for urine samples. In patients with suspected MTB, there was no significant difference in the detection rates between M tuberculosis in urine using a combination of PCR and culture (85.6%[12.14]) and bone marrow aspiration (66.7%[8/12])(p> 0.05)

Conclusion: Using PCR and culture, we demonstrated high detection rates of M. tuberculosis in the urine of patients with suspected MTB. A combination of PCR and culture compared favorably with the detection rates achieved with bone marrow aspiration. We believe that detection of M tuberculosis from urine and sputum samples may be easy and safe in patients with disseminated tuberculosis infections such as definitive MTB.

Comment: Why the authors included in their conclusion "sputum samples" is unclear to me. With such small numbers, we need a larger study for validity.

JT

Impact of larger sputum samples on Xpert MTB/RIF assay detection of Mycobacterium tuberculosis in smear-negative individuals with suspected tuberculosis.

Badal-Faesen et al Johannesburg, South Africa; Boston, MA, Temple, Silver Spring, MD, Sunnyvale, CA, Newark, NJ, Atlanta, GA, Washington, DC, San Francisco, CA, USA; Rio de Janeiro, Brazil.

J Clin Med 2017; Aug 7: epub

Abstract: As a strategy to improve the sensitivity of nuclear acid-based testing in acid-fast(AFB) negative samples, larger volumes of sputum (5-10 mls) were tested with Xpert. MTB/RIF from 176 individuals with smear-negative sputum undergoing tuberculosis evaluation. Despite larger volumes, this strategy had a suboptimal sensitivity of 50%.

Comment: It is refreshing to see that some journals publish negative results.

Prevention

Targeting isocitrate lyase for the treatment of latent tuberculosis

Bhusal et al Auckland, New Zealand

Drug Discov Today 2017; Apr 27

Abstract: Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis that can remain dormant for many years before becoming active. One way to control and eliminate TB is the identification of and treatment of latent TB, preventing infected individuals from developing active TB and thus eliminating subsequent spread of the disease. Isocitrate lyase (ICL) is involved in the mycobacterial glyoxylate and methyl isocitrate cycles. ICL is important for the growth and survival of M. tuberculosis. ICL is not present in humans and is therefore a potential therapeutic target for the development of anti-TB agents. Here we explore the evidence linking ICL to the growth and survival of M. tuberculosis. The structure, mechanism and inhibition of the enzyme is also discussed.

Comment: Even if a substance can be found which blocks this enzyme, will it penetrate the macrophage harboring the bacillus?

Imaging

18F-FDG-PET/CT Imaging of Thoracic and Extrathoracic Tuberculosis in Children.

Pelletier-Galameau et al Ottawa, Montreal, Canada

Semin Nucl Med 2017; 47: 304

Abstract: Tuberculosis (TB) remains a major health problem, affecting approximately one third of the world's population. The tubercle bacillus can affect virtually any organ of the human body and if left untreated can lead to severe morbidity and death. Diagnosis of active TB is challenging, especially in children. As a "great imitator", the disease can mimic numerous other pathologies, both clinically and at imaging. Although recognition of active TB is crucial to initiate adequate treatment in a timely fashion, thereby preventing transmission of disease, differentiation of active and quiescent disease is not always straightforward. Since the first reports more than 20 years ago, FDG –PET/CT imaging has been shown to detect active disease with accuracy equal or superior to other conventional imaging modalities. The role of FDG-PET in evaluating patients with TB is rapidly expanding. FDG-PET/CT can effectively identify foci of intrathoracic and extrathoracic TB, assess disease activity, differentiate between active and latent disease, and monitor response to therapy, identify potential; biopsy targets, and serve as a surrogate end point for new drug trials. Efficacy of FDG-_ET/CT in the especially challenging pediatric population will be the focus of the review.

Comment: Given that present doses of radiation for this modality lie between 25 and 30 msv, it seems hard to justify its use in children,

JT

Better completion of pediatric latent tuberculosis treatment using 4 months of rifampin in a US-based tuberculosis clinic.

Gaensbauer et al Denver, CO, USA

Pediatric Infect Dis 2017; Aug 1

Background: Children less than five years old have the highest age-specific rate of progression from latent tuberculosis infection (LTBI) to active disease. Therefore, regimens for treatment of LTBI must be not only efficacious but also practical enough to overcome the unique childhood barriers to regimen adherence. Since 2012, a 4-month regimen of daily rifampin (4R) has been the standard recommendation for pediatric LTBI at the Denver Metro Tuberculosis Clinic (DMTBC).

Methods: Using univariate and multivariate analysis we compared treatment completion rates between 4R and 9-month isoniazid (9H) regimens for all pediatric patient treated for LTBI t the DMTBC between 1/1/2006 and 31/12/2015, and assessed the influence of clinical and demographic characteristics on successful completion of the two regimens.

Results: There were 395 children in the 4R cohort and 779 in the 9H cohort. Completion rates overall were

significantly higher for 4R than 9H (83.5% vs 68.6 %, p<0.001). Drug toxicity leading to treatment non-completion was low in both groups (1.5% in 4R; 0.7% in 9H; p=0.23) and no patient progressed to active tuberculosis in either cohort. The 9H cohort was likely fail treatment completion due to barriers potentially related to the longer duration of treatment due to relocation or loss to follow-up.

Conclusions: Pediatric patients were significantly likely to complete LTBI treatment a 4-month daily rifampin regiment than with a 9-month regimen. Better completion rates of 4R may increase efficacy of TB prevention and decrease demand on public health resources.

Comment: Should the next step be a trial of 3 months weekly rifapentin **+** isoniazid vs 4R?

JT

Non Tuberculosis Mycobacteria

Mycobacterium chimaera and cardiac surgery.

Stewardson et al Melbourne, Vic, Australia

Med J Aust 2017; 206: 132

Abstract: There is an ongoing investigation into infections with non-tuberculous mycobacteria associated with contaminated heater-cooler units used in cardiac surgery. The overall risk is low, but surgical site and disseminated infections have been reported, including one possible case in Australia, mainly with surgery involving implantation of prosthetic material. Mycobacterium chimaera infection should be considered in patients who have previously undergone surgery with cardiopulmonary bypass and who present with cardiac or disseminated infection or sternal wound infection, unresponsive to standard antibiotic therapy. Where cases are suspected, patients should be investigated and managed with an infectious diseases physician and /or clinical microbiologist. If cases are confirmed or heater-cooler systems are found to be contaminated, details should be3 reported to the infect5ion infection control team, the jurisdictional health department, the Therapeutic Goods Administration and the Australian distributor of the affected heater-cooler unit(s). Measures to manage risk should include communicating with relevant hospital departments, ensuring that the manufacturer's updated for instructions for use are followed, regular testing of machines and reviewing the location of machines when in use.

Comment: It seems to have been forgotten that many thoracic physicians are knowledgeable about non-tuberculous mycobacteria.

JT

Exposure risk for infection and lack of human to human transmission of Mycobacterium ulcerans disease in Australia.

O'Brien et al London, UK; Melbourne and Geelong, Vic, Australia

Emerg Infect Dis 2017; 23: 837

Abstract: We conducted epidemiologic and genetic analyses of family clusters of Mycobacterium ulcerans (Buruli ulcer) in south eastern Australia. We found the incidence of M.ulcerans disease in family members was increased. However, the risk for exposure appeared short-term and not related to human to human transmission.

Comment: Presumably, this is also true for such cases emanating from the Daintree river valley in far north Queensland.

JT

In vitro activity of bedaquiline against rapidly growing nontuberculous mycobacteria.

Aquilar-Avala et al Mexico City, Mexico; Ghent, Beerse, Louvain, Brussels, Belgium

J Med Microbiol 2017; 66: 1140

Abstract: Bedaquiline (BDQ) has been proven to be effective in the treatment of multidrug resistant tuberculosis. We hypothesized that BDQ could be a potential agent to treat nontuberculous mycobacterial (NTM) infection. The objective of this study was to evaluate the in vit5ro activity of BDQ against rapidly growing mycobacteria by assessing the minimal inhibitory

(MIC) and minimal bactericidal concentration (MBC) against 18 NTM strains. For MIC determination, we performed the resazurin micotitre broth dilution, and for the mbcx the cfu was determined. BDQ exhibited a strong inhibitory effect against most NTM tested; however, for some NTB strains the MBC was significantly higher than the MIC. A new finding is that Mycobacterium flavescens has a mutation in the gene atpE associated with natural resistance to BDQ. These preliminary promising results demonstrate that BDQ could be potentially useful for the treatment of NTM.

Comment: Potentially useful in rapid growing pathogens such as M abscessus, M chelonae and M.fortuitum, but only if the right combination of drugs can be found.

JT

Treatment:

Rifampin vs. rifapentine: What is the preferred rifamycin for tuberculosis?

Alfarisi et al Baltimore, MD, Gainsville, FL, USA

Expert Rev Clin Pharmacol 2017; Aug 14

Introduction: One-third of the world's population is infected with Mycobacterium tuberculosis (Mtb). Latent tuberculosis infection (LTB) can progress to tuberculosis disease, the leading cause of death by infection. Rifamycin antibiotics like rifampin and rifapentine, have unique sterilizing activity against M tb. What are the advantages of each for LTBI or tuberculosis treatment?

Areas covered: We review studies assessing the pharmacokinetics (PK), pharmacodynamics (PD), drug interaction risk, safety and efficacy of rifampin and rifapentine and provide basis for comparing them.

Expert commentary: Rifampin has shorter half-life, higher MIC against M tb, lower protein binding and better distribution into cavitary contents than rifapentine. Drug interactions for the two drugs are maybe similar in magnitude. For LTBI, rifapentine is effective as convenient, once weekly, 12 –week course of treatment.

Rifampin is also effective for LTBI, but must be given daily for 4 months, therefore drug interactions are more problematic. For drug-sensitive tuberculosis disease, rifampin remains the standard of care. Safety profile is better described, adverse events differ somewhat for the two drugs. The registered once-weekly rifapentine regimen is inadequate, but higher doses of either drugs may shorten the treatment duration required for effective management of TB. Results of clinical trials evaluating high-dose rifamycin regimens are eagerly awaited.

Comment: This review is centered on the use of a rifamycin only regimen.

JT

Comparing efficacies of moxifloxacin, levofloxacin and gatifloxicin in tuberculosis granulomas using a multi-scale systems pharmacology approach.

Pienaar et al Ann Arbor, MI, Newark, NJ, USA

PLoS Comput Biol 2017; Aug 17

Abstract: Granulomas are complex lung lesions that are the hallmark of tuberculosis (TB). Understanding antibiotic dynamics within lung granulomas will be vital to improving and shortening the long course of TB treatment. Three fluoroquinolones (FQs) are commonly prescribed as part of multidrug-resistant TB therapy: moxifloxacin (MXF), levofloxacin (LVX) or gatofloxacin (GFX). To date insufficient data are available to support selection of of one FQ over another, or to show that these drugs are clinically equivalent. To predict the efficacy of MXF, LVX and GFX at a single granuloma level, we integrate computational modeling with experimental data sets into a single mechanistic framework, GranSim. GranSim is a hybrid agent based computational model that simulates granuloma formation and function, FQ plasma and tissue pharmacokinetics pharmacodynamics and is based of extensive in -vitro and in-vivo data. We treat in silico granulomas with recommended daily doses of each FQ and compare efficacy by multiple metrics, bacterial load, sterilization rates, early bactericidal activity and efficacy under noncompliance and treatment interruption. GranSim reproduced in vivo pharmacodynamics of these FQs. We predict that MXF kills intracellular bacteria more quickly than LVX and GFX due in part to a higher cellular accumulation ratio. We also show that three struggle to sterilize non-replicating bacteria residing in caseum. This is due to modest drug concentrations inside caseum and high inhibitory concentrations for this bacterial subpopulation. MXF and LVX have higher granuloma sterilizations rates compared to GFX, performs better in a simulated non-

compliance or treatment interruption scenario. We conclude that MXF has a small but potentially clinically advantage over LVX as well as LVX over GFX. We illustrate how a systems pharmacology approach combining experimental and computational methods can guide antibiotic selection for TB.

Comment: Yet another study to show the superiority of moxifloxacin over fluoroquinolones in the treatment of TB and also some nontuberculous mycobacterial lung diseases.

JT

Case Management

Decentralized care for multidrug-resistant tuberculosis: a systematic review and meta-analysis.

Ho et al Sydney, NSW, Australia; Geneva, Switzerland

Bull World Health Organ. 2017; 95, 584

Objective: To assess the effectiveness of decentralized treatment and care for patients with multidrug-resistant (MDR-TB) tuberculosis, in comparison with centralized approaches

Methods: We searched ClinicalTrials.gov, the Cochrane Library, Embase, Google scholar, LILACS, PubMed, Web of Science and the World Health Organisation portal of clinical trials for studies reporting treatment outcomes for decentralized and centralized care of MDR-TB. The primary outcome was treatment success. When possible, we also evaluated, death, loss to follow up, treatment adherence and health system costs. To obtain pooled relative risk (RR) estimates, we performed random – effects meta-analyses.

Findings: Eight studies met the eligibility criteria for review inclusion. Six cohort studies, with 4026 participants in total, reported on treatment outcomes. The pooled RR estimate for decentralized versus centralized care for treatment success was 1.13 (95% CI 1.01-1.27). The corresponding estimate for loss to follow up was RR: 0.66 (95%CI 0,38-1.13), for death RR: 1.01 (95% CI 0;67-1.52) and for treatment failure was RR 1.07 (95%CI 0;48-2.40). Two of three studies evaluating health-care costs reported lower costs for the decentralized models of care than for the centralized models.

Conclusion: Treatment success was more likely among patients with MDR tuberculosis treated using a decentralized approach. Further studies are required to explore the effectiveness of decentralized MDR tuberculosis care in a range of different settings

Comment: Unfortunately, decentralized care does not appear to be superior to in-patient care, but then decentralized care represents a very heterogeneous group. For a proper comparison, standardization of outpatient facilities would be needed.

JT

Zoonoses

Tuberculous joint infections in four domestic cats.

Lalor et al Solihull, Ledbury, Godalming, Roslyn, UK

JFMSOpen Rep. 2017; 25: 2055

Case Series summary: This paper describes the clinical presentation, diagnostic imaging findings and outcome in four cats with confirmed joint-associated tuberculosis. The cats were 2-6 years of age and immune competent. Three cases had tuberculosis affecting only one joint, whereas one case had at least three joints affected. Two cases were caused by Mycobacterium bovis and two were caused by Mycobacterium microti. Radiological findings included osteolysis, periosteal reaction and associated soft tissue swelling. Two cases were euthanized and two cases responded well to amputation and follow-on antibiotic therapy.

Relevance and novel information: To our knowledge, this the first publication of a series of cats with joint-associated tuberculosis. Although tuberculosis is not common, a high degree of suspicion is needed to avoid delayed diagnosis. This case series highlights the importance of considering mycobacterial disease as a differential for joint disease in cats.

Comment: It seems that cats with M microti disease have been infected by field rodents. We don't know the source of infection in the few human cases described.

JT

Risk Factors

Solid organ transplant-transmitted tuberculosis linked to a community outbreak.

Kay et al Sacramento, CA, USA

MMWR Morb Mort Wkly Rep 2017; 66: 801

Abstract: In the Spring of 2015, a local health department (LHD) in county A notified the California Department of Public Health (CDPH) about three adults with close ties to one another and a congregate community site who had received diagnoses of tuberculosis (TB) disease within a 3-month period. Subsequent review revealed matching TB genotypes indicating that the cases were likely part of a chain of TB transmission. Only three TB cases in California in the preceding 2 years shared this same genotype. One of these previous cases occurred in a lung –transplant recipient who had no identified epidemiologic links to the outbreak. CDPH, multiple LHDs and CDC conducted an investigation and determined that the lung-transplant donor (patient 1) was epidemiologically linked to the three outbreak cases and had a tuberculin test (TST) conversion detected in 2012 upon reentry at a local jail. Three other solid organ recipients from this donor were identified; none had developed TB disease. This investigation suggests that review of organ donors' medical records from high-risk environments, such as jails, might reveal additional information about TB risk. The evaluation of TB in organ recipients could include genotyping analysis and coordination among local, state and national partners to evaluate the potential for donor-derived TB.

The human microbiome in the fight against tuberculosis.

Wood et al Ithaca, NY, USA

Am J Trop Med Hyg 2017; 96: 1274

Abstract: The human microbiome is an intriguing potentially modifiable risk factor in our arsenal against Mycobacterium tuberculosis, the leading infectious killer globally. Previous studies have shown associations between the human microbiome and pulmonary disease states; however, aetiological links between the microbiome and tuberculosis (TB) infection or disease remain unclear. Immunomodulary roles of the microbiome may prove to be a critical asset in the host response against TB, including TB infection, reducing progression from latency, mitigating disease severity and lowering the incidence of drug resistance and coinfections. This review examined the associations between TB and the gut and lung microbiome. Eight studies were identified through a PubMed database search, including one animal study (N=1), case report (n=1), and case-control studies (n=6). TB infection and disease were associated with reduced gastrointestinal microbial diversity in a murine model and human case report. Sputum microbial diversity differed by TB status in case-control studies, although some reported heterogeneous findings. Current evidence suggests that the gut and lung microbiome are associated with TB infection and disease. However, as studies are limited, etiological and longitudinal research is needed to determine clinical relevance.

Comment: The immunological link between the GI and respiratory tracts has long been known, but what comes first; microbiome imbalance resulting in disease or the opposite?

JT

Tea drinking and its association among middle-aged and elderly adults: the Singapore Chinese health study.

Soh et al, Singapore; Wuhan, China; Pittsburgh, PA, USA

Nutrients 2017; May 25:9

Abstract: Experimental studies showed that tea polyphenols may inhibit growth of Mycobacterium tuberculosis. However, no prospective epidemiologic study has investigated tea drinking and the risk of active tuberculosis. We investigated this association in the Singapore Chinese Health study, a prospective population-based cohort of 63,257 Chinese aged 45 to 74 years recruited between 1993 and 1998 in Singapore. Information on habitual drinking of tea (including black

and green tea) and coffee was collected via structured questionnaires. Incident cases of active tuberculosis were identified via linkage with the nationwide tuberculosis registry up to 31 December 2014. Cox proportional hazard models were used to estimate the relation of tea and coffee consumption with tuberculosis risk. Over a mean 16.8 years of follow-up, we identified 1249 cases of active tuberculosis. Drinking either black or green tea was associated with with a dose dependent reduction in tuberculosis risk. Compared to non-drinkers, the hazard ratio (HR) (95% CI) was 1.01 (0.85-1.21) in monthly tea drinkers. 0.84 (0.73-0.98) in weekly drinkers and 0.82 (0.71-0.96) in daily drinkers (p for trend =0.003). Coffee or caffeine intake was not significantly associated with tuberculosis risk. In conclusion, regular tea drinking was associated with a reduced risk of active tuberculosis.

Comment: Yet another study to claim that tea drinking is healthy for you, but not by much.

JT

TB and HIV

Regional differences in the prevalence of major opportunistic infections among antiretroviral-naïve human immuno-deficiency virus patients in Japan, northern Thailand, northern Vietnam and the Philippines.

Gangcuango et al Bridgeport, CN, USA; Nagasaki, Miyagi, Nagoya, Japan; Hanoi, Vietnam; Nonthaburi, Lampang, Thailand;

Manilla, Philippines.

AM J Trop Med Hyg 2017; 97: 49

Abstract: To identify regional differences in the distribution of opportunistic infections (OIs) among human immunodeficiency virus (HIV)-infected patients in Asia, the medical records of antiretroviral-naïve patients who attended the following tertiary hospitals from 2003 to 2011 were reviewed. Nagoya Medical Center (NMC, Nagoya, Japan), Lampang Hospital (LPH, Lampang, northern Thailand), Bach Mai hospital (BMH, Hanoi, northern Vietnam), and Philippine General Hospital (PGH, Manilla, Philippines). Logistic regression analyses were performed to identify associations between country of origin and risk of OIs. In total, 1505 patients were included: NMC, n=365, LPH, n=442; BMH, n=384; and PGH, n=314. The median age was 32 years and 73.3% of patients were male. The median CD4 count was 200 cells /microL. Most patients at NMC and PMC were men who have sex with men. Injection drug users were most common at BMH (35.7%). Mycobacterium tuberculosis (TB) was most common at PGH (n=75) but was rare at NMC (n=4). Pneumocystis pneumonia (PCP) prevalence was highest at NMC (n=74) and lowest at BMH (n=13). Multivariable logistic regression showed increased odds of TB at PGH ([aOR]= 42.2, 95% CI 14.6-122.1), BMH (aOR=12.6 , CI=3.9-40.3. and LPH (aOR= 6.6, CI= 2.1-21.1. but decreased odds of PCP at BMH (aOR=0.1). CI =0.04 -0.2) and LPH (aOR=0.2,CI=0.1-0.4) compared to those at NMC. Cryptococcus risk was increased at LPH (aOR=6.2, CI=0.9-41.0) compared with that at NMC. Cytomegalovirus (CMV) retinitis prevalences were similar in all countries. OI prevalence remained high among ART-naïve patients in our cohort. The risks of TB, PCP and cryptococcosis, but not CMV retinitis, differed between countries. Improved early HIV detection is warranted.

Comment: This report may be useful for Australian and New Zealand colleagues who intend to work in east and Southeast Asia.

JT

Surgery

Smith-Petersen osteotomy combined with anterior debridement and allografting for active thoracic and lumbar spinal tuberculosis with kyphotic deformity in young children

Abulizi et al Urumqi, Shinziang, China

Medicine (Baltimore) 2017; 96: e 7614

Abstract: The purpose of this study is to determine the efficacy and safety of Smith-Petersen osteotomy combined with anterior debridement and allogenic strut bone grafting for the treatment of thoracic and lumbar spinal tuberculosis with kyphotic deformity in young children. Spinal tuberculosis is more destructive in young children and often causes severe kyphosis and paraplegia,

Despite much progress being made, surgical treatment is still controversial and technically challenging. From October 2010 to August 2014. 254 children (11 males, 14 females, aged under 6 years) with active thoracic and lumbar spinal tuberculosis treated by Smith-Petersen osteotomy combined with anterior debridement and allogenic strut bone grafting were enrolled in the study. The pre-and postoperative data, follow-up, medical records, imaging studies and laboratory data were collected prospectively. Clinical outcomes were evaluated on the basis of kyphotic angle and the Frankel motor score system. The changes in C-reactive protein protein (CRP) levels, erythrocyte sedimentation rate (ESR), clinical symptoms and complications were investigated. Graft fusion was evaluated using the Bridwell grading criteria. The mean age was 3.5 +/- 1.76 years ((range 1-6 years). All patients were followed up for 25 to 45 months (average 34.2 +/- 5.86). The average kyphotic angle was changed significantly from a preoperative value of 44.1 +/- 10.8 degrees to a postoperative value of 11.4 +/- 3.9 degrees with an average correction rate of 74% (P,0.05). According to the Frankel motor score system, neurological deficits were significantly improved by the time of the last follow-up, with an average improvement of 1.7 grades (P<0.05). There were two cases of rod breakage and 1 case of graft bone displacement. No patients experienced a recurrence of tuberculosis. According to the Bridwell criteria, the degree of fusion was grade 1 in 23 patients and grade 11 in 2 patients with a fusion rate of 92%. For young children with active thoracic and lumbar spinal tuberculosis Smith Petersen osteotomy combined with anterior debridement and allogenic strut bone grafting is a safe and simple procedure to achieve sufficient kyphosis correction, good neurological recovery and reliable anterior column reconstruction.

Comment: Such a surgical approach may be rarely if ever needed in Australia but in regions of the world where many young patients develop spinal TB and where diagnosis may be delayed and kyphosis becomes extreme or MDR-TB is present, it should be part of an orthopedic surgeon's repertoire

JT

Extrapulmonary Tuberculosis

Intestinal tuberculosis: a diagnostic challenge

Kentley et al London, UK

Trop Med Int Health 2017; 22: 994

Objective: To describe characteristics, presentation, time to diagnosis and diagnostic findings of patients with intestinal tuberculosis (ITB) in a low-burden country.

Method: Retrospective study of 61 consecutive ITB patients diagnosed between 2008 and 2014 at a large east London hospital.

Results: Forty of sixty-one patients were male. Mean age was 34.6 years. 93% of patients were born abroad, mostly from TB-endemic areas (Indian subcontinent: 88%, Africa, 9%). 25% had concomitant pulmonary TB. Median time from symptom onset to ITB diagnosis was 13 weeks (IQR 3-26 weeks)**.** Ten patients were initially treated for IBD, although patients had ITB. The main sites of ITB involvement were the ileocaecum (44%) or small bowel (34%). Five patients had isolated perianal disease. Colonoscopy confirmed a diagnosis of ITB in 77% of those performed. 42of 61 patients had a diagnosis of ITB confirmed on positive histology and/or microbiology.

Conclusion: Diagnosis of ITB is often delayed, which may result in significant morbidity. ITB should be included in patients with abdominal complaints who come from TB-endemic areas to establish prompt diagnosis and treatment. Diagnosis is challenging but aided by axial imaging, colonoscopy and tissue biopsy for TB culture and histology.

Comment: An article relevant to Australia and New Zealand.

The incidence of ocular tuberculosis in Australia over the past 10 years. (2006-2015

Darian-Smith et al Melbourne, Vic, Hobart, Tas, Sydney, NSW, Australia

Ophthalmic Epidemiol 2017; Sep13:1

Purpose: To determine the incidence and clinical phenotype of ocular tuberculosis in Australia based on the mandatory jurisdictional health notification records for TB.

Methods: A whole population retrospective case series (Australia). Patients diagnosed with ocular tuberculosis were identified over the past 10 years (1January 2006 to 31 December 2015) as recorded by individual Health Department jurisdictions per mandatory health notifications. The incidence rates were calculated based

on the available Australian census data. Incidence rates were age and sex standardized.

Results: A total of 162 cases of ocular tuberculosis were identified across Australia over a 10-year time period. Of these 156 participants were overseas born. The 10-year Australian incidence of ocular tuberculosis was 0.77 per 100,000 people. While there has been a downward trend in overall TB annual incidence rates from 2010 to 2015, over the same period the annual incidence of ocular tuberculosis has increased compared to the 4 previous years. Descriptive clinical data regarding the ocular manifestations was available in 73/157 patients. In these 73 patients the commonest manifestations of ocular TB were unspecified uveitis (50.1%), focal, multifocal or serpiginous choroiditis or chorioretinitis (12.3%) and retinal vasculitis (11%). Of patients with ocular TB, 4/162 (2.47%) had associated pulmonary TB and 8/162 (4.94%) had associated systemic (non-pulmonary) TB. Systemic anti-TB therapy was administered to 161 patients.

Conclusions: The annual Australian incidence of ocular tuberculosis was 0.077 per 100,000 people. Increasing notifications in the past 6 years may demonstrate increasing awareness and changing diagnostic criteria of the disease in the Australian population.

Comment: While it is important to describe the incidence of ocular TB in Australia, there are gaps in this study. Why do less than 50% of patients have insufficient clinical data? In those with adequate data the types of manifestation don't add up to 100%. Finally, how many cases were TB disease and how many tubercles?

JT

Infection

Optimization and interpretation of serial QuantiFERON testing to measure acquisition of Mycobacterium tuberculosis infection.

Nemes et al Cape Town, South Africa; Copenhagen, Denmark; Stanford, CA, Rockville, MD, USA.

AM J Respir Crit Care Med 2017; 196: 638

Rationale: Conversion from a negative to positive QuantiFERON –TB test is indicative of Mycobacterium tuberculosis (Mtb) infection, which predisposes individuals to tuberculosis disease. Interpretation of serial tests is confounded by immunological and technical variability.

Objectives: To improve the consistency of serial QuantiFERON testing algorithms **and** provide a data-driven definition of conversion.

Methods: Sources of QuantiFERON variability were assessed, and optimal procedures were identified. Distributions of IFN-gamma response levels were analyzed in healthy adolescents, Mtb unexposed control subjects and patients with pulmonary tuberculosis.

Measurements and main results: Individuals with no known MTB exposure had IFN-gamma values less 0.2 IU/ml. Among individuals with IFN-gamma values less than 0.2 IU.ml, 0.2-0.34 IU/ml,0.34-0.7 IU/ml and greater than 0.7 IU/ml, tuberculin skin test positivity results were 15%, 53%,.66% and 01% (P<0.005), respectively. Together, these findings suggest values less than 0.2 IU/ml were true negatives. In short term serial testing, "uncertain"

Conversions, with at least one value within the uncertainty zone (0.2-0.7 IU/ml), were partly explained by technical assay variability. Individuals who had a change in QuantiFERON –TB IFN-gamma values from less than 0.2 to greater than 0.7IU/ml had 10-fold higher tuberculosis incidence rates than those who maintained values of less than 0.2 IU/ml over 2 years (P=0.0003). By contrast "uncertain" converters were not at higher risk than nonconverters (P=0.229). Eight5y seven percent of patients with active tuberculosis had IFN-gamma values greater than 0.7 IU/ml, suggesting that these values are consistent with established Mtb infection.

Comment: This could be as important as the Prophit study of 70 years ago. By setting the bar too low to diagnose LTBI we may be causing more harm than good.

JT

Social and Political issues

Denholm et al Melbourne, Vic., Canberra, ACT, Australia; Paris, France; Honolulu, HW, USA; Lower Hutt, New Zealand; Noumea, New Caledonia; London, UK; Suva, Fiji.

Public Health Action 2017; 7:6

Abstract: There has been a range of developments in recent years to stimulate increasing public health research activity throughout the Pacific. Development of local

capacity for ethics committee review and oversight is, however frequently underdeveloped. This is reflected in the number of Pacific Island nations where ethics committees have not been established or where only informal processes exist for ethics review and oversight. This is problematic for the optimal development of relevant and culturally appropriate research, and building up local ethics committees should be part of continued research development in the Pacific. Three areas in which local ethics committees may add value are 1) offering better capacity to reflect local priorities 2) Providing broader benefits for research capacity building , and 3) assisting to strengthen systems beyond research ethics. This article considers benefits and challenges for ethics committees in the Pacific, and suggests directions for regional development to further strengthen public health research activity.

Comment: Yes, as long as we don't go down the dog's breakfast path in Australia where even in a single center trial, the approval of more than one ethics committee may be required, I believe the record for a multicenter study required the approval of 21 ethics committees**.** This led to a delay of over two years.

JT

Pharmacology

Assessment of the activity of anti-tuberculosis medicines in Almaty, Kazakhstan, 2014.

Nabirova et al Almaty,Dushambe,

Kazakhstan; Tampere, Finland; Darmstadt, Germany; Geneva, Switzerland

Int J Tuberc Lung Dis 2017; 1161

Setting: In 2009, the World Health Organization (WHO) conducted a survey of the quality of four anti-tuberculosis drugs in the former Soviet Union countries. Kazakhstan had the highest proportion of substandard drugs.

Objective: To assess the quality of anti-tuberculosis drugs used in Kazakhstan in 2014**.**

Design: Fourteen anti-tuberculosis drugs from the Almaty interdistrict TB Dispensary were randomly selected and screened for quality using Global Pharma Health Fund Minilab testing. First, the product and package were physically inspected to determine whether the tablets/capsules were intact and whether they contained the full amount of the drug, and whether the packaging was genuine. Second, the tablets/ capsules were dissolved in water to test whether they could be completely absorbed by the body. Finally, semi-quantitative analyses were undertaken using thin-layer chromatography to verify the presence and concentration of the active pharmaceutical ingredient and to detect impurities.

Results: We discovered no counterfeit medicines. However, 163 (19%) of the anti-tuberculosis drugs sampled failed at least one of the three tests. These samples were found among 24/50 batches of 14 anti-tuberculosis drugs.

Conclusion: Our study identified a high proportion of poor-quality first-and second-line anti-tuberculosis drugs. Use of these medicines may lead to treatment failure and the development of drug resistance. Confirmatory testing should be performed to determine if they should be removed from the marked.

Comment: A potential problem for Australasia where migrants have received substandard drugs, are in remission, and screening shows them suitable for admission.

Microbiology

Opening Pandora's box: mechanisms of Mycobacterium tuberculosis resuscitation.

Veatch et al New Orleans, LA, USA

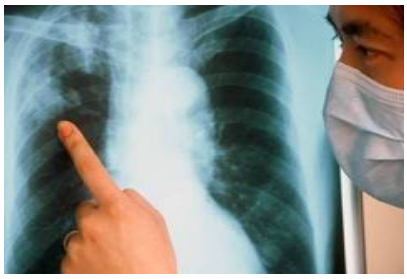
Trends Microbiol 2017; Sept 11; epub

Abstract: Mycobacterium tuberculosis (Mtb) characteristically causes an asymptomatic infection. While this latent tuberculosis infection (LTBI) is not contagious, reactivation to active tuberculosis disease (TB) causes the patient to become infectious. A vaccine has existed for TB for a century, while drug treatment have been available for over 70 years; despite this, TB remains a major global health crisis. Understanding the factors which allow the bacillus to control responses to host stress and mechanisms leading to latency are critical for persistence. Similarly, molecular switches which respond to

reactivation are important. Recently, research in the field has sought to focus on reactivation, employing system-wide approaches and animal models. Here, we describe the current work that has been done to elucidate the mechanisms of reactivation and stop reactivation in its tracks.

Comment: It is many years since the chances of infection turning into disease have been estimated by Hsu and other researchers. Given the better health of those not only in wealthy societies but also middle income counties, we need to repeat these studies to see if the likelihood of reactivation has decreased. Mind you we still don't have a gold standard to diagnose infection.

JT



Cavitating PTB (courtesy IUAT&LD