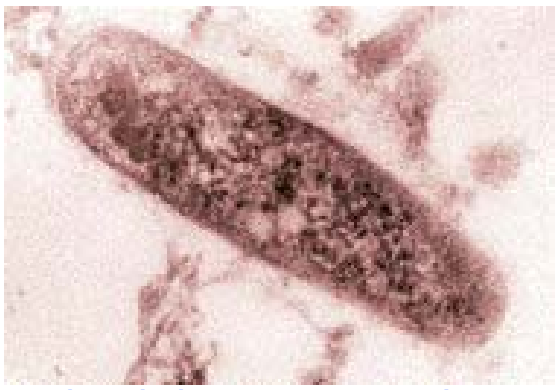
The Australian Tuberculosis Review

February 2013



M. tuberculosis EM Photo

Forthcoming Meetings

44 Union World Conference on Lung Health 30 October-3 November 2013 Paris, France

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Editorial

This edition contains several studies by Australasian researchers on human tuberculosis; in fact more than any other edition. It has long been the policy of the Australian Tuberculosis Review and its predecessor the Australian Tuberculosis Newsletter to give preference to publications emanating from Australian and New Zealand researchers working from their home countries. Thirty years ago , the then editor, Tony Proust found it difficult to find material in the scientific literature from researchers outside Australasia. Published studies from Australasia were virtually absent. We believed that tuberculosis was conquered so there was little incentive for researchers to enter the field. How wrong we were! The New York and north east coast USA epidemic, HIV and MDR-TB changed all this, culminating in WHO declaring TB a "global emergency". Centers across the world obtained funding for TB research and by 1996, the editors were faced with an embarrassment of riches. Which papers to select? But in Australasia the gold emerged more slowly. After all we in Australia had the lowest incidence of TB in the world and what happened overseas was none of our business. Two factors have changed this outlook: the large immigrant and refugee intake from countries with a high TB prevalence and a more global outlook whereby Australia and New Zealanders are working outside their countries on projects involving tuberculosis or tuberculosis and HIV. Such countries are China, Indonesia, South Africa and the Pacific. It would be invidious to name the centers in Australia that are prominent in this work, although Melbourne has contributed a considerable share. A study from Melbourne in this edition revisits the issue of migrants from high TB prevalence countries and their likelihood of developing tuberculosis disease after arrival. This revisit suggests that rather than 5 years being the cut point beyond which such migrants developed TB after arrival in Australia, only 50 % did so by seven years. This is a considerable change from half a century ago when studies, mostly unpublished, showed that of those migrants to Australia who developed TB after arrival, two thirds did so within 5 years. The reason for this change may involve factors such as a variation in the mix of populations from different countries as well as the emergence of those infected with the HIV virus. Whatever the causes it does look as if longer surveillance is required, particularly in those tested as genuinely positive for LTBI.

Prevention

A human challenge model for Mycobacterium tuberculosis using Mycobacterium bovis bacille Calmette-Guerin.

Minassian et al Oxford UK

J Infect Dis 2012; 205: 1035

Background: There is currently no safe human challenge model of Mycobacterium tuberculosis infection to enable efficacy evaluation of candidate vaccines against tuberculosis. In vivo

antimycobacterial activity immunity could be assessed using intradermal Mycobacterial bovis bacille as a surrogate for M tuberculosis infection.
Methods: Healthy BCG-naïve and BCG vaccinated volunteers were challenged with intradermal BCG. BCG load was quantified from skin biopsy specimens by polymerase chain reaction (PCR) and culture colony forming units. Cellular infiltrate was isolated by suction blister and examined by flow cytometry. Prechallenge immune readouts were correlated with BCG after challenge.
Results: In BCG-naïve volunteers, live BCG was detected at the challenge site for up to 4 weeks and peaked at 2 weeks. Infiltration of mainly CD15(+) neutrophils was observed in blister fluid. In previously BCG-vaccinated individuals, PCR analysis of skin biopsy specimens reflected a degree of mycobacterial immunity. There was no significant correlation between BCG load after challenge and mycobacterial-specific specific memory T cells measured before challenge by cultured enzyme-linked immunospot assay.
Conclusions: This novel experimental human challenge model provides a platform for the identification of correlates of antimycobacterial immunity and will greatly facilitate the rational down-selection of candidate tuberculosis vaccines. Further evaluation of this model with BCG and new vaccine candidates is warranted.
Comment: We also need to know how long these effects last.

JT

Control

Financial reinforcers for improving medication adherence: findings from a meta-analysis.

Petry et al Farmington Conn USA

Am J Med 2012; 125: 888

Background: Increasingly, financial reinforcement interventions based on behavioral economic principles are being applied in health care settings, and this study examined the use of financial reinforcers for enhancing adherence to medications.
Methods: Electronic databases and bibliographies of relevant references were searched, and a meta-analysis of identified trials was conducted. The variability in effect size and the impact of potential moderators (study design, duration of intervention, magnitude of reinforcement and frequency of reinforcement) on effect size were examined.
Results: Fifteen randomized studies and 6 nonrandomized studies examined the efficacy of financial reinforcement interventions for medication adherence. Financial reinforcers were applied for adherence to medications for **tuberculosis,** substance abuse, HIV, hepatitis, schizophrenia and stroke prevention. Reinforcement interventions significantly improved adherence relative to control conditions with an overall effect size of 0.77 (95% CI, 0.70-0.84; P<0.001). Nonrandomized studies had a larger average effect size than randomized studies, but the effect study of randomized studies remained significant at 0.44 (95%CI, 0.35-0.53; P<0.001).
Conclusion: These results demonstrate the efficacy of medication adherence interventions and underscore principles that should be considered in designing future adherence interventions. Financial reinforcement interventions hold potential for improving medication adherence and may lead to benefits for both patients and society.
Comment: The Tuberculosis Allowance certainly played a role as an incentive in the early years of the National TB eradication program in Australia. It was more generous than any other social security payment of the time.

JT

Computerized surveillance system of tuberculosis in Japan: its evolution, achievement and challenges.
Ohmori et al Tokyo Japan

Kekkaku 2012; 87: 15

Abstract: The nationwide computerized tuberculosis (TB) surveillance system was revised in 2007. It was developed to be user-friendly and to allow the evaluation of current TB problems and control issues in Japan. All public health centers in Japan (518 as of April 2007) have system terminals connected to a central computer, and the data entered at these terminals are sent to the online central computer excluding personal identification data. All the figures and tables in this paper were created using the annual report database which are compiled from the system. The revision in 2007 added many new functions, such as a function for automatically sending data upon transfer. The monitoring information for assisting case management of TB patients by the DOTS was also enhanced. The algorithm for classifying treatment outcomes automatically based on data entered regarding cancellations from cancellations from registration, bacteriological results and drug usage each month was revised. The proportion of “Failed” and “Defaulted” combined was 4.6% among new sputum smear positive pulmonary TB patients newly registered in 2009, while “Died” accounted for as high as 19.3%, due largely to a high percentage of the elderly. A new system for contact examination management is provided as a subsystem. Feedback

of data analysis has been strengthened by various methods. This TB surveillance system is indispensable for implementing the evidence-based TB control program in Japan. An important role of the Research Institute of Tuberculosis is to support the planning and execution of TB control with provision of useful epidemiological information from the system.
Comment: Let us hope this system provides a more up to date profile of tuberculosis than we have in Australia.

JT

Screening

QuantiFERON-TB Gold In-Tube assay vs. tuberculin skin test in Indonesian children living with a tuberculosis case.

Rutherford et al Dunedin New Zealand

Int J Tuberc Lung Dis 2012; 16: 496

Setting and Objectives: The tuberculin skin test (TST) has limitations in diagnosing latent tuberculosis (TB) infection (LTBI). Interferon-gamma release assays may improve diagnostic accuracy. We compared QuantiFERON-TB Gold In-Tube (QFT-GIT) and TST in Indonesian children.
Design: Children aged from 6 months to 9 years exposed to a TB case at household and neighborhood levels were recruited. The children underwent QFT-GIT and TST. Test responsiveness was expressed according to an exposure gradient.
Results : A total of 299 household-exposed and 72 neighborhood-exposed children were analysed. Overall, respectively 46% and 41 % were positive using QFT-GIT and the TST. Test positivity increased with exposure (QFT-GIT P value for trend <0.001, and TST P<0.001); however, only QFT-GIT responded significantly to a 'within household' gradient. The TST was less likely to be positive than the QFT-GIT on neighborhood-exposed children (P=0.05). BCG –vaccinated children were less likely to be QFT-GIT positive , while the older children were more likely to be QFT-GIT positive. Both tests had increasing positivity with increasing smear grade.
Conclusion: QFT-GIT performed similarly to the TST in Indonesian children living with an infectious TB case. Test accuracy was not compromised by young age or BCG vaccination. Our findings suggest that QFT-GIT offers little advantage over the TST in this population. High rates of LTBI diagnosed in household-exposed children by both tests support preventive therapy.
Comment: Note that 2 units of human PPD was used so that an induration of 10mm might well be translated to 15mm if 10 units of Australian PPD was used.

JT

Challenges of interferon-gamma release assay conversions in serial testing of health care workers in a TB control program.

Fong et al Cleveland OH USA

Chest 2012; 142: 55

Background: Clinical data with use of serial interferon-gamma release assay (IGRA) testing in US health-care workers (HCWs) are limited.
Methods: A single-center, retrospective chart review was done from 2007 to 2010 of HCWs who underwent pre-employment QuantiFERON TB Gold-In-Tube TESTING. Demographic data, bacille Calmette-Guerin history, prior tuberculin skin test result if done, and baseline and serial IGRA values were obtained. The number of IGRA converters and reverters and their subsequent management by infectious disease physicians were reviewed. Quantitative IGRA-negative values were not available.
Results: A total of 7374 IGRAs were performed on newly hired HCWs. Of these tests, 486 (6.6%) were positive at baseline, 305 (4.1%) were indeterminate, and 6583 were negative. From 2007 to 2010, 52 of 1857 HCWs (2.8%) were identified as converters, with a serial IGRA median value of 0.63 IU/ml. Seventy one percent of HCWs with IGRA conversion had values of </= 1 IU/ml. None of the converters had active TB or were part of an outbreak investigation.
Conclusions: Clinical significance of most QuantiFERON-TB-Gold In-Tube conversions in serial testing remains a challenging task for clinicians. The use of a single cutoff point criterion for IGRA may lead to over diagnosis of new TB infections. Clinical assessment and evaluation may help to prevent unnecessary therapy in these cases. The criteria for defining conversions and reversions by establishing new cutoffs needs to be evaluated further, especially in HCWs.
Comment: Another reason to combine the TST and IGRA in such screening.

JT

Evidence for airborne infectious disease transmission in public ground transport—a literature review.

Mohr et al Berlin Germany

Euro Surveill 2012; 17: 20255

Abstract: While guidelines on contact tracing (CT) after exposure to certain infectious pathogens during air travel exist, no guidance documents are available on CT in response to potential exposure on public ground transport. We reviewed scientific and non-scientific literature on transmission of airborne pathogens in public ground transport and on factors potentially affecting transmission. We identified 32 relevant publications (15 scientific and 17 nonscientific). Most of the selected studies dealt with transmission of tuberculosis. However, the relation between travel duration, proximity to the index case and environmental factors, such as ventilation, on disease transmission in public ground transport is poorly understood. Considering the difficulty and probably limited effectiveness of CT in ground transport, our results suggest that only exceptional circumstances would justify CT. This contrasts with the high level of attention CT in air travel seems to receive in international regulations and recommendations. We question whether the indication for CT should be revisited after a risk-benefit assessment that takes into account exposure in both ground and air transport.
Comment: Certainly air travel risk is much less than we had feared.

JT

Interferon-gamma release assays for tuberculosis screening of healthcare workers: a systematic review.

Zwerling et al Montreal Canada

Thorax 2012; 67: 62

Abstract: Healthcare workers (HCWs) are at increasing risk of exposure to tuberculosis (TB). Traditionally, screening for latent TB infection (LTBI) is done using the tuberculin skin test (TST). Interferon gamma release assays (IGRAs) are now increasingly being used. For diagnosis of LTBI, but their role in HCW screening is unclear. A systematic review was conducted of all IGRA studies in HCWs to summarize their performance in cross sectional and serial testing settings. By searching four electronic data bases and other sources, all available studies using any one of the commercial IGRA assays in HCWs were retrieved and screened. 50 unique studies were identified which met the inclusion criteria including five from high TB incidence settings. Among 24 cross-sectional studies in low TB incidence settings, the pooled prevalence of positive IGRA using either test was significantly lower than for a positive TST. However, in high incidence settings (n=2) there were no consistent differences in the prevalence of positive tests. IGRAs showed good correlation with occupational risk factors for TB exposure in low-incidence settings. Only 10 studies assessed use of IGRA for serial testing and all showed large variation in the rates of conversions and reversions, with no data suggesting that IGRAs are better at identifying the incidence of new TB infection than the TST. The use of IGRAs instead of TST for one-time screening may result in a lower prevalence of positive tests and fewer HCWs who require LTBI treatment, particularly in low TB incidence settings. However, the use of IGRAs for serial testing is complicated by lack of data on optimal cut-offs for serial testing and unclear interpretation and prognosis of conversions and reversions. Further longitudinal research will be required to inform guidelines on serial testing using IGRAs.
Comment : Another study to support the use of both tests in low incidence countries.

JT

Drug Resistance

Prevalence of and risk factors for resistance to second-line drugs in people with multidrug-resistant tuberculosis in eight countries: a prospective cohort study.

Dalton et al Atlanta GA USA

Lancet 2012; 380: 1406

Background: The prevalence of extensively drug-resistant (XDR) tuberculosis is increasing due to the expanded use of second-line drugs in people with multi-resistant (MDR) disease. We prospectively assessed resistance to second-line antituberculosis drugs in eight countries.
Methods: From Jan.1 2005, to Dec. 31,2008, we enrolled consecutive adults with locally confirmed MDR tuberculosis at the start of second-line treatment in Estonia, Latvia, Peru, Philippines, Russia, South Africa, South Korea and Thailand. Drug susceptibility testing for study purposes was done centrally at the Centers for Disease Control and Prevention for 11 first-line and second-line drugs. We compared the results with clinical and epidemiological data to identify risk factors for resistance to second-line drugs and XDR tuberculosis.
Findings: Among 1278 patients, 43.7% showed resistance to at least one second-line drug, 20.0% to at least one second line injectable drug and 12.9% to at least one fluoroquinolone. 6.7% of patients had XDR tuberculosis (range across study sites 0.8 –

15.2%). Previous treatment with second line drugs was consistently the strongest risk factor for resistance to these drugs, which increased the risk of XDR tuberculosis by more than four times. Fluoroquinolone resistance and XDR tuberculosis were more frequent in women than in men. Unemployment, alcohol abuse and smoking were associated with resistance to second-line injectable drugs across countries.

Interpretation: Previous treatment with second line drugs is a strong, consistent risk factor for resistance to these drugs, including XDR tuberculosis. Representative drug-susceptibility results could guide in-country policies for laboratory capacity and diagnostic strategies.

Comment: It would be interesting to learn how the dosages of second-line drugs vary and what relationship this variation has to development of further resistance**.**

JT

Treatment outcomes for children with multidrug-resistant tuberculosis: a systematic review and meta-analysis.

Ettehad et al South Africa, UK, Switzerland

Lancet Infect Dis 2012; 12: 449

Background: Paediatric multidrug-resistant (MDR) tuberculosis is a public health challenge of growing concern, accounting for an estimated 15% of all global cases of MDR tuberculosis. Clinical management is especially challenging, and recommendations are based on restricted evidence. We aimed to assess existing evidence for the treatment of MDR tuberculosis in children.

Methods: We did a systematic review and meta-analysis of published and unpublished studies reporting treatment outcomes for children with MDR tuberculosis. We searched PubMed, Ovid, Embase, Cochrane Library, PsychINFO and BioMedCentral databases up to Oct 31, 2011. Eligible studies included five or more children (aged </=16 years) with MDR tuberculosis within a defined treatment cohort. The primary outcome was treatment success. Defined as a composite of cure and treatment completion.

Results: We identified eight studies, which reported treatment outcomes for a total of 315 patients. We recorded much variation in the characteristics of patients and programmes. Time to appropriate treatment varied from 2 days to 46 months. Average duration of treatment ranged from 6 months to 34 months and duration of follow-up ranged from 12 months to 37 months. The pooled estimate for treatment success was 81.67% (95% CI 72.54-90.80). Across all studies, 5-9% (95% CI, 1.3-10.5) died, 6.2% (2.3-10.2) defaulted and 39.1% (28.7-49,4) had an adverse event. The most common adverse events were nausea and vomiting. Other serious adverse events were hearing loss, psychiatric effects and hypothyroidism.

Interpretation: The treatment of paediatric MDR tuberculosis has been neglected, but when children are treated outcomes can be achieved that are at least as good as those reported for adults.

Comment: Almost as good as the WHO goal for drug sensitive disease, but we still have to do better.

JT

Children

Pyrazinamide pharmacokinetics and efficacy in adults and children.

Donald et al Tygerberg South Africa

Tuberculosis (Edinb) 2012; 92: 1

Abstract: Pyrazinamide (PZA) is an essential sterilizing drug and with rifampicin enables six-month short-course antituberculosis chemotherapy. Despite routine use for nearly forty years uncertainty remains regarding the most appropriate PZA dosage for children. In view of this uncertainty, literature relating to the efficacy and pharmacokinetics of PZA in children treated for tuberculosis and in adult volunteers and patients was reviewed. Making use of the PZA maximum concentration (C (max)) fin different groups straight line regression of concentration on dosage was fitted through the origin by least squares and weighted for the numbers of subjects. The fitted line offers an approximation of the likely PZA C (max) that would result from a particular dosage. The slopes of C(max) dosage of the fitted lines are 1.32 (SE 0.099) for paediatric patients; 1.36 (SE 0.051) for adult volunteers and 1.35 (SE 0.037) for adult patients; there is little difference between the C (max) concentrations achieved in children and adults. Whether patients or healthy volunteers, following various mg/Kg body weight dosages, suggesting that children and adults receiving the same mg/kg body weight PZA dosage will reach a similar C (max). Children can receive the same mg/kg body weight PZA dosage as adults.

Comment: Now that's settled for a 15mg/kg dose we still have to decide on the relative toxicities of higher doses in children.

JT

Evaluation of an interferon gamma release assay in children with suspected tuberculosis in Papua New Guinea.

Uluk et al Port Moresby PNG, Sydney NSW Australia, Melbourne Vic Australia

Pediatr Infect Dis J 2012; Sept 24

Abstract: There are few data from TB endemic settings of the performance and outcome predictors of the QuantiFERON-TB Gold-in Tube assay (QFT-GIT) in children with suspected TB. A prospective cross-sectional study was conducted in Papua New Guinea children with suspected TB evaluated at Port Moresby General Hospital. 216 children were enrolled including 106 probable TB, 87 possible TB and 23 without TB. Concordance between QFT and TST results was 86% (P value <0.001, K=0.70). QFT was significantly more likely to be positive than TST, overall and within the probable or possible TB categories, with no difference in pr4evalence of positivity between these two categories. The role of QFT in supporting the clinical diagnosis of TB in endemic settings, where resources are limited, remains unclear especially as cost and technical requirements remain considerable.
Comment: The diagnosis of extrapulmonary TB in children in poor countries remains difficult.

JT

Treatment

A novel dry powder inhalable formulation incorporating three first-line anti-tubercular antibiotics.

Chan et al Sydney NSW Australia

Eur J Pharm Biopharm 2012; Sept 13, Epub

Abstract: Treatment for tuberculosis (TB) using the standard oral antibiotic regimen is effective but inefficient, requiring high drug dosing and lengthy treatment times. Three concurrent first –line antibiotics recommended by the World Health Organisation (WHO) guidelines are pyrazinamide, rifampicin and isoniazid. Combining these antibiotics in a novel formulation for dry powder inhalation (DPI) may facilitate rapid and efficient resolution of local and systemic infection. However, spraaed individually, these antibiotics were found to be physically unstable. A solution of the three antibiotics , at the WHO –recommended ratio, was spray dried. The collected powder was assessed by a series of in-vitro methods to investigate aerosol performance, particle physico-chemical characteristics and dissolution profile. Particle obtained were spherical with a surface composed primarily of rifampicin, as identified by TOF-SIMS. A mass median aerodynamic diameter of 3.5 +/- 0.1 microm. and fine particle fraction (< 5microm) of 45+/- % indicated excellent aerosol performance. The combination powder was differentiated by the presence of rifampicin dihydrate and the delta polymorph of pyrazinamide. Quantitative analysis indicated individual particles contained the three antibiotics at the expected proportions (400: 150: 75 w/w). This excipient-free triple antibiotic DPI formulation could be used as a significant enhanced treatment for TB.
Comment: Particularly in those whose absorption of oral medication is compromised; e.g. diabetics, advanced HIV, and a full stomach: and now for the blood levels!

JT

Extrapulmonary Tuberculosis

Diagnosis of tuberculous lymph-adenitis using fine needle aspiration biopsy.

Knox et al Melbourne Vic Australia

Int Med J 2012; 42: 1029

Background: Tuberculous lymphadenitis is the commonest form of extrapulmonary tuberculosis. However, the optimal approach to diagnosis, employing biopsy by either fine needle aspiration (FNA) or surgical excision, remains uncertain.
Aims: To evaluate the diagnostic value of biopsy using each of the diagnostic modalities of FNA (microscopy, cytology and culture), and compare these with excision biopsy in the diagnosis of tuberculous lymphadenitis in a predominantly migrant population in Melbourne
Methods: A retrospective examination of tuberculous lymphadenitis cases presenting to Western Health over 12 years was conducted. Using a reference method of positive culture of Mycobacterium tuberculosis, the diagnostic sensitivities of each modality employed in FNA were determined.
Results: Forty-two subjects having FNA and 30 having excision biopsy as the initial investigation were compared. Among specimens obtained by FNA, sensitivity of microscopy was 18% (95% CI : 5-40%) and sensitivity of cytology 38% (CI: 20-59%). For specimens obtained by excision biopsies, sensitivities for microscopy and histology were 17% (95% CI: 2-32%) and 96% (95%CI: 88-100),

respectively. Sensitivity of culture performed on FNA specimens was 86% (95% CI: 65-97%).
Conclusions: Given the relatively high sensitivity of mycobacterial culture from FNA, this study supports its routine use as the initial investigation in most patients with suspected tuberculous lymphadenitis. Microscopy and cytology add relatively little to the clinical utility of FNA.
Comment: It is surprising that the FNA samples were not subjected to DNA amplification. The authors' conclusions are valid for migrants from high prevalence tuberculosis countries, but not necessarily for Australian born children where nontuberculous mycobacterial lymphadenitis predominates and requires surgical excision as treatment of choice.

JT

Population Studies

Risk of active tuberculosis in immigrants: effects of age, region of origin and time since arrival in a low-exposure setting.

McBryde et al Melbourne Vic Australia

Med J Aust 2012; 197: 458

Objective: To estimate the risk of active tuberculosis (TB) in immigrants to Victoria, Australia, as a function of time since arrival and stratified by age group and region of origin.
Design, Setting and Subject: Longitudinal study of the incidence of active TB in Victorian immigrants, excluding New Zealanders, who arrived in Australia between 1975 and 2007. Victorian immigration data were used to describe annual arrival cohorts by age and region of origin, and TB case notification data for 1995 to 2010 were matched to the cohorts. Survival analysis was performed to determined incidence rates of active TB.
Main Outcome Measures: Incidence of active TB, stratified by age, region of origin and time since arrival in Australia.
Results: Incidence of active TB following immigration to Australia was highly dependent on region of origin, with the highest risks being in immigrants from South Asia and sub-Saharan Africa. For immigrants from high-risk regions (Asia, Africa and the Pacific) the incidence of active TB infection was 100-150 per 100,000 person years in the first 6 years following immigration. Overall, we estimate that 50 % of TB occurred within 7 years of arrival. A bimodal age distribution was evident, with peaks of incidence in 20-24-year- olds and 70-74-year-olds.
Conclusions: Our data show that substantial risk of TB in Victorian migrants persists well beyond the first2-3 years following arrival, and that risk is highly dependent on region of origin. The regional dependence suggests that public health strategies would benefit from more refined regional stratification of risk , which could be used to determine risk thresholds for the use of TB prevention strategies and predict rates of TB in Australia following particular patterns of immigration.
Comment: TB prevention strategies won't work until all workers in the field are clear on the distinction between TB infection and disease.

JT

The health of newly arrived refugees to the Top End of Australia: results of a clinical audit at the Darwin Refugee Health Service.

Johnston et al Darwin NT, Melbourne Vic, Australia

Aust J Prim Hlth 2012; 18: 242

Abstract: Accurate data on the health of refugees is vital to inform clinical practice, monitor disease prevalence and promote coordination. We undertook a retrospective clinical audit of newly arrived refugees attending the Darwin primary health service in its first 12 months of operation. Data were collected from the clinic files of refugee patients who attended for their initial health assessment from 1` July 2009 to 30 June 2010 and were analysed descriptively. Among 187 refugees who attended in 2009-2010, ~60% were from Asia and 42% were female. The most common diagnoses confirmed by testing were vitamin D deficiency (23%), hepatitis B carrier status (22%), tuberculosis infection (18%), schistosomiasis (17%) and anaemia (17%). The most common documented health conditions recorded the GPs were vitamin D deficiency or insufficiency (66%), followed by schistosomiasis (24%) and dental disease (24%).This clinical audit adds to a limited evidence base suggesting a high prevalence of infectious disease, nutrient deficiency and dental disease among refugees arriving in Australia. GPs involved in the care of refugees must be aware of the epidemiology of disease in this group, as some diseases are rare among the general Australian population. Our results also highlight the ongoing need for advocacy to address service constraints such as limited public dental access for this population.
Comment: Unfortunately the definition of tuberculosis infection based on a tuberculin skin test was set at 10mm for adults and 5-9 mm for children and did not seem to allow for those who had received BCG vaccination. Even for non-vaccinated children, the ' cut point' is far too low. One has to

conclude that the prevalence of true LTBI is surprisingly low in this group.

JT

Groups at risk

Tests for latent tuberculosis in people with ESRD: a systematic review.

Rogerson et al Sydney NSW Australia

Am J Kidney Dis 2012; Oct 13. Pii: S0272

Background: The relative diagnostic accuracy of interferon gamma release assays (IGRAs), based on ELISA [enzyme-linked immunosorbent spot], i.e., the QuantiFERON and T-SPOT-TB tests, respectively and the tuberculin skin test (TST) for latent tuberculosis (TB) infection in people with end stage kidney disease is uncertain and national guidelines for their use are inconsistent.
Study Design: Systematic review.
Selection Criteria for Studies: Evaluated performance of tests for latent TB with clinical risk-factor assessment.
Setting and Population: People with end-stage kidney disease (chronic kidney disease stage 5 [eGFR <15] or kidney transplant recipients). No limits on setting.
Index Tests: ELISA- or ELISPOT- based IGRAs, TST, assays to detect antimycobacterial antibodies, and flow cytometry-based tests.
Outcomes: Odds of test positivity with clinical risk factor for latent TB, expressed as ORs and relative ORS (RORs)
Results: 47 studies (6,828 participants) were included, but only 30 studies (4,546 participant) contained sufficient data to contribute to meta-analysis. Studies were predominantly in the dialysis population (23/30; 3,700 participants) in countries with low to moderate TB prevalence (0.0-50.0 cases/10(5) persons). BCG vaccination rate was variable (2.7% -100%). 9 studies compared IGRAs with the TST directly, 17 studies evaluated the TST only and the other four studies evaluated other tests. Compared to a positive TST result, a positive ELISA-based IGRA result was associated more strongly with radiological evidence of past TB (ROR, 4.29; 95% CI, 1.83-10.3; P= 0.001) and contact with active TB (ROR, 3.36; 95%CI, 1/61-7.01; P=0.001). Compared to a negative TST result, a negative ELISA-based IGRA result was associated more strongly with BCG vaccination (ROR, 0.30; 95% CI, 0.14-0.63; P=0.002). There were insufficient data to compare performance of the ELISPOT-based IGRA with the TST or ELISA-based IGRA.
Limitations: 17 of 47 included studies (36.2%) did not contain sufficient data to contribute to meta-analysis.
Conclusions: Compared to the TST, the ELISA-based IGRA was associated more strongly with risk factors for latent TB in end-stage kidney disease.
Comment: Once again**,** it seems that to obtain maximum sensitivity and specificity in diagnosing LTBI we should use both an ELISA-based IGRA (QuantFERON-GIT) with 10 units of PPD(h),except where the person has received BCG vaccination.

JT

Previous lung diseases and lung cancer risk: a pooled analysis from the International Lung Cancer Consortium.

Brenner at al Toronto, Ontario Canada

Am J Epidemiol 2012; 176: 573

Abstract: To clarify the role of previous lung diseases (chronic bronchitis, emphysema, pneumonia and **tuberculosis**) in the development of lung cancer, the authors conducted a pooled analysis of studies in the International Lung Cancer Consortium. Seventeen studies including 24,607 cases and 81,829 controls (noncases), mainly conducted in Europe and North America, were included (1984-2011). Using self-reported data on previous diagnoses of lung diseases, the authors derived study-specific effect estimates by means of logistic regression models or Cox proportional hazards models adjusted for age, sex and cumulative tobacco smoking. Estimates were pooled using random- effects models. Analyses stratified by smoking status and histology were also conducted. A history of emphysema conferred a 2.44-fold increased risk of lung cancer (95% CI: 1.64-3.62 [16 studies]). A history of chronic bronchitis conferred a relative risk of 1.47 (95% CI: 1.29-1.68 [13 studies]).
Tuberculosis (RR=1.48, 95% CI: 1.17-1.87 [16 studies]) and pneumonia (RR =1.57: 95% CI1.57: 95% CI: 1.22-2.01 [12 studies]) were also associated with lung cancer risk. Among never smokers, elevated risks were observed for emphysema, pneumonia and **tuberculosis.** These results suggest that previous lung diseases influence lung cancer risk independently of tobacco use and that these diseases are important for assessing individual risk.
Comment: It is a pity that data on occupation and social class were not gathered on these subjects.

JT

Innate immune gene polymorpisms in tuberculosis.

Azad et al Columbus OH USA

Infect Immun 2012; 80: 3343

Abstract: Tuberculosis (TB) is a leading cause worldwide of human mortality attributable to a single infectious agent. Recent studies targeting candidate genes and "case control" association have revealed numerous polymorphisms implicated in host susceptibility to TB. Here we review current progress in the understanding of causative polymorphisms in host innate immune genes associated with TB pathogenesis. We discuss genes encoding several types of proteins: macrophage receptors, such as the mannose receptor (MR, CD206), dendritic cell-specific ICAM-3-grabbing nonintegrin (DC-SIGN,CD209), Dectin-1, Toll-like receptors (TLRs), complement receptor 3 (CR3, CD11b/CD18, nucleotide oligomerization domain 1 (NOD1) and NOD2, CD14, P2X7, and the vitamin D nuclear receptor (VDR); soluble C-type lectins, such as surfactant protein A (SP-A), SP-D and mannose – binding lectin (MBL); phagocyte cytokines, such as tumor necrosis factor (TNF), interleukin-1beta (IL-1beta), IL-6, IL-10, IL-12, and IL-18; chemokines, such as IL-8, monocytes chemoattractant protein 1 (MCP-1), RANTES, and CXCL10; and other important innate immune molecules, such as inducible nitric oxide synthase (iNOS) and solute carrier protein 11A1 (SLC11A1). Polymorphisms in these genes have been variably associated with susceptibility to TB among different populations. This apparent variability is probably accounted for by evolutionary selection pressure as a result of long-term host-pathogen interactions in certain regions or populations and, in part, by lack of proper study design and limited knowledge of molecular and functional effects of the implicated genetic variants. Finally, we discuss genomic technologies that hold promise for resolving questions regarding the evolutionary paths of the human genome, functional effects polymorphisms, and corollary impacts of adaptation on human health, ultimately leading to novel approaches to controlling TB.

Comment: Even if an individual has all 25 of these polymorphisms, we don't what their risk of developing TB may represent.

JT

Drug Reactions

Physicians' practices regarding management of antituberculosis drug-induced hepatotoxicity.

Thongraung et al Songkhla Thailand

Southeast Asian J Trop Med Public Health 2012; 43: 724

Abstract: To investigate the practices of physicians regarding the diagnosis and management of antituberculosis drug-induced hepatotoxicity (ATH). A cross sectional descriptive survey using a self-administered questionnaire with multiple choice questions was conducted among physicians who treated adult tuberculosis (TB) patients at 74 public Hospitals in southern Thailand. Of the 272 questionnaires mailed, 204 (75%) were returned. Sixty two physicians (31.0%) said they used alanine aminotranferase (ALT) , aspartate aminotranferase (AST) and bilirubin concurrently to diagnose ATH. Only 9.0% of physicians adhered to the American Thoracic Society (ATS) guidelines of using either an ALT or AST level. Nearly all physicians (96.6%) withheld suspected antituberculosis (anti-TB) drugs in their management of ATH patients. While waiting for normalization of liver enzymes, the alternative combination regimen of ethambutol , ofloxacin and streptomycin (EOS) was used by most physicians (99/197). Of the 197 physicians who withheld anti-TB drugs, 175 (88.5%) decided to reintroduce them. Among these, 169 (96.6%) used a sequential rechallenge method (16,6% prescribed a full dosage, 71.4% prescribed an increasing dosage) and 1 (0.6%) used a simultaneous rechallenge method. Isoniazid was prescribed as the first drug for rechallenge in 77.5% of physicians. Only 6.5% of physicians complied with the ATS guidelines by prescribing rifampicin as the first agent. The reported practices of physicians in the diagnosis and management of ATH noticeably diverged from ATS guidelines. However, alternative regimen selection and rechallenge methods complied with ATS guidelines.

Comment: How many of us who treat antituberculosis drug reactions in Australasia comply with ATS guidelines, and are they the last word?

JT

Immune Studies

Is interferon-gamma the right marker for bacille Calmette-Guerin-induced immune protection? The missing link in our understanding of tuberculosis immunology.

Abebe F Oslo Norway

Clin Exp Immunol 2012; 169: 213

Abstract: Bacille Calmette Guerin (BCG), developed a century ago, is the only licensed tuberculosis (TB) vaccine in use to date. The protective efficacy of BCG against TB varies with no apparent protection in some populations, and mechanism of its immune protection is poorly known, and yet BCG is the most widely used vaccine, with more than 4 billion BCG-vaccinated children globally. BCG is probably the only licensed vaccine currently in use believed to mediate immune protection through the production of interferon (IFN)-gamma by CD4 T cells, which in turn activated macrophages to kill Mycobacterium tuberculosis (Mtb). Currently, a number of new TB candidate vaccines are in different phases of clinical trial. The majority of these new vaccines are either recombinant forms of BCG or prime boosters of BCG (rBCG) and their immunogenicity is tested using BCG as a benchmark by measuring Specific IFN-gamma produced by CD4(+) T cells as a protective immune marker. However, some recent studies that examined mechanisms of immune protection of BCG in animals and humans have reported a lack of correlation between IFN-gamma production by CD4 cells and BCG –induced immune protection. These studies point to the fact that there is a missing link in our understanding of TB immunology. Conversely, there is emerging evidence that other T cell subsets (gamma delta, [gammadelta]), CD8(+) T cells and natural killer cells may play a vital roles in immune protection against Mtb infection and BCG-induced immune protection. Gammadelta cells and NK cells, which were considered to be part of the innate immunity in the past, have been shown to develop immunological memory upon re-encounter with the same pathogen. In this paper, the controversy over the role of IFN-gamma as a marker for protective immunity against TB, and emerging data on the role of gammadelta cells, CD8)+) and NK cells will be presented.

TB and HIV

The immune reconstitution inflammatory syndrome after antiretroviral therapy initiation in patients with tuberculosis: findings from the SAPiT trial.

Naidoo et al Durban South Africa

Ann Intern Med 2012; 157: 313

Background: Concerns about the immune reconstitution inflammatory syndrome (IRIS) remain a barrier to antiretroviral therapy (ART) initiation during antituberculosis treatment in co-infected patients.

Objective: To assess IRIS incidence, severity and outcomes relative to the timing of ART initiation in patients with HIV-related tuberculosis.

Design: Randomized, open–label clinical trial (ClinicalTrials.gov registration number: NC T00398996)

Setting: An outpatient clinic in Durban, South Africa.

Patients: 642 patients co-infected with HIV and tuberculosis.

Measurements: In a secondary analysis of the SAPit (Starting Antiretrovitral therapy at three points in Tuberculosis) trial, IRIS was assessed in patients randomly assigned to initiate ART within 4 weeks of tuberculosis treatment initiation (early integrated treatment group), within 4 weeks of completion of the intensive phase of tuberculosis treatment completion (late integrated treatment group), or within 4 weeks after tuberculosis therapy completion (sequential treatment group). The syndrome was defined as new-onset or worsening symptoms, signs or radiographic manifestations temporally related to treatment initiation, accompanied by a treatment response. Severity of IRIS, hospitalization and time to resolution were monitored.

Results: Incidence of IRIS was 19.5 (n=43), 7.5 (n=18), and 8.1(n=19) per 100 person-years in the early integrated, late integrated and sequential treatment groups, respectively. Among patients with a baseline CD4+ count less than 0.050 / 10^9 cells /L. IRIS incidence was 45.5, 9.7 and 19.7 per 100 person-years in the early integrated group than in the late integrated (IRR, 2.6 [95% CI, 1.5-4.8]; P<0.001) or sequential (IRR, 2.4 {95%CI, 1.4-4.4]; P<0.001) treatment groups. More severe IRIS cases occurred in the early integrated treatment group than in the other 2 groups (35% vs. 14%; P=0.179), and patients in the early integrated group had significantly higher hospitalization rates (42% vs. 14%; p=0.007) and longer time to resolution (70.5 vs. 29-0 days; P=0.001) than patients in the other 2 groups.

Limitations: It was not possible to assess IRIS in more patients in the sequential treatment group (n=74) than in the late integrated (n=50) and early integrated (n=32) treatment groups because of loss to follow-up, withdrawal or death within 6 months of scheduled ART initiation. This study did not assess IRIS risk in nonambulatory patients or in those with extrapulmonary and smear-negative tuberculosis.

Conclusion: Initiation of ART in early stages of tuberculosis treatment resulted in significantly higher IRIS rates, longer times to resolution and more sever cases requiring hospitalization. These findings are particularly relevant to patients initiating ART with a CD4+ count of less than 0.050 per 10^9 cells /L, given the increased survival benefit of early ART initiation in this group.

Comment: A CD4+ cell count of less than 50 represents very severe immunosuppression, so delaying ART for more than 4 weeks (or even 2

weeks), may submit the person to a considerable risk of dying.

JT

HIV and tuberculosis - science and implementation to turn the tide and reduce deaths.

Harries et al Paris France

J Int AIDS Soc 2012; 15: 17396

Introduction: Every year, HIV-associated tuberculosis deprives 350,000 mainly young people of productive and healthy lives. People die because TB is not diagnosed and treated in those with known HIV infection and HIV infection is not diagnosed in those with TB. Even in those in whom both HIV and TB are diagnosed and treated, this often happens far too late. These deficiencies can be addressed through the application of new scientific evidence and diagnostic tools.
Discussion: A strategy of starting antiretroviral therapy (ART) early in the course of HIV infection has the potential to considerably reduce both individual and community burden of TB and needs urgent evaluation for efficacy, feasibility and broader social and economic impact. Isoniazid preventive therapy can reduce the risk of TB and, if given strategically in addition to ART, provides synergistic benefit. Intensified TB screening as part of the "Three I's " strategy should be conducted at every clinic, home or community –based attendance using a symptoms-based algorithm, and new diagnostic tools should increasingly be used to confirm or refute TB diagnoses. Until such time when more sensitive available, bolder approaches such as empirical anti-TB treatment need to be considered and evaluated. Patients with suspected or diagnosed TB must be screened for HIV and given cotrimoxazole preventive therapy and ART if HIV-positive. Three large randomized trials provide conclusive evidence that ART initiated within two to four weeks of start of anti-TB treatment saves lives, particularly in those with severe immunosuppression. The key to ensuring that these collaborative activities are delivered is the co-location and integration of TB and HIV services within the health system and the community.
Comment: Although this article is directed to the third world in its advocacy of mass empirical therapy, we must never forget that mass treatment of disease in Africa played a role in the spread of HIV in that continent.

JT

For those who are unaware of the "Three I's" strategy , this is popularized by the WHO to signify: 1)INH therapy, 2) intensified case finding, 3) infection control. (Ed)

Diagnosis

Performance of the 2007 WHO Algorithm to Diagnose Smear-Negative Pulmonary Tuberculosis in a HIV Prevalent Setting. Huerga H et al Paris, France.

PLoS One. 2012;7(12):e51336.

Background
The 2007 WHO algorithm for diagnosis of smear-negative pulmonary tuberculosis (PTB) including Mycobacterium tuberculosis (MTB) culture was evaluated in a HIV prevalent area of Kenya.

Methods:PTB smear-negative adult suspects were included in a prospective diagnostic study (2009-2011). In addition, program data (2008-2009) were retrospectively analysed. At the first consultation, clinical examination, chest X-ray, and sputum culture (Thin-Layer-Agar and Lowenstein-Jensen) were performed. Patients not started on TB treatment were clinically re-assessed after antibiotic course. The algorithm performance was calculated using culture as reference standard.

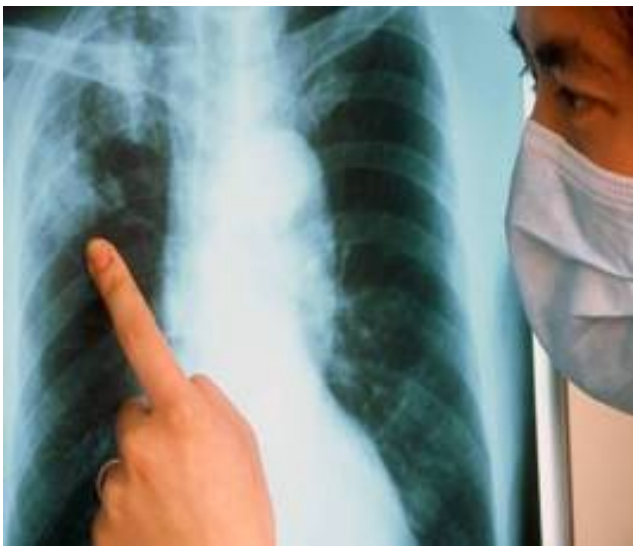
Results: 380 patients were included prospectively and 406 analyzed retrospectively. Culture was positive for MTB in 17.5% (61/348) and 21.8% (72/330) of cases. Sensitivity of the clinical-radiological algorithm was 55.0% and 31.9% in the prospective study and the program data analysis, respectively. Specificity, positive and negative predictive values were 72.9%, 29.7% and 88.6% in the prospective study and 79.8%, 30.7% and 80.8% in the program data analysis. Performing culture increased the number of confirmed TB patients started on treatment by 43.3% in the prospective study and by 44.4% in the program data analysis. Median time to treatment of confirmed TB patients was 6 days in the prospective study and 27 days in the retrospective study. Inter-reader agreement for X-ray interpretation between the study clinician and a radiologist was low (Kappa coefficient=0.11, 95%CI: 0.09-0.12). In a multivariate logistic analysis, past TB history, number of symptoms and signs at the clinical exam were independently associated with risk of overtreatment.

Conclusion: The clinical-radiological algorithm is suboptimal to diagnose smear-negative PTB. Culture

increases significantly the proportion of confirmed TB cases started on treatment. Better access to rapid MTB culture and development of new diagnostic tests is necessary.

Comment: Even the most experienced clinician and radiologist will disagree on what represents non-cavitating TB.

JT



Cavitating pulmonary tuberculosis (courtesy IUATLD)

Microbiology

Hepcidin and the iron-infection axis.

Drakesmith et al Oxford United Kingdom

Science 2012; 338: 768

Abstract: Iron lies at the center of a battle for nutritional resource between higher organisms and their microbial pathogens. The iron status of the human host affects the pathogenicity of numerous infections including malaria, HIV1 and **tuberculosis**. Hepcidin, an antimicrobial –like peptide hormone, has emerged as the master regulator of iron metabolism. Hepcidin controls the absorption of dietary iron and the distribution of iron among cell types in the body, and its synthesis is regulated by both iron and innate immunity. We describe how Hepcidin integrates signals from diverse physiological inputs, forming a key molecular bridge between iron trafficking and response to infection.
Comment: Does this mean that reduced iron stores in the human body will decrease the immune response to invasion by M.tuberculosis?

JT