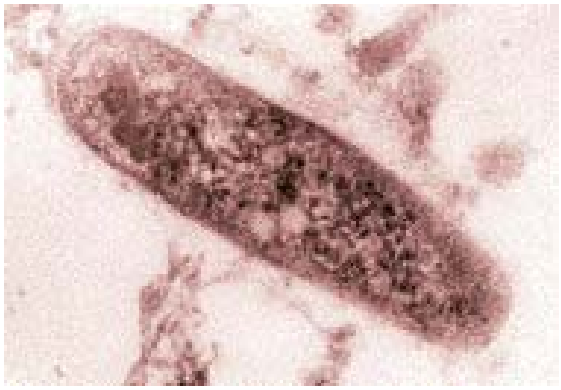
The Australian Tuberculosis Review

February 2012



M. tuberculosis EM Photo

Forthcoming Meetings

6th Conference of the Union Europe Region: London, United Kingdom
4-6 July 2012

43 rd World Conference of the Union, Kuala Lumpur, Malaysia
13- 17 November 2012

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In this Edition:

Editorial

A report from Krause's group in Darwin demonstrates the utility of using IGRAs in remote areas to diagnose tuberculous infection. (Communicable Diseases Intelligence 2011). Not only did they demonstrate the superior specificity of the QuantiFERON Gold–In Tube test over the injection of 10 units of standardized PPD, but also show that a 15 mm Mantoux reading corresponds more closely with a positive IGRA. The numbers in this study are small , but significant enough to call for a really large trial in Australia using and comparing both diagnostic methods.. The trial should be designed to tell us if we should use both tests at the same time, use the TST first and if 10-15 mm in reaction size, take blood for an IGRA; or test for Interferon gamma release first and if negative, proceed to an TST. Finally the trial should include a sufficient number of BCG vaccinated, for they will be largely those born overseas in high TB settings.

Population Studies

Tuberculosis in Australia: bacteriologically confirmed cases and drug resistance, 2008 and 2009.

Lumb et al Australian Mycobacterium Reference Laboratory Network

CDI 2011; 35: 154

Abstract: There were 886 an 1062 bacteriologically-confirmed cases of tuberculosis (TB) in 2008 and 2009, representing an annual rate of 4.1 and 4.9 per 100,000 population respectively. Over the 2 years, a total of 23 children aged under 10 years (male n=13, female n=10) had bacteriologically confirmed tuberculosis , including 3 children with TB meningitis. Results of in vitro drug susceptibility testing were

available for 885 of 886 and 1060 of 1062 isolates for isoniazid(INH),rifampicin(RIF), ethambutol (EMB)and pyrazinamide(Z) in 2008 and 2009 respectively. In 2008, a total of 94 (10.7%) isolates of Mycobacterium tuberculosis complex were resistant to at least one of the anti-tuberculosis agents. Any resistance to INH was noted for 76 (8.7%), 23 (2.6%) for RIF, 10 (1.1%) for EMB and 9 (1.0%) for Z. Resistance to at least INH and RIF (defined as multidrug resistant TB, [MDR-TB]) was detected in 21 (2.4%) isolates. None of the 21 MDR-TB isolates had resistance to either ofloxacin or the injectable agents. In 2009, a total of 168 (15.9%) were resistant to at least one of the anti-TB agents. Any resistance to INH was noted for 150 (14.2%) isolates, 37 (3.5%) for RIF, 5 (0.5%) for EMB, and 13 (1.2%) for Z. A total of 31 (2.9%) were MDR-TB. In 2009, there were 2 cases of quinolone resistance in MDR-TB from persons born overseas. Mono-resistance to INH was the most commonly detected resistance with 33 and 80 isolates in 2008 and 2009 ,respectively. Mono-resistance to RIF was infrequently encountered with 2 and 5 isolates in 2008 and 2009 respectively. There 6 and 11 MDR-TB patients from the Papua New Guinea (PNG)-Torres Strait Islands (TSI) cross-border region in 2008 and 2009 respectively. The PNG-TSI zone now contributes a substantial proportion of MDR-TB cases to the database. In addition there were 24 isolates of Mycobacterium bovis bacille Calmette Guerin (BCG). 15 were cultured from males (4 aged, </= 5years and from 9 females (5 aged </=5 years. The predominant site of isolation was from vaccination abscess. Eight males (range 57- 87 years) had M.bovis BCG isolated from urine or blood culture.

Comment: Given Australia's migration program, these figures come as no surprise, even the slow rise in drug resistance.

Tuberculosis in Indigenous peoples in the US, 2003-2008.

Bloss et al Atlanta GA USA

Public Health Rep 2011; 126: 677

Objectives: We examined trends and epidemiology of tuberculosis (TB) across racial/ethnic groups to better understand TB disparities in the United States, with particular focus on American Indians/Alaska Natives (AI/AN) and Native Hawaiians/other Pacific Islanders (NH/PIs)

Methods : We analyzed cases in the US national Tuberculosis Surveillance System and calculated TB case rates among all racial/ethnic groups from 2003 to 2008. Socioeconomic and health indicators for countries in which TB cases were reported came from the Health Resources and Services Administration Area Resource File.

Results: Among the 82,836 TB cases, 914 (1.1%) were in AI/ANs and 362 (0.4%) were in NH/PIs. In 2008, TB case rates for AI/ANs and NH/PIs were 5.9 and 14.7 per 100,000 population, respectively, rates that were more than five and 13 times greater than for non-Hispanic white people (1.1 per 100,000 population). From 2003 to 2008, AI/ANs had the largest percentage decline in TB case rates (-27.4%) for any racial/ethnic group, but NH/PIs had the smallest percentage decline (-3.5%). AI/ANs were more likely than any other racial/ethnic groups to be homeless, to excessively use alcohol, receive totally directly observed therapy, and come from counties with a greater proportion of people living in poverty and without health insurance. A greater proportion of NH/PIs had extrapulmonary disease and came from counties with a higher proportion of people with a high school diploma.

Conclusions: There is a need to develop flexible TB-control strategies that address the social determinates of health and that are tailored to the specific needs of AI/ANs and NH/PIs in the US.

Comment: This report could apply to Australia.

JT

Risk factors associated with fluoroquinolone-resistant tuberculosis in a Beijing tuberculosis referral hospital.

Liu et al Beijing China

Respirology 2011; 16: 918

Background and Objective: The rapid increase in the number of multidrug-resistant tuberculosis (MDR-TB) cases worldwide emphasizes the importance of rational use of key important life-saving anti-TB drugs such as fluoroquinolones in order to provide information for better case management, so as to minimise the further spread of extensively drug-resistant TB, a retrospective study was performed to assess the risk factors associated with fluoroquinolones resistance among TB patients attending the 309 Hospital in Beijing, China.

Methods: Drug susceptibility testing results and clinical data for hospitalised TB patients for the period 2000-2010 were analysed. Univariate and multivariate analyses were used to determine the risk factors associated with fluoroquinolones resistant TB.

Results: From July 2000 to July 2010, ofloxacin resistance was observed in 306 of 3456 (8.6%) hospitalised TB patients who were tested. The independent risk factors associated with fluoroquinolones resistant TB were being single (adjusted OR 1.65), being a migrant living in Beijing (adjusted OR 2.15), being a migrant from another area (adjusted OR 5.07), being a patient who was retreated (adjusted OR 2.84), exposure to fluoroquinolones (adjusted OR 2.73), having COPD (adjusted OR 3.53), having COPD with known exposure to fluoroquinolones (adjusted OR 2.47), having MDR-TB (adjusted OR 1.67), and having polyresistant TB (adjusted OR 2.34).

Conclusions: These findings suggest that in high-risk populations continuous surveillance of fluoroquinolones resistance should be maintained. In addition, programs should be implemented for the management of persons with MDR-TB and more complicated TB, so as to minimise the further spread of fluoroquinolone resistance and extensively drug-resistant TB.
Comment: The extensive use of fluoroquinolones for respiratory infections explains the connection with COPD. Unfortunately the horse has bolted in this respect.

JT

Controversies over Control

Tuberculosis control in the Torres Strait Islands.

Konstantinos et al Cairns, Brisbane, Sydney, Australia

MJA 2011; 195: 512

Recent articles in the journal have noted the first case of extensively drug resistant tuberculosis (TB) in New Zealand (see Oct Edition, Ed) and emphasized the exponential cost and complexity in managing drug-resistant TB. We thus wish to caution against the proposed premature closure of TB treatment services for Papua New Guinea (PNG) citizens who access health care in the Torres Strait Islands. A protected zone under the Torres Strait Island Treaty allows selected inhabitants from the South Fly District of Western Province, PNG, to conduct traditional practices in the outer Torres Strait Islands. Because access to health care in the South Fly District is difficult and local TB control is poor, many of these people use TB services in the Torres Strait Islands, which are under Australian jurisdiction. Around 60 PNG patients, 50 of whom have multidrug-resistant TB, currently receive treatment from Australian TB services for humanitarian and public health reasons- to limit the transmission of TB into Australia. This is especially important given the high rates of transmissible drug-resistant disease. We thus support the strategy of the Australian and Queensland governments, which aims to strengthen PNG TB control as the best long-term solution. However, establishing effective TB control in resource-poor settings such as PNG is complex and confounded by competing health priorities. We are very concerned by the assumption that care for all PNG patients with TB should be transferred back to PNG by February 2012. To avoid making TB control in this area even harder, and particularly to avert the emergence of extensively drug-resistant TB with subsequent transmission to Australia, we believe that such transfer of care should be based on an objective assessment of the capacity of services to manage the increasing number of patients and the complexity of their treatment…….
Comment : This is a welcome response to a serious issue. It is over 30 years since the first Papuans received treatment in the Torres Straits for TB, but then their treatment was not complicated by drug resistance and HIV infection.

JT

A clinician's perspective on providing TB services in the Torres Strait.

Vincent S Cairns Qld Australia

MJA 2011; 195: 506

For many decades Australia has been fortunate to have a low prevalence of tuberculosis (TB). This has resulted from a firm commitment to screening for and managing TB since early last century. Because of the low rates of disease, the current population, unfortunately, perceives TB to be a "disease of the past" Such a perception leads to complacency, even among subgroups of policymakers, who place importance on short-sighted spending cuts over long term TB control in an era in which drug-resistant TB is an emergency biosecurity threat to Australia.
One component of effective TB control is prompt identification and treatment and monitoring of index cases and screening of contacts. In 2001, the Cairns Regional TB Control Unit initiated this response when the first case of multidrug-resistant TB (MDR-TB) was detected in the Torres Strait region. The initial and subsequent cases were in people from Western province in Papua New Guinea (PNG) who resided in the Torres Strait Island Protected Zone and, by treaty law, are free to travel back and forth from Western Province to the outer islands of Torres Strait for traditional purposes.
As new cases emerged from Western Province, the regional control unit established TB outreach services on Saibai and Boigu Islands to treat these patients, both for humanitarian purposes and to reduce the health risk to Australian citizens. The clinics employed medical, nursing and radiographic staff and had access to the Brisbane TB reference laboratory. They carried out ongoing surveillance during a patient's treatment cycle, to detect any treatment failure or default, and post treatment follow-up, to ensure the patient was cured. Over the past decade, the number of TB and MDR-TB cases originating from Western Province has increased substantially and the demand on the clinics has been large. However the actions of the clinics have been credited with their being no MDR-TB cases detected in the Australian population in this region. The Australian clinics were set up out of necessity, as Western Province has no established comprehensive TB service. Further, Western Province has been plagued by long-term political unrest, poverty and lack of transportation., resulting in minimal access for local residents to their regional hospital on Daru Island. The intention of the Saibai

and Boigu clinics has always been to hand over care of PNG residents once a clinic and a TB outreach program were established on the PNG side of the border. Over the past few years, there have been regular meetings between Queensland TB control units, the Australian Government, the Western Province local government, the PNG national program team and Daru hospital staff. The aim of the meetings has been to facilitate, step by step, the transfer of responsibility for TB management to PNG, including clinical input from both Queensland and PNG health services. As yet, there is no such service within Western Province or through a clinical base at Daru Hospital with an outreach service to Western Province.

Unexpectantly, during the first half of 2011, the Queensland Government directed that the TB outreach clinics on Saibai and Boigu Islands be closed in June 2011. No remedial plan for treatment continuation was included, leaving the 50 patients from PNG who were being treated for TB in a dire situation. Importantly, there was no plan for the ongoing management of patients from Western Province. Through strong pressure from TB clinicians in Australia, operation of the Australian services has been extended, and they will remain open until early in 2012 to ensure completion of treatment cycles for current patients. AusAID is supplying funding to establish TB health services within Western Province, but the program is in its infancy. There is considerable concern that extensively drug-resistant will emerge in the region and eventually infect Australian citizens residing in the outer Torres Strait Islands.

Comment: Certainly Papuans from the Western Province have preferred to camp with their distant relatives on Saibai and Boigu Islands. Despite immigration controls, it is still not impossible for them to travel to the Australian mainland, and therefore potentially spread MDR-TB to inhabitants of that mainland.

JT

Molecular Biology and Immunity

Rv3615c is a highly immunodominant RD1(region of difference1)-dependant secreted antigen specific for Mycobacterium tuberculosis infection.

Millington et al London UK and Boston MA USA

PNAS 2011;108: 5730

Abstract: The 6kDa early secretory antigenic target of Mycobacterium tuberculosis (ESAT6) and the 10kDa culture filtrate antigen (CFP10), encoded in region of difference1 (RD1) and secreted by the ESAT-6 system 1 (Esx-1) secretion system, are the most immunodominant and highly M. tuberculosis (MTB-specific antigens. These attributes are responsible for their primary importance in tuberculosis (TB) immunodiagnosis and vaccine development. Rv3615c(Esx-1) substrate protein C(ESP-C), encoded outside RD-1 is similar in size and sequence homology to CFP-10, suggesting it might be a target for cellular immunity in TB. Using ex vivo enzyme- linked immunospot- and flow cytometry based cytokine secretion assay , we comprehensively assessed cellular immune responses to EspC in patients with active TB, latently infected persons and uninfected bacillus Calmette Guerin (BCG)-vaccinated controls. EspC was at least as immunodominant as ESAT-6 and CFP-10 in both active and latent TB infection. EspC contained broadly recognized CD4+ and CD8+ epitopes, inducing a predominantly CD4+ T-cell response comprising functional T-cell subsets secreting both IFN-gamma and IL-2 as well as functional T-cell subsets secreting only IFN-gamma. Surprisingly T-cell responses to EspC were as highly specific (93%) for MTB infection as responses to ESAT-6 and CFP-10, with only 2 of 27 BCG-vaccinated controls responding to each antigen. Using quantitative proteomics and metabolically labelled mutant and genetically complemented MTB strains, we identified the mechanism of the specificity of anti-EspC immunity as the Esx-1 dependence of EspC secretion. The high immuno-dominance of EspC, equivalent to that of ESAT-6 and CFP-10, makes it a TB vaccine candidate, and its high specificity confers strong potential for T-cell based immunodiagnosis.

Comment: Sounds promising but does MTB have even more antigenic tricks up its sleeve?

JT

BCG vaccination induces different cytokine profiles following infant BCG vaccination in the UK and Malawi.

Lalor et London UK

J Infect Dis 2011; 204: 1075

Background: BCG vaccination of infants is thought to provide good protection in all settings. This study investigated whether Malawian infants made weaker responses across a cytokine panel after BCG vaccination, compared with UK infants.

Methods: Diluted whole blood samples were cultured with Mycobacterium tuberculosis purified protein for 6 days from BCG-vaccinated infants 3 months (n= 40 Malawi, 28 UK) and 12 months (n=34 Malawi, 26 UK) after vaccination, and also from UK unvaccinated infants (n=9 at 3 months, n=10 at 12 months). Forty two cytokines were measured in supernatants using a multiplex bead array assay.

Principal component analysis was used to summarize the overall patterns in cytokine responses.
Results: We found differences in median responses in 27 of the 42 cytokines; 7 higher in the UK and 20 higher in Malawi. The cytokines with higher responses in the UK were all helper T1 related. The cytokines with higher responses in Malawi included innate proinflammatory cytokines, regulatory cytokines, interleukin 17, T helper 2 cytokines, chemokines, and growth factors. Principal component analysis separated the BCG-vaccinated infants from Malawi from the UK vaccinated infants and from the unvaccinated infants .
Conclusions: Malawian infants make cytokine responses following BCG vaccination, but the cytokine profile is different from that in the UK. The different biosignatures following BCG vaccination in the 2 settings may indicate variability in the protective efficacy of infant vaccination.
Comment: Although the numbers are small, these observations raise many questions that need answers. Are we dealing with genetic difference or environmental influences?

JT

Infection

Feasibility of latent tuberculosis infection diagnosis by interferon-gamma release assay remote from testing facilities.

Trauer et al Darwin NT

CDI 2011; 35:168

Abstract: Although the tuberculin skin test (TST) has been the mainstay of the diagnosis of latent tuberculosis infection (LTBI) for many decades. Interferon gamma release assays (IGRAs) are gaining acceptance and are more specific for the diagnosis. The characteristics of one such IGRA, the QuantiFERON- TB Gold In-Tube, make it feasible for use in a remote setting, This study performed 62 IGRAs with this test on individuals testing positive by TST, in a clinical setting over 3000 km from the testing laboratory. Of these 42 patients (68%) recorded negative results, 19 (31%) were positive, with only 1 result (2%) indeterminate. Negative, and therefore discordant in this study, test results were more common in those known to have been previously vaccinated with bacillus Calmette Guerin. These results are consistent with other reports, indicating that this approach to testing is logistically feasible, and has the potential to complement LTBI to assist tuberculosis control programs in settings remote from the testing laboratory.
Comment : Agreed, although I wish the authors in their abstract, would quantify the TST results rather than designate them as positive or negative.

JT

Three months of rifapentine and isoniazid for latent tuberculosis infection.

Sterling et al Nashville TN USA

N Eng J Med 2011; 365: 2155

Background: Treatment of latent Mycobacterium tuberculosis infection is an essential component of tuberculosis control and elimination. The current standard regimen of isoniazid for 9 months is efficacious but is limited by toxicity and low rates of treatment completion.
Methods: We conducted an open-label, randomized noninferiority trial comparing 3 months of directly observed once-weekly therapy with rifapentine (900 mgs) plus isoniazid (900 mgs) (combination-therapy group) with 9 months of self-administered isoniazid (300 mg) (isoniazid-only group) at subjects at high risk for tuberculosis. Subjects were enrolled from the United States, Canada, Brazil and Spain and followed for 33 months. The primary endpoint was confirmed tuberculosis, and the noninferiority margin was 0.75%.
Results: In the modified intention-to-treat analysis, tuberculosis developed in 7 of 3986 subjects in the combination-therapy group (cumulative rate, 0.19%) and in 15 of 3745 subjects in the isoniazid–only group (cumulative rate, 0.43%), for a difference of 0.24 percentage points. Rates of treatment completion were 82.1% in the combination-therapy group and 69.0% in the isoniazid only group ($P<0.001$). Rates of permanent drug discontinuation owing to an adverse event were 4.9% in the combination-therapy group and 3.7 % in the isoniazid-only group. ($P=0.009$). Rates of investigator-assessed drug related hepatotoxicity were 0.4% and 2.7%, respectively ($P< 0.001$).
Conclusions: The use of rifapentine plus isoniazid for 3 months was as effective as 9 months of isoniazid alone in preventing tuberculosis and had a higher treatment completion rate. Long term safety monitoring will be important.
Comment: A 33 month follow up in infants may be adequate to predict for tuberculous disease, but not I believe for adults.

JT

Screening

Is premigration health screening for tuberculosis worthwhile?

King et al Sydney NSW

Med J Aust 2011; 195: 534

Objective: To determine whether premigration screening for tuberculosis is worth undertaking in visa applicants, and whether screening resources are being appropriately directed towards intending migrants at highest risk of tuberculosis.
Design, Setting and Participants: A 12-month survey of all intending migrants with tuberculosis necessitating treatment detected during the premigration health assessment process, whose medical examinations were submitted to the Department of Immigration and Citizenship's Global Health Branch for assessment by a Medical Officer of the Commonwealth between 1 July 2009 and 30 June 2010.
Main Outcome Measures: individuals diagnosed with active tuberculosis, proportions diagnosed by sputum smear and culture tests or clinically, and with susceptibility test results; distribution of visa types among people diagnosed.
Results: In premigration assessments, 519 people were diagnosed with active tuberculosis (prevalence, 137 per 100,000 in examined population). The top source countries for people with tuberculosis were the Philippines (21.8%), India (16.8%), Vietnam,(16.2%), and China (8.3%). Positive sputum smear test results were submitted for 67 cases (12.9%). Positive culture test results were obtained in 230 cases (44.3%), but only 95 of these (41.3%) had susceptibility test results, with 83 fully susceptible.. Four people had multidrug resistant tuberculosis (prevalence 1.06 per 100,000 population). Five people had both active tuberculosis and HIV infection. Of those diagnosed with tuberculosis, 162 (31.2%) were intending students, 82 (15.8%) were intending visitors and 53 (10.2%) were applicants for humanitarian visas
Conclusions: Premigration health screening of intending migrants is identifying substantial numbers of people who would have required treatment for tuberculosis after arrival in Australia. The high proportion of students, visitors and refugee and humanitarian entrants with tuberculosis validates the current screening program. The screening is of benefit to the applicants, whose tuberculosis is treated earlier than it otherwise would have been , and to the Australian population, by averting exposure to people with active tuberculosis.
Comment: If anything, the yield of such case detection seems to be increasing.

JT

Imaging

Detection of pulmonary tuberculosis: comparing MR imaging with HRCT.

Rizzi et al Rome Italy

BMC Infect Dis 2011; 11: 243

Background: Computer tomography (CT) is considered the gold standard for assessing the morphological changes of lung parenchyma. Although novel CT techniques have substantially decreased the radiation dose, radiation exposure is still high. Magnetic Resonance Imaging (MRI) has been established as a radiation-free alternative to CT for several lung diseases, but its role in infectious diseases still needs to be explored further. Therefore, the purpose of our study was to compare MRI with high resolution CT (HRCT) for assessing pulmonary tuberculosis.
Methods: 50 patients with culture-proven pulmonary tuberculosis underwent chest HRCT as the standard of reference and were evaluated by MRI within 24 h after HRCT. Altogether we performed 60 CT and MRI examinations, because 10 patients were also examined by CT and MRI at follow-up. Pulmonary abnormalities, their characteristics, location and distribution were analyzed by two readers who were blinded to the HRCT results.
Results: Artifacts did not interfere with the diagnostic value of MRI. Both HRCT and MRI correctly diagnosed pulmonary tuberculosis and identified pulmonary abnormalities in all patients. There were no significant differences between the two techniques in terms of identifying the location and distribution of the lung lesions, though the higher resolution of MRI did allow for better identification of parenchymal dyshomogeneity, caseous and pleural or nodal involvement.
Conclusion: Technical developments and the refinement of pulse sequences have improved the quality and speed of MRI. Our data indicate that in terms of identifying lung lesions in non-AIDS patients with non-miliary pulmonary tuberculosis, MRI achieves diagnostic performances comparable to those obtained by HRCT but with better and more rapid identification of pulmonary tissue abnormalities due to excellent contrast resolution.
Comment: MRI could be helpful in the diagnosis of childhood pulmonary TB, given that plain chest radiographs lack both sensitivity and specificity and HRCT still gives too much ionizing radiation.

JT

Chest computed tomography is more likely to show latent tuberculosis foci than simple chest radiography in liver transplant candidates.

Lyu et al Seoul South Korea

Liver Transpl 2011; 17: 963

Abstract: Although the detection and treatment of latent tuberculosis infections (LTBIs) in transplant candidates are essential, current diagnostic methods for LTBIs are limited, especially in immunocompromised subjects. Pretransplant chest computed tomography (CT) may reveal more LTBI foci and thus predict the development of post transplant tuberculosis (TB) more efficiently; however this hypothesis has not yet been investigated.. Thirty six liver transplantation (LT) recipients who

developed (the TB group) and 144 LT recipients who did not develop TB (the control group) were retrospectively enrolled into a study with a nested case control design, and their clinical characteristics and radiological findings were compared. Tuberculin skin tests (TSTs) were not performed and none of these patients had been treated for LTBIs. Thirty six of 2549 LT recipients (1.4%) were diagnosed with TB after LT (median=10 months, range 1-80 months). Twenty eight patients (77.8%) successfully completed the treatment. There were no significant differences in the clinical characteristics of the 2 groups. Abnormal CT findings (40.0% versus 17.3%, P=0.018 and chest X-ray (CXR) findings (25.0% versus 11.8%. P= 0.044) suggestive of healed TB were significantly more frequent in the TB group versus the control group. Of the 10 patients who underwent chest CT and developed TB, 5 (50%) showed abnormal findings only on chest CT scans, whereas their CXR results were normal. In conclusion, a pretransplant chest CT scan is more likely to show an LTBI than a CXR in those with post LT TB. The usefulness of chest CT along with traditional methods such as TSTs for LTBI screening should be further investigated.

Comment: Yes, but testing with IGRAs and TSTs alone would detect LTBI alone. The authors are confused about the difference between latent TB and inactive TB.

JT

TB and HIV

Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis.

Blanc et al Paris France

N Eng J Med 2011; 365: 1471

Background: Tuberculosis remains an important cause of death among patients infected with the human immunodeficiency virus (HIV). Robust data are lacking with regard to the timing for the initiation of antiretroviral therapy (ART) in relation to the start of antituberculosis therapy.

Methods: We tested the hypothesis that the timing of ART initiation would significantly affect mortality among adults not previously exposed to antiretroviral drugs who had newly diagnosed tuberculosis and CD4+ T-cell counts of 200 per cubic millimeter or lower. After beginning the standard 6 month treatment for tuberculosis, patients were randomly assigned to either earlier treatment (2 weeks after beginning tuberculosis treatment) or later treatment (8 weeks later) with stavudine, lamivudine and efavirenz. The primary end point was survival.

Results: A totals of 661 patients were enrolled and were followed for a median of 25 months. The median CD4+ T-cell count was 25 per cubic millimeter, and the median viral load was 5.54 log (10) copies per milliliter. The risk of death was significantly reduced in the group that received ART earlier, with 59 deaths among 332 patients (18%) as compared with 90 deaths among 329 patients (27%) in the later ART group (HR, 0.62; 95% CI , 0,44 to 0.86; P=0.006). The risk of tuberculosis-associated immune reconstitution inflammatory syndrome (IRIS) was significantly increased in the earlier ART group (HR, 2.51; 95% CI. 1.78 to 3.59; P<0.001). Irrespective of the study group, the median gain in the CD4+ T-cell count was 114 per cubic millimeter, and the viral load was undetectable at week 50 in 96.5% of the patients.

Conclusions: Initiating ART 2 weeks after the start of tuberculosis treatment significantly improved survival among HIV-infected adults with CD4+ T-cell counts of 200 per cubic millimeter or lower. *(Funded by the French National Agency for Research on AIDS and Viral Hepatitis and the National Institutes of Health)*

Timing of antiretroviral therapy for HIV-1 infection and tuberculosis.

Havlir et al San Francisco CA USA

N Engl J Med 2011; 365: 1482

Background: Antiretroviral therapy (ART) is indicated during tuberculosis treatment in patients infected with human immunodeficiency virus type 1 (HIV-1), but the timing for the initiation of ART when tuberculosis is diagnosed in patients with various levels of immune compromise is not known.

Methods: We conducted an open label, randomized study comparing earlier ART (within 2 weeks after initiation of treatment for tuberculosis) with later ART (between 8 and 12 weeks after the initiation of treatment for tuberculosis) in HIV-1 infected patients with CD4+ T-cell counts of less than 250 per cubic millimeter and suspected tuberculosis. The primary endpoint was the proportion of patients who survived and did not have a new (previously undiagnosed) AIDS-defining illness at 48 weeks.

Results: A total of 809 patients with a median baseline CD4+ T-cell count of 77 per cubic millimeter and an HIV-1 RNA level of 5.43 log (10) copies per milliliter were enrolled. In the earlier ART group , 12.9% of patients had a new AIDS-defining illness or died by 48 weeks, as compared to 16.1% in the later ART group. (95% CI, -1.8 to 8.1 P=0.45). Among patients with screening CD4 T-cell counts of less than 50 per cubic millimeter, 15.5% of patients in the earlier ART group versus 26.6% in the later ART group had a new AIDS-defining illness or died (95% CI, 1.5-to 20.5; P=0.02) Tuberculosis-associated immune reconstitution inflammatory syndrome (IRIS) was more common with earlier ART than with later ART (11% vs. 5%, P=0.002). The rate of viral suppression at 48 weeks was 74% and did not differ between the groups (P=0.38)

Conclusions: Overall, earlier RT did not reduce the rate of new AIDS-defining illness and death, as

compared with later ART. In persons with CD4+ T-cell counts of less than 50 per cubic millimeter, earlier ART was associated with a lower rate of new AIDS-defining illnesses and death.
Comment: Both studies have many similarities and strongly suggest that if the patient has a CD4+ T-cell count no greater than 50 per cubic millimeter, then ART should be started within 2 weeks of beginning antituberculosis treatment. With higher CD4+ counts, a delay of 8 weeks in starting ART will not increase mortality but reduce the likelihood of IRIS.

JT

Diagnosis

Interferon-gamma assays for active pulmonary tuberculosis diagnosis in adults in low-and middle-income countries: systematic review and meta-analysis.

Metcalfe et al San Francisco CA USA

J Infect Dis 2011; 204 Suppl-4:S1120

Background: The diagnostic value of interferon-gamma releases assays (IGRAs) for active tuberculosis in low and middle income countries is unclear.
Methods: We searched multiple databases for studies published through May 2010 that evaluated the diagnostic performance of QuantiFERON-TB Gold-In-Tube (QFT-GIT) and T-SPOT.TB (T-SPOT) among adults with suspected active tuberculosis or patients with confirmed cases in low-and middle-income countries. We summarized test performance characteristics with use of forest plots, hierarchical summary receiving operating characteristic (HSROC) curves and bivariate random effects models.
Results: Our search identified 789 citations, of which 27 observational studies (17 QFT-GIT and 10 T-SPOT) evaluating 590 human immunodeficiency virus (HIV) –uninfected and 844 HIV-infected individuals met inclusion criteria. Among HIV-infected patients, HSROC/ bivariate pooled sensitivity estimates (highest quality data) were 76% (95% CI 45-92%) for T-SPOT and 60% (95%CI 34-82%) for QFT-GIT. HSROC/ bivariate pooled specificity estimates were low for both IGRA platforms among all participants (T-SPOT, 61%[95% CI 40-79%]; QFT-GIT 52% [95% CI, 41-62%]) and among HIV-infected persons (T-SPOT, 52%[95% CI,40-63%], QFT-GIT, 50% [95% CI, 35-65%]) There was no consistent evidence that either IGRA was more sensitive than the tuberculin skin test for active tuberculosis diagnosis.
Comment: Neither IGRA nor tuberculin skin test seem essential in the diagnostic workup when pulmonary tuberculosis is suspected and this may apply to high income countries.

JT

Reporter phage and breath tests: emerging phenotypic assays for diagnosing active tuberculosis, antibiotic resistance, and treatment efficacy.

Jain et al New York USA

J Infect Dis 2011; 204: S 1142

Abstract: The rapid and accurate diagnosis of active tuberculosis (TB) and its drug susceptibility remain a challenge. Phenotypic assays allow determination of antibiotic susceptibilities even if sequence data are not available or informative. We review 2 emerging diagnostic approaches, reporter phage and breath tests, both of which assay mycobacterial metabolism. The reporter phage signal , Green florescent protein protein (GFP) or beta-galactosidase, indicates transcription and translation inside the recipient bacilli and its attenuation by antibiotics. Different breath tests assay (1) exhaled antigen 85, (2) mycobacterial urease activity, and (3) detection by trained rats of disease –specific odor in sputum, have also been developed . When compared with culture, reporter phage assays shorten the time for initial diagnosis of drug susceptibility by several days. Both reporter phage and breath tests have promise as early markers to determine the efficacy of treatment . While sputum often remains smear and Mycobacterium tuberculosis DNA positive early in the course of efficacious antituberculous treatment, we predict that both breath and phage tests will rapidly become negative . If this hypothesis proves correct, phage assays and breath tests could become important surrogate markers in early bactericidal activity (EBA) studies of new antibiotics.
Comment: These approaches seem interesting. However M. tuberculosis can show initial response even if it is susceptible to only one antituberculous drug in a regimen.

JT

Non Tuberculous Myco-bacteria

Mycobacterium shinjukuense sp. nov., a lowly growing, non-chromogenic species isolated from human clinical specimens.

Saito et al Hiroshima Japan

Int J Syst Evol Microbiol 2011; 61: 1927

Abstract: Seven isolates of a slowly growing, non-chromogenic Mycobacterium species were obtained from sputum and bronchial lavage fluid samples from elderly patients in different regions of Japan. These isolates were distinguished from related nontuberculous species by colony morphology,

positive results for TWEEN hydrolysis, catalase at 68 degrees C, nitrate reductase and pyrazinamidase and negative results for semi-quantitative catalase , urease and arylsulfatase. The mycolic acid pattern obtained by HPLC revealed a single cluster of late eluting mycolic acids similar to but different from those of Mycobacterium malmoense ATCC 29571 (T). The 16S RNA gene, 16S-23S internal transcribed spacer (ITS), rpoB and hsp65 sequences were unique in comparison with those of other mycobacteria. Comparison of 16S rRNA gene sequences showed that the isolates were most closely related to Mycobacterium tuberculosis H37Rv (T)(21 base differences in 158 bp; 98.6% 16S rRNA gene sequence similarity). A representative strain, GTC 2738(T) showed 91.9% rpoB sequence similarity with Mycobacterium marinum strain M, 95% hsp65 sequence similarity with Mycobacterium kansasii CIP 104589(T) and 81.1% 16S-23S ITS sequence similarity with Mycobacterium gordonae ATCC 14470(T). Phylogenetic analysis of concatenated sequences of the 16S rRNA, rpoB and hsp65 genes showed that the strain GTC 2738(T) was located on a district clade adjacent to .tuberculosis, M. ulcerans and M.marinum with bootstrap values of 81%. DNA-DNA hybridization demonstrated less than 70% reassociation with type strains of genetically related species and supported the novel status of the isolates. On the basis of this evidence, a novel species with the name Mycobacterium shinjukuense sp. nov. is proposed. The type strain, isolated from a sputum sample, is strain GTC 2738(T)(=JCM 14233(T)=CCUG53584 (T)).

Comment: Yet another Mycobacterium isolated from human secretions. What is of most interest in this report is the extensive range of tools used by a reference laboratory to define such an organism.

JT

Microbiology

The ins and outs of Mycobacterium tuberculosis drug susceptibility testing.

Boettger E Zurich Switzerland

Clin Microbiol Infect 2011; 17: 1128

Abstract: Drug susceptibility testing of Mycobacterium tuberculosis in the diagnostic laboratory classifies clinical isolates as either drug “resistant” or drug “susceptible” on the basis of their ability to grow in the presence of a “critical concentration” of the test compound. From -knowledge of the mechanisms that underlie drug resistance, it has become evident that drug resistance to M. tuberculosis is quite heterogeneous and involves low-level, moderate level and high level drug resistant phenotypes. Different mutations are associated with different levels of phenotypic resistance, and the acquisition of a genetic alteration leading to a decrease in drug susceptibility does not inevitably exclude the affected compound from treatment regimens. As a result, the simple categorization of clinical M.tuberculosis isolates as “resistant” on the basis of susceptibility testing at “critical concentrations” may need to be revised and supplemented by quantitative measures of resistance testing to reflect the biological complexity of drug resistance, with the view of optimally exploiting the compounds available for treatment.

Comment: Isoniazid has long been a good example of this problem. JT

Identification and characterization of breakthrough contaminants associated with the conventional isolation of Mycobacterium tuberculosis.

McClean et al Belfast Northern Ireland

J Med Microbiol 2011; 60: 1292

Abstract: Breakthrough contamination of tuberculosis (TB) cultures is a problem in that it allows the overgrowth of another bacterium present in the sputum specimen, which can potentially mask the presence of Mycobacterium tuberculosis. The aim of this study was to isolate and characterize the bacterial organisms responsible for such overgrowth and contamination, and to examine their susceptibility to (i) various chemical decontamination steps and (ii) antibiotics in liquid culture media, in an attempt to develop a method to help alleviate contamination problems associated with the conventional isolation of M. tuberculosis from routine patient sputum specimens. Bacterial contaminants from 102 routine sputum cultures were identified molecularly by 16S rRNA gene PCR and direct sequencing from contaminated Lowenstein-Jensen(LJ) slopes and BacT/Alert liquid medium. It was found that the contaminants from LJ slopes belonged to 11 different genera and were composed largely of Gram negative organisms (84.9%; 45/53), whereas the liquid culture contaminants belonged to 13 different genera, with 37/66 isolates (56.1%) being Gram negative. Pseudomonas aeruginosa was the dominant contaminant in both media. The effect of six different selective decontamination protocols was examined. Four of the six methods were effective at eliminating the culturable organisms present; these were 5% oxalic acid, 5% oxalic acid/2% NaOH, 5% oxalic acid/ 4% NaOH, and 1% chlorhexidine. NaOH at a concentration of 2 to 4% was less effective as it was unable to eliminated all organisms of each species tested, with the exception of P aeruginosa. In conclusion, breakthrough contamination of TB cultures is due to a diverse range of at least 17 different bacterial genera, with P aeruginosa and Staphylococcus epidermidis accounting for the dominant contaminating flora.. Employment of chemical decontaminating protocols solely involving NaOH may lead to higher rates of

contamination. Where such contamination is encountered, TB laboratories should consider the reprocessing of such sputum samples with an alternative decontamination method such as 1% chlorhexidine.
Comment: Are we to assume that the mycobacterial yield will not be affected?

JT

Treatment

Treatment of tuberculosis and optimal dosing schedules.

Chang et al Hong Kong China

Thorax 2011; 66: 997

Abstract: Intermittent tuberculosis treatment regimens have been developed to facilitate treatment supervision. Their efficacy has been substantiated by clinical trials and tuberculosis control programmes, notwithstanding the lack of head to head comparison between daily and intermittent regimens. Recently, there has been opposing evidence from observational studies, pharmacokinetic-pharmacodynamic studies and animal models that intermittent treatment increases the risk of relapse, treatment failure or acquired rifa mycin resistance, especially among HIV-infected patients. Systematic reviews have been conflicting. PubMed, OvidMEDLINE and EMBASE were systematically searched for publications in English to evaluate the evidence about dosing schedules and treatment efficacy. Levels of evidence and grades of recommendation were assigned largely according to clinical evidence with reference to the Scottish Intercollegiate Guidelines Network guideline development handbook. A total of 32 articles were included after excluding 331 ineligible articles, 8 controlled studies, 9 pharmacokinetic-pharmacodynamic studies, 5 mouse studies and 1 article about guinea pig experiments. Findings suggest high levels of evidence for using daily dosing schedules, especially during the initial phase in the presence of cavitation, isoniazid resistance and advanced HIV co-infection, to reduce the risk of treatment failure, recurrence and acquired drug resistance including acquired rifamycin resistance. This review justifies the use of daily schedules in standard tuberculosis treatment regimens (particularly in the initial phase), corroborates prevailing understanding of pharmacokinetics-pharmacodynamics and mycobacterial persisters, and supports exploration of rifapentine-containing regimens in higher dose and frequency.
Comment: Anyone who has been forced by necessity to use intermittent supervised treatment in the initial phase of therapy will find this review fits their personal impressions.

JT

Children

Advances in the diagnosis of pulmonary tuberculosis in HIV-infected and HIV-uninfected children.

Connell et al Melbourne Vic. Australia

J Infect Dis 2011; 204: S1151

Abstract: The identification of improved diagnostic tests for tuberculosis has been identified as a global research priority. Over the past decade, there has been renewed interest in the development and validation of novel diagnostic tools for pulmonary rtuberculosis that are applicable to resource-poor settings. These techniques are aimed primarily at improving the detection of the organism or a specific host immune response. Although most studies have focused on determining the accuracy of novel tests in adults, it is likely they will also have the capacity to significantly improve the diagnosis of childhood tuberculosis. Improving the quality of clinical samples obtained from children suspected of tuberculosis remains an important search priority while awaiting validation of novel diagnostic tests. This review will focus on a number of recent developments for the diagnosis of tuberculosis, with a special emphasis on the application of these new tests to children in settings where tuberculosis is endemic.
Comment: There is a great need for imaging techniques to detect intrathoracic disease, that do not expose the child to excessive ionizing radiation.

JT

Cavitating Pulmonary Tuberculosis
(courtesy IUATLD)