Correspondence

Dr Justin Denholm, Medical Director, Victorian Tuberculosis Program corrects an outdated assertion in the October 2015 Australian Tuberculosis Review. He writes: “For the record, the issue about Victoria not linking HIV and TB notifications is a historical anomaly now. When I took over the TB program last year, convincing the government to change this policy was the first item of business and now future reports will have full HIV/TB data included…..”

The Bali Declaration

The UIUAT& LD, Indonesian Ministry of Health and World Diabetes Foundation.

Bali November 2015

Tuberculosis and diabetes represent two of the greatest health challenges of our time, and their convergence globally represents a looming co-epidemic.

This looming co-epidemic represents progress against TB
Based on what we have learned from past co-epidemics, particularly TB/HIV, we must act early and decisively to avoid large numbers of avoidable deaths.

And Research:

From Bangkok the Treatment Action Group (TAG) have announced that funding for tuberculosis research fell US $ 1.3 billion short of global targets in 201. TB death rates have dropped 47% since 1990, but the disease still kills 4,000 people every day. In 2014, 480,000 people developed multidrug-resistant TB.

Editorial: The Bali declaration highlights what we have known for a long time, that diabetes mellitus is a risk factor for tuberculosis. In the past such a relationship was confined to wealthy countries where access to unlimited calories would lead to weight gain and type two diabetes. In the third world the equivalent groups were confined to a very small number of people. This is changing rapidly, where despite the persistence of extreme poverty, many more people are able to eat well, gain weight, become diabetic while at the same time be exposed to those with infectious tuberculosis. Such a phenomenon was described at the Bali conference when a study from India was presented. Over 50,000 people were screened for both diseases. 2.8% had suffered from TB and 5.9% had diabetes. Among TB patients, 26.4% had diabetes. We now know that patients with both diseases respond less well to antituberculosis therapy than those who are non-diabetic. They remain contagious for longer, sputum conversion may be delayed and relapse is more frequent. TB causes blood glucose levels to rise while such drugs as rifampicin makes diabetic control more difficult. Studies often show suboptimal blood levels of anti tuberculosis drugs when TB in diabetics is being treated. All this assumes that across the world those with the two diseases are being offered and take optimal therapy for both, but this far from certain. Closer to home, we know that diabetic control in our Indigenous population is far from optimal. It is a paradox, where poverty encourages TB and increasing affluence encourages diabetes. In wealthy countries big is no longer beautiful, but we must convince people in all countries that this is so and that in poor countries to be slim is to have prestige, and the large are the real losers.

Population studies

Comparison of characteristics and mortality in multidrug resistant (MDR) and non-MDR tuberculosis patients in China.

Sun et al Canberra & Melbourne, Australia

BMC Public Health 2015; 15: 1027

Background: We conducted a cohort study to compare the characteristics of MDR-TB with non-MDR-TB patients and to measure long term (9 year) mortality rate and determine factors associated with death in China.

Methods: We reviewed the medical records of 250 TB cases from a 2001 survey to compare 100 MDR-TB patients with 150 non-MDR-TB patients who were treated in 2001-2002. Baseline attributes extracted from the records were compared between the two cohorts and long term mortality and risk factors were determined at nine-year follow-up in 2010.

Results: Among the 234 patients successfully followed up, 63 (26.9%) were female and 171 (73.1%) were male. MDR-TB patients had poorer socio-economic status compared to non-MDRTB. Nine years after the diagnosis of TB, 69 or 29.5% of the 234 patients had died (32 or 21.6% of non-MDR-TB versus 37 or 43% of MDR-TB) and the overall mortality rate was 39/1000 per year (PY) (27/1000 PY among non-MDR versus 63/1000 PY among MDR-TB). Factors associated with death included MDR status (hazard ratio (HR): 1.86; CI: 1.09-3.13), limited education of primary school or lower (HR: 2.51; CI 1.34-4.70) and received TB treatment during the nine –year period (HR 1.82: 95%CI 1.02-3.26).

Conclusions: MDR-TB was a strong predictor for poor long term outcome. High quality diagnosis and treatment must be ensured. Greater reimbursement or free treatment may be needed to provide access for the poor and vulnerable populations and to treat treatment compliance.

Comment: 57% of MDR-TB still alive after 9 years is a surprisingly good result in those treated some 14 years ago as compared to other series of the time. It should remind us that these figures reflect pre-chemotherapy days when the same numbers might be alive after 9 years.

Diagnosis

Responding to cough presentations: an interview study with Cambodian pharmacies participating in a National Tuberculosis Referral Program.

Bell et al Sydney, Melbourne, Australia; Phnom Penh, Cambodia

J Eval Clin Pract 2015; Oct 8 Epub

Rationale, Aims and Objectives: Asia-Pacific carries a high burden of respiratory related mortality. Timely referral and detection of tuberculosis cases optimizes patient and public health outcomes. Registered private pharmacies in Cambodia in a
National Tuberculosis Referral Program to refer clients with cough suggestive of tuberculosis to public sector clinics for diagnosis and care. The objective of this study was to investigate clinical intentions of pharmacy staff when presented with a hypothetical case of a client with prolonged cough suggestive of tuberculosis.

Method: A random sample of 180 samples was selected. Trained interviewers administered a hypothetical case scenario to trained pharmacy staff. Participants provided "yes/no" responses to five clinical actions presented in the scenario. Actions were not mutually exclusive. Data were tabulated and compared using chi-square tests or Fisher's exact test.

Results: Overall, 156 (92%) participants would have referred the symptomatic client in the case scenario. Participants who would have referred the client were less likely to sell a cough medicine (42% vs 100%, P<0.001) and less likely to sell an antibiotic (19% vs 79%), P<0.001) than those who would not have referred the client.

Conclusion: Involving pharmacies in a referral program may have introduced concepts of appropriate clinical care when responding to clients presenting with cough suggestive of tuberculosis. However, results showed an enhancing clinical competence among all referral programme participants, particularly non-referring pharmacies and those making concurrent sales of cough-related products would optimize pharmacy-initiated referral. Further research into actual clinical practices at referral program pharmacies would be justified.

Comment: I wonder how many pharmacies referred people with cough to a private doctor.

The diagnosis of pleural effusion

Porcel et al  Leida, Spain; Perth Western Australia; Cape Town, South Africa; Nashville, TN, USA, Oxford, UK.

Expert Rev Respir Med 2015; Oct8; 1

Abstract: Pleural effusions arise from a variety of systemic, inflammatory, infectious and malignant conditions. Their precise etiological diagnosis depends on a combination of medical history, physical examination, imaging tests and pertinent pleural fluid analyses, including specific biomarkers (e.g. natriuretic hormones for heart failure, adenosine deaminase for tuberculosis or mesothelin for mesothelioma), invasive procedures, such as pleuroscopic biopsies, may be required for persistently symptomatic effusions which remain undiagnosed after the analysis of one or more pleural fluid samples. However, whenever parietal pleural nodularity or thickening exist, image –guided biopsies should first be attempted. This review addresses the current diagnostic approach to pleural effusions secondary to heart failure, pneumonia, cancer, tuberculosis and other less frequent conditions.

Comment: It is so important to follow investigations to diagnose a tuberculous pleural effusion to the end, since so many will spontaneously regress, then return as pulmonary involvement down the track.

Socio-cultural aspects

Sociocultural dimensions of tuberculosis: an overview of key concepts.

Mason et al Sydney, NSW, Melbourne, Victoria, Australia

Int J Tuberc Lung Dis 2015; 19: 1135

Abstract: Biomedical innovations are unlikely to provide effective and ethical tuberculosis (TB) control measures without complementary social science research. However, a strong interest in interdisciplinary work is often undermined by differences in language and concepts specific to each disciplinary approach. Accordingly, biological and social scientists need to learn how to communicate with each other. This article will outline key concepts relating to TB from medical anthropology and health sociology. Distilling these concepts in an introductory framework is intended to make this material accessible to researchers in laboratory, clinical and fieldwork settings, as well as encourage more social scientists to engage with TB research among target groups critical for successful programmatic interventions. For pedagogical purposes, the relevant concepts are grouped into three categories: 1) structures and settings, which includes overarching themes such as syndemics, local biologies, medicalisation, structural violence and surveillance: 2) practices and processes, encompassing gender, stigma, taboo, and victim blaming: and 3) experience and enculturation, which includes illness narratives, biographic disruption and dynamic nominalism. By helping to to navigate this literature, we hope to foster more cross-disciplinary conversations between qualitative and quantitative researchers. TB, a quintessential social disease, will be controlled more effectively using a multistranded research approach.

Comment: Many of us had to learn the hard way when coping with TB in Australian Aboriginal communities.

Are free anti-tuberculosis drugs enough? An empirical study from three cities in China.
Chen et al  Hong Kong, Beijing, Guangzhou, Kunshan, Wuhan, China: Durham, NC, USA; Brighton, UK.

Infect Dis Poverty 2015; 4: 47

Background: Tuberculosis (TB) patients in China still face a number of barriers in seeking diagnosis and treatment. There is evidence that the economic burden on TB patients and their households discourages treatment compliance.

Methods: A cross-sectional study was conducted in three cities of China. Patients were selected using probability proportional to size (PPS) cluster sampling of rural townships or urban streets, followed by list sampling from a patient register. Data were collected using a questionnaire survey, key informant interviews and focus group discussions with TB patients to gain an understanding of the economic burden of TB and implications of this burden for treatment compliance.

Results: A total of 797 patients were surveyed, of which 60 were interviewed in-depth following the survey. More than half had catastrophic health expenditure. TB patients with higher household income were less likely to report non-compliance (OR 0.355, 95% CI 0.140-0.830) and patients who felt that the economic burden relating to TB treatment was high, more likely to report non-compliance (OR 0.355, 95% CI 0.1278-21.999). The findings from the qualitative studies supported those from the survey.

Conclusion: The economic burden for TB patients in China. Reducing the cost of treatment and giving patients subsidies for transportation, lodging and food is likely to improve treatment compliance. Improving doctors’ salary system to cut off the revenue-orientated incentive, and expanding insurance’s coverage can be helpful to reduce patients’ actual burden or anticipated burden. Future research on this issue is needed.

Comment: Yet another study from China confirming the work of co-editor Sleigh et al on that topic.

Transmission
Review of economic evaluations of mask and respirator use for protection against respiratory infection transmission.

Mukerji et al Sydney, NSW, Australia

BMC Infect Dis 2015; 15: 413

Background: There has been increasing debate surrounding mask and respirator interventions to control respiratory infection transmission in both healthcare and community settings. As decision makers are considering the recommendations they should evaluate how to provide the most efficient protection with minimum cost. The aim of this review is to identify and evaluate the existing economic evaluation in this area and to offer advice on how future evaluations on this topic should be conducted.

Methods: We searched the Scopus database for all literature on economic evaluation or mask or respirator use to control respiratory infection transmission. Reference lists from the identified studies were also manually searched. Seven studies met our inclusion criteria from the initial 806 studies identified by the search strategy and our manual search.

Results: Five studies considered interventions for seasonal and/or pandemic influenza, with one also considering SARS (Severe Acute Respiratory Syndrome). The other two studies focused on tuberculosis transmission control interventions. The settings and methodologies of the studies varied greatly. No low-middle income settings were identified. Only one of the reviewed studies cited clinical evidence to inform their mask/respirator intervention effectiveness parameters. Mask and respirator interventions were generally reported by the study authors to be cost saving or cost effective when compared to no intervention or other control measures, however the evaluations had important limitations.

Conclusions: Given the large cost differential between masks and respirators, there is a need for more comprehensive economic evaluations to compare the relative costs and benefits of these interventions in situations and settings where alternative options are potentially applicable. There are at present insufficient well conducted cost-effectiveness studies to inform decision-makers on the value for money of alternative mask/ respirator options.

Comment: It is good to know that at present we don’t have to frighten our TB patients by wearing a respirator whenever we visit them. We must remember that pulmonary TB is far from the most contagious respiratory disease.

Spatiotemporal evidence for cross-border spread of MDR-TB along the Trans-Siberian Railway line.

Gurjav et al Sydney, NSW, Australia; Ulaanbaatar, Mongolia

Int J Tuber Lung Dis 2015; 19: 1376

Background: Mongolia has the fifth highest incidence of tuberculosis (TB) in the Western Pacific Region, with high rates of multidrug-resistant TB (MDR-TB).

Objective: To examine the recent spatiotemporal dynamics of MDR-TB in Mongolia.

Methods: All MDR-TB cases diagnosed from 2004 to 2012, identified from the National Tuberculosis Control Programme database, were included in the study. Cases diagnosed from 2006 to 2012 were further examined using spatial scan statistics.
Results: Few MDR-TB cases (n=29) were diagnosed before the programmatic management of MDR-TB was introduced in 2006. During 2006-2012, 1106 MDR-TB cases were detected, at an annualised rate of 5.9 cases per 100,000 population. Most (>80%) cases were identified in the 15-44 year age group, 45% were among those aged 15-29 years. Case notification rates were highest in the capital city, Ulaanbaatar, with an increasing trend over time in all locations. Three MDR-TB hotspots were identified, all in close proximity to the Trans-Siberian Railway line. The majority of the MDR-TB isolates were resistant to all first-line drugs tested.

Conclusion: Spatiotemporal analysis indicates likely cross-border spread of MDR-TB along the Trans-Siberian Railway line, with subsequent spatial expansion across Mongolia. The frequency of MDR-TB among young patients with pan-resistance to all first-line drugs suggests ongoing MDR-TB transmission within the community.

Comment: Presumably it has been possible to carry out sensitivity tests on the sputa of Mongolians, at least since 2004, and this in itself is a considerable advance.

JT

Children

The epidemiology of tuberculosis in children in Australian, 2003-2012

Teo et al Sydney, NSW, Melbourne, Vic., Darwin, NT, Australia

Med J Aust 2015; 203: 440

Objective: To describe the burden of and trends in paediatric tuberculosis (TB) in Australia between 2003 and 2012.


Results: TB notifications in Australia during the study period included 538 children (range, 37-66 cases per year), representing 4.6% of the total TB case load during the period (3.8%-5.8% each year). Place of birth was recorded for 524 patients (97.4%); of these 230 943.9%) were born in Australia, 294 (56.1%) overseas. The average annual notification rate was 1.31 (95%CI 1.120-1.43) cases per 100,000 child population. The rate was higher for overseas born than for Australian-born children (9.7 [95% CI 8.5110.73] v 0.61 [95%CI 0.53-0.69]) per 100,000 children. The overall rate was highest among those aged 0-4 years. The annual notification rate was three times higher for Indigenous children than for non-Indigenous Australian-born children Of 427 patients (79.4% of total) for whom the method of case detection was recorded, 37.0% were detected by contact screening, 8.7% by post-arrival immigration screening, and 54.3% by passive case detection. Pulmonary TB was the most common diagnostic classification (64.7% of patients). The most common risk factors were close contact with a TB case and recent residence in a country with a high incidence of TB. Treatment outcomes were satisfactory; 89.1% of children had completed treatment or were cured.

Conclusions: The burden of paediatric TB in Australia is low but has not changed over the past decade. The highest rates are among children born overseas, emphasizing the important role of immigration screening as Australia aspires to eliminate TB.

Comment: No surprises here.

JT

No added value of interferon-gamma-release to a prediction model for childhood tuberculosis.

Togun et al Banjul, The Gambia; Dunedin, New Zealand; London, UK.

Eur Resp J 2015; Oct 22

Abstract: The predictive value of a combination of clinical and radiological features with interferon-gamma-release assay (IGRA) for diagnosis of active tuberculosis (TB) disease among TB-exposed is unknown. 150 symptomatic HIV-negative children (aged 3 months to 14 years), prospectively recruited through active contact tracing, were included. Backward stepwise logistic regression and bootstrapping techniques were used for the development and internal validation of a clinical prediction model for active TB disease. Model discrimination and incremental value of a positive IGRA test were assessed by area under the receiver operating characteristic curve (AUC). 35 (23%) children were diagnosed with active TB disease and started on treatment and 115 (77%) had other respiratory tract infections. A final parsimonious model clinical model, comprising age <5 years (adjusted OR 4.8, 95% CI 2.0-11.5) and lymphadenopathy on clinical examination (aOR 4.9, 95% CI 1.8-13.0) discriminated active TB disease from other disease with an AUC of 0.70 (95% CI 0.61-0.80). A positive IGRA result did not improve the discriminatory ability of the model (c-statistic 0.72 versus 0.70; p =0.644). A clinical algorithm, including age ≤5 years and lymphadenopathy classified 70% of active TB disease among symptomatic TB-exposed children. IGRA does not add any discriminatory value to this prediction model.

Comment: But then these TB-exposed children will have IGRA testing as well as TST, anyway. It is helpful that the authors do differentiate between infection and disease.

JT
Mycobacteria-specific cytokine responses detect tuberculosis infection and distinguish latent from active tuberculosis.

Tebruegge et al  Melbourne, Vic, Australia; Southampton, UK: Basel, Switzerland; Cape Town, South Africa. Am J Respir Crit Care Med 2015; 192: 485

Rationale: Current immunodiagnostic tests for tuberculosis (TB), including the tuberculin skin test and IFN-gamma release assay (IGRA) have significant limitations, which include their inability to distinguish between latent TB infection (LTBI) and active TB, a distinction critical for clinical management.

Objectives: To identify mycobacteria-specific cytokine biomarkers that characterize TB infection, determine their diagnostic performance characteristics, and establish whether biomarkers can distinguish between LTBI and active TB.

Methods: A total of 149 children investigated for TB infection were recruited; all participants underwent a tuberculin skin test and QuantiFERON-TB Gold assay. In parallel, whole blood assays using early secretory antigenic target-6 (ESAT-6), culture filtrate protein-10 (CFP-10), and PPD as stimulatory antigens were undertaken and cytokine responses were determined by xMAP multiplex assays.

Measurements and Main Results: IFN-gamma, interferon-inducible protein-10 (IP-10), tumor necrosis factor (TNF)-alpha, IL-1ra, IL-2, IL-13, and MIP-1 beta (macrophage inflammatory protein-1beta) responses were significantly higher in LTBI and active TB cases than in TB-uninfected individuals irrespective of the stimulant. Receiver operating characteristic analyses showed that IP-10, TNF-alpha, and IL-2 responses achieved high sensitivity and specificity for the distinction between TB-uninfected and TB-infected individuals. TNF-alpha, IL-1ra, and IL-10 responses had the greatest ability to distinguish between LTBI and active TB cases; the combinations of TNF-alpha/IL-1ra and TNF-alpha/IL-10 achieved correct classification of 95.5% and 100% of cases, respectively.

Conclusions: We identified several mycobacteria-specific cytokine biomarkers with the potential to be exploited for immunodiagnosis. Incorporation of these biomarkers into future immunodiagnostic assays for TB could result in substantial gains in sensitivity and allow the distinction between LTBI and active TB based on a blood tests alone.

Comment: if this study can be confirmed by a larger sample, we are seeing a major break through in diagnosis.

Control

Controlling the seed beds of tuberculosis: diagnosis and treatment of tuberculosis infection.

Rangaka et al  London, UK: Cape Town, Soweto, South Africa; Rio de Janeiro, Brazil; Sydney, Australia; Phnom Penh, Cambodia; Chennai, India; Baltimore, MD, USA. Lancet 2015; Oct 23

Abstract: The billions of people with latent tuberculosis infection serve as the seedbeds for future cases of active tuberculosis. Virtually all episodes of tuberculosis disease are preceded by a period of asymptomatic Mycobacterium tuberculosis infection; therefore, identifying infected individuals most likely to progress to disease and treating such subclinical infections to prevent future disease provides a crucial opportunity to interrupt tuberculosis transmission and reduce the global burden of tuberculosis disease. Programmes focusing on single strategies rather than comprehensive programmes that deliver an integrated arsenal for tuberculosis control might continue to struggle. Tuberculosis preventive therapy is a poorly used method that is essential for controlling the reservoirs of disease that drive the epidemic. Comprehensive control strategies that combine preventive therapy for the most high risk populations and communities with improved case-finding and treatment, control of transmission and health systems strengthening could ultimately lead to tuberculosis elimination. In this Series paper we outline challenges to implementation of preventive therapy and provide pragmatic suggestions for overcoming them. We further advocate for tuberculosis preventive therapy as the core of a renewed worldwide focus to implement a comprehensive epidemic control strategy that would reduce new tuberculosis cases to elimination targets. This strategy would be underpinned by accelerated research to further understand the biology of subclinical tuberculosis infections, develop novel diagnostics and drug regimens specifically for subclinical tuberculosis infection, strengthen health systems and community engagement and enhance sustainable large scale implementation of preventive therapy programmes.

Comment: A unique international consensus to call us to arms.

JT

Microbiology

False-negative BD MGIT™ TBc Identification results in routine
tuberculosis diagnosis: a New Zealand perspective.

Basu et al  Auckland  New Zealand

Int J Tuberc Lung Dis 2015; 19: 1073

Abstract: We previously reported on a comparison of the AccuProbe ® GenProbe ®, MTBC assay (AccuProbe) (BioMerieux, Marcy L’Etoile, France) with the Becton Dickinson (BD MGIT ™ TBc identification (TBc) Test (BD, Franklin Lakes, NJ, USA) in our laboratory. In the period following the shift from the Accuprobe assay to the TBc test, we obtained six false-negative tests. On sequencing the mpt64 gene, we found that these false negative cases had mutations in the mpt64, due to deletion, insertion or substitution. Despite the occurrence of false-negative results, we found that the reduced cost and minimal technical expertise, combined with a new testing algorithm, still make this test the preferred option for rapidly identifying Mycobacterium tuberculosis complex in MGIT cultures in a low TB burden country.

Comment: We continue to search for the perfect test, but we will continue to be misled if we ignore the clinical context.

JT

Prevention:

Fluoroquinolone therapy for the prevention of multidrug-resistant tuberculosis in children.

Fox et al  Montreal, Quebec, Canada

Am J Respir Crit Care Med 2015; 192: 229

Rationale: Fluoroquinolone (FQN) therapy of latent tuberculosis infection among contacts of individuals with multidrug-resistant tuberculosis (MDR-TB) is controversial.

Objectives: To determine the potential benefits, risks (including acquired FQN resistance) and cost-effectiveness of FQN therapy to prevent TB in contacts of individuals with MDR-TB.

Methods: We used decision analysis to estimate costs and outcomes associated with no therapy compared with a 6-month course of daily FQN therapy to treat latent TB infection in contacts of individuals with MDR-TB, MDR-TB with FQN resistance, TB-related death, quality-adjusted life years, and health system costs.

Measurements and Main Results: FQN preventive therapy resulted in health system savings, lower incidence of MDR-TB, and lower mortality than no treatment. We found the incidence of MDR-TB with acquired FQN resistance would also be lower with FQN therapy of infected contacts.

Conclusions: In our model, FQN preventive therapy resulted in substantial health systems savings and in reduced mortality, incidence of MDR-TB, and incidence of acquired FQN-resistant disease as well as improved quality of life. FQN therapy remained cost saving with improved outcomes even if the effectiveness of therapy in preventing MDR-TB was as low as 10%.

Comment: It seems like sex months of FQN is the universal panacea.

JT

Genomic expression catalogue of a global collection of BCG vaccine strains show evidence for highly diverged metabolic and cell-wall adaptations.

Abdallah et al  Jeddah, Saudi Arabia; Sydney, NSW, Australia; Cambridge & London, UK; Amsterdam, the Netherlands; Paris, France; Montreal, Canada; Sapporo, Japan.

Sci Rep 2015; 5: 15443

Abstract: Although Bacillus Calmette-Guerin (BCG) vaccines against tuberculosis have been available for more than 90 years, their effectiveness has been hindered by variable protective efficacy and a lack of lasting memory responses. One factor contributing to this variability may be the diversity of the BCG strains that are used around the world, in part from genomic changes accumulated during vaccine production and their resulting differences in gene expression. We have compared the genomes and transcriptomes of a global collection of fourteen of the most widely used BCG strains at single base pair resolution. We have also used quantitative proteomics to identify key differences in expression of proteins across five representative BCG strains of the four tandem duplication (DU) groups. We provide a comprehensive map of single nucleotide polymorphisms (SNPs), copy number variation and insertions and deletions (Indels) across fourteen BCG strains. Genome-wide SNP characterization allowed the construction of a new and robust phylogenetic genealogy of BCG strains. Transcriptional and proteomic profiling revealed a metabolic remodeling in BCG strains that may be reflected by altered immunogenicity and possibly vaccine efficacy. Together, these integrated –omic data represent the most comprehensive catalogue of genetic variation across a global collection of BCG strains.

Comment: This takes the study of the heterogeneity of BCG strains to new levels. We had all known of this heterogeneity by differences in vaccine efficacy and TST reactivity after vaccination.

JT

Cell Pathology
Mycobacterium-infected Dendritic cells Disseminate Granulomatous Inflammation.

Harding et al Maddison, Wis, USA

Sci Rep 2015; 5: 15248

Abstract: The disappearance and reformation of granulomas during tuberculosis has been described using PET/CT/X-ray in both human clinical settings and animal models, but the mechanisms of granuloma reformation during active disease remains unclear. Granulomas can recruit inflammatory dendritic cells (iDCs) that can regulate local T-cell responses and can carry bacteria into the lymph nodes, which is crucial for generating systemic T-cell responses against mycobacteria. Here, we report that a subset of mycobacterium-infected iDC are associated with bacteria-specific T-cells in infected tissue, outside the granuloma, and that this results in the formation of new and/or larger multi-focal lesions. Mycobacterium-infected iDCs express less CCR7 and migrate less efficiently compared to the non-infected iDCs, which may support T-cell capture in granulomatous tissue. Capture may reduce antigen availability in the lymph node, thereby decreasing systemic priming, resulting in a possible regulatory loop between systemic T-cell responses and granuloma reformation. T-cell-infected iDC clusters outside the granuloma can be detected during the acute and chronic phase of BCG and Mtb infection. Our studies suggest a direct role for inflammatory dendritic cells in the dissemination of granulomatous inflammation.

Comment: Given the role dendritic cells play in cellular immunity, this finding seems a paradox. JT

Treatment

Phenothiazines as a solution for multidrug-resistant tuberculosis: from the origin to present.

Kristiansen et al Odense, Grasten, Copenhagen, Denmark; Kalkota, India

Int Microbiol 2015; 18: 1

Abstract: Historically, multiplicity of actions in synthetic compounds is a rule rather than exception. The science of non-antibiotics evolved in this background. From the antimalarial and antitrypanosomal dye methylene blue, chemically similar compounds, the phenothiazines, were developed. The phenothiazines were first recognised for their antipsychotic properties, but soon after their antimicrobial functions came to be known and then such compounds were designated as non-antibiotics. The emergence of highly drug-resistant bacteria had initiated an urgent need to search for novel affordable compounds. Several phenothiazines awakened the interest among scientists to determine their antimycobacterial activity. Chlorpromazine, trifluoperazine, methdilazine and thioridazine were found to have distinct antitubercular activity. Thioridazine took the lead as researchers repeatedly claimed its potentiality. Although Thioridazine is known for its central nervous system and cardiototoxic side-effects, extensive and repeated in vitro and in vivo studies by several research groups revealed a very small dose of thioridazine is required to kill tubercle bacilli within macrophages in the lungs, where the bacteria try to remain and multiply silently. Such a small dose is devoid of its adverse side-effects. Recent studies have shown that the (-) thioridazine is a more active antimicrobial agent and devoid of the toxic side-effects normally encountered. This review describes the possibilities of bringing down thioridazine and its (-) form to be combined with other antitubercular drugs to treat infections by drug-resistant strains of Mycobacterium tuberculosis and try to eradicate this deadly disease.

Comment: I wonder how many other derivatives of aniline dyes could be active against tubercle bacilli?

Directly observed therapy for treating tuberculosis

Karumi et al Kampala, Uganda

Cochrane Database Syst Rev 2015; 5: CD00343

Background: Tuberculosis (TB) requires at least six months of treatment. If treatment is incomplete, patients may not be cured and drug resistance may develop. Directly Observed Therapy (DOT) is a specific strategy, endorsed by the World Health Organisation, to improve adherence by requiring health workers, community volunteers or family members to observe and record patients taking each dose.

Objectives: To evaluate DOT compared to self-administered therapy in people on treatment for active TB or on prophylaxis to prevent active disease. We also compared the effects of different forms of DOT.

Search Methods: We searched the following databases up to 13 January 2015: the Cochrane Infectious Diseases Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library; MEDLINE; EMBASE; LILACS and mRCT. We also checked article reference lists and contacted relevant researchers and organizations.

Selection Criteria: Randomized controlled trials (RCTs) and quasi-RCTs comparing DOT with routine self-administration or prophylaxis at home.

Data Collection and Analysis: Two review authors independently assessed risk of bias of each included
trial and extracted data. We compared interventions using risk ratios (RR) with 95% confidence intervals (CI). We used a random-effects model if meta-analysis was appropriate, but heterogeneity present (I^2 statistic > 50%). We assessed the quality of the evidence using the GRADE approach.

**Main Results:** Eleven trials including 5662 participants met the inclusion criteria. DOT was performed by a range of people (nurses, community health workers, family members or former TB patients) in a variety of settings (clinic, the patient’s home or the home of a community volunteer). DOT versus self-administered therapy in South Africa, Thailand, Taiwan and Pakistan compared DOT with self-administered therapy for treatment. Trials included DOT at home by family members, community health workers (who were usually supervised), DOT at home by health staff and DOT at health facilities. TB cure was low with self administration across all studies (range 41% to 67%) and direct observation did not improve this (1.08, 95% CI 0.91-1.27; five trials, 1645 participants, moderate quality evidence). In a subgroup analysis stratified by the frequency of contact between health services in the self treatment arm, daily DOT may improve TB cure when compared to self-administered treatment where patients in the self-administered only visited the clinic every month (RR 1.15; 95% CI 1.06-1.25; two trials, 900 participants); but with contact in the control becoming more frequent, this small effect was not apparent (every two weeks: RR 0.96, 95% CI 0.83-1.12; one trial, 497 participants; every week; RR 0.90; 95% CI 0.68-1.21; two trials, 248 participants). Treatment completion showed a similar pattern, ranging from 59% to 78% in the self treatment groups, and direct observation did not improve this (RR 1.07; 95% CI 0.96-1.19; six trials, 1839 participants, moderate quality evidence). DOT at home versus DOT at health facility in four trials that compared DOT at home by family members, or community health workers, with DOT by health workers at a health facility there was little or no difference in cure or treatment completion (cure RR 1.02; 95% CI 0.88-1.18, four trials, 1556 participants, moderate quality evidence; treatment completion, RR 1.04; 95% CI 0.91-1.17, three trials, 1029 participants, moderate quality evidence). DOT by family member versus DOT by community health workers. There was also little or no difference in cure or treatment completion (cure RR 1.02; 95% CI 0.86-1.21; two trials, 1493 participants, moderate quality evidence; completion: RR 1.05; 95% CI 0.90-1.22, two trials, 1493 participants, low quality evidence). Specific patient categories. A trial of 300 intravenous drug users in the USA evaluated direct observation with no observation in TB prophylaxis to prevent active disease and showed little difference in treatment completion (RR 1.0, 95% CI 0.88 to 1.13; one trial, 300 participants, low quality evidence).

**Authors’ Conclusions:** From the existing trials, DOT did not a solution to poor adherence in TB treatment. Given the large resource and cost implications of DOT, policy makers might want to reconsider strategies that depend on direct observation. Other options might want into account financial and logistic barriers to care, approaches that motivate patients and staff; and defaulter follow-up.

**Comment:** There seems to be one problem with the selection of patients for these trials and that is the low rate of cure in those participants from Australia and Taiwan, rates not reflected in both nations’ official statistics.

**Imaging**

**MR spectroscopy of intracranial tuberculomas: a singlet peak at 3.8 ppm as potential marker to differentiate them from malignant tumors.**

**Morales et al Cincinnati, OH, USA; Lima, Peru; Marbella, Spain.**

**Neuroradiol J 2015; 28: 294**

**Purpose:** The diagnosis of intracranial tuberculomas is often challenging. Our purpose is to describe the most common metabolic patterns of tuberculomas by MR spectroscopy (MRS) with emphasis on potential specific markers.

**Methods:** Single-voxel MRS short echo time was performed in 13 cases of tuberculosis proven by histology and/or response to antimycobacterial therapy. For comparison MRS was also performed in 19 biopsy malignant tumours (13 high-grade gliomas and six metastases). Presence of metabolic peaks was assessed visually and categoric variables between groups were compared using chi-square. Metabolite ratios were compared using Mann-Whitney test and diagnostic accuracy of the metabolite ratios was compared using receiver-operating characteristic (ROC) curves analysis.

**Results:** Spectroscopic peaks representing lipids and glutamate/glutamine (Glx) as well as a peak at ~3.8 ppm were well defined in 77% (10/13), 77% (10/13) and 69% (9/13) of tuberculomas, respectively. Lipid and Glx peaks were also present in most of the malignant lesions, 79% (15/19) and 74% (14/19), respectively. However, a peak at ~3.8 ppm was present in only 10% (2/19) of the tumor cases (P<0.001). Higher Cho/Cr and ml/Cr ratios helped discrimination malignant lesions with an area under the ROC curve of 0.86 (SE= 0.078, p<0.002, CI 0.7-1.0) and 0.8 (SE 0.1, p<0.009, CI 0.6-1) respectively. Threshold values between 1.7-1.9 for Cho/Cr and 0.8-0.9 for ml/Cr provided high specificity (91% for both metabolites) and adequate sensitivity (75% and 80%, respectively) for discrimination of malignant lesions.

**Conclusion:** A singlet peak at ~3.8 ppm is present in the majority of tuberculomas and absent in most malignant tumors, potentially a marker to differentiate these lesions. The assignment of the peak is difficult from our analysis; however guanidinoacetate is a
possibility. Higher Cho/Cr and ml/Cr ratios should favor malignant lesions over tuberculomas. The presence of lipids and Glx is non-specific.

Comment: Is the sensitivity enough to avoid brain biopsy? JT

Extrapulmonary tuberculosis

Is abdominal tuberculosis a surgical problem?

Pattanayak et al Beranpore, India

Introduction: Abdominal tuberculosis (TB) has always been a diagnostic challenge, even for the astute surgeon. In developing countries, extrapulmonary TB often presents as an acute abdomen in surgical emergencies such as perforations and obstructions of the gut. Abdominal TB in different forms has been more often as an aetiology for the chronic abdomen. This paper aims to evaluate TB as a surgical problem.

Methods: a comprehensive review of the literature on abdominal TB was undertaken. PubMed searches for articles listing abdominal TB / different types / diagnosis/treatment (1980-2012) were performed.

Results: TB is still a global health problem and the abdomen is one of the most common sites of extrapulmonary TB. Presentation may vary from an acute abdomen to a number of chronic presentations, which can mimic other abdominal diseases. While some may benefit from antitubercular therapy, others may develop surgical problems such as strictures or obstruction, which may necessitate surgical intervention.

Conclusions: Abdominal TB should always be considered one of the differential diagnoses of acute or chronic abdomen in endemic areas.

Comment: The authors don’t mention Tuberculosis ascites which like tuberculous pleural effusion may go into remission even without treatment, only to return as more aggressive disease later. JT

TB and HIV


Van Halsema et al London, UK: Johannesburg, South Africa

J Acquir Immune Defic Syndr 2015; 70: 104

Abstract: Clinical features of tuberculosis influence infectiousness. This cross-sectional study examined the effect of combination antiretroviral therapy (cART) and CD4 on sputum smear positivity (SS+) and pulmonary cavitation among 1589 (1189/1589HIV-positive) miners in South Africa. Proportions SS+ varied nonlinearly by CD4 with greatest proportions SS+ (55.3%) in the lowest stratum (<100 cells microgram / L) Adjusted prevalence ratio for SS+: on vs. off cart 0.9 (95% CI 0.73-1.11) Proportions with cavitation varied linearly with CD4, with no independent cart effect (adjusted prevalence ratio 1.17; 95% CI 0.80- 1.71). cart did not independently affect SS+ or cavitation but may increase infectiousness through CD4 recovery.

Comment:- This study may have implications for length of isolation following onset of treatment. JT

Case Finding

Supplemental use of an interferon - gamma release assay in a state-wide tuberculosis contact tracing program in Victoria: a six –year study.

Goebel et al Melbourne, Vic, Australia

Comm Dis Intell 2015; 39: e191

Introduction: Tuberculin skin testing (TST) has been the accepted Australian standard for investigating contacts following exposure to infectious tuberculosis (TB). In recent years, the availability of the interferon-gamma release assays (IGRAs) has introduced a potential alternative test but data on its use in this context are limited.

Methods: A prospective longitudinal cohort study was conducted from 2008- 2013 to review the use of IGRA and subsequent TB disease following testing in a state-wide contact tracing program. Additional information on the experience and acceptability of of IGRA in this context was also obtained through program staff reviews following implementation.

Results: IGRA testing was performed on 643 contacts, with a mean follow -up of 3.7 years.. IGRA was primarily used to supplement TST, most commonly due to borderline TST reactivity in individuals who had Calmette- Guerin vaccination. Where both TST and IGRA were performed, correlation of test results was poor (kappa= 0.35). The negative predictive for the later development of active TB was 99.5%.

Conclusions: Our experience suggests that IGRA are able to be incorporated safely and effectively as a supplement to TST based contact tracing.

Comment: This supplementation should become routine in all contact investigations in Australia and countries that can afford it. The study seems to show that a TST induration of 15mm or more correlates better with a positive IGRA. JT
Acquired resistance to Bedaquiline and Delamanid in therapy for tuberculosis.

Bloemberg et al Zurich, Basel, Davos, Switzerland

NEJM 2015; 373: 1956

Letter: Multidrug-resistant tuberculosis (MDR-TB) and extensively resistant tuberculosis (XDR-TB) are an increasing public health threat. Bedaquiline and Delamanid are two drugs that were recently approved by the Food and Drug Administration for treatment of MDR-TB and XDR-TB. Here we describe the stepwise amplification of drug resistance in a patient who had emigrated from Tibet to Switzerland in December 2010 and who presented to a Swiss hospital with pre-extensively drug-resistant tuberculosis at that time. Genome sequencing revealed that the initial Mycobacterium tuberculosis isolate harboured nine mutations in genes associated with resistance to seven drugs. The isolate also showed a compensatory mutation in rpoC, indicating a “mature” pre-extensively drug resistant strain that had evolved under drug pressure for some time. Given that the patient reported no previous treatment for tuberculosis, he was probably infected with a strain that was already resistant to these drugs. In November, Bedaquiline was added to the regimen, which had consisted of four drugs (ethambutol, aminosalicylic acid*, intravenous capreomycin and cycloserine). The patient was considered to be clinically cured in March 2013, but he had a relapse in August 2013. Genome sequencing of five follow-up isolates revealed a mutation in mmpfR that was associated with Bedaquiline resistance. The mutation persisted even though Bedaquiline was discontinued in February 2012; this suggests it did not cause any clinically significant reduction of the infecting bacteria. Additional resistance to second-line injectable agents (like capreomycin) also developed. This was reflected in the emergence of mutations in tlyA and rrs. The latter mutation remained at low frequency and was detected only in drug containing bacterial cultures. All the molecular findings were supported by phenotypic drug-susceptibility testing. Following the amplification in resistance, Delamanid was added to the regimen in March 2014. However, two mutations fbiA and fgb1 increased in frequency by June 2014, which coincided with the emergence of phenotypic resistance to Delamanid. These genes have previously been associated with Delamanid resistance. The fgd1 mutation increased in frequency thereafter indicating the presence of multiple Delamanid-resistant clones in the patient. In August and September 2014, the patient underwent a lobectomy. After surgery, the sputum specimens obtained from the patient were culture-negative and the patient received treatment on an ambulatory basis.

This case highlights the development of resistance in the context of inadequate MDR-TB and XDR-TB treatment regimens, despite personalized care in a well-resourced health-care setting. It serves as a warning for the future roll-out of new antituberculosis drugs and emphasizes the need for the use of appropriate companion drugs when Bedaquiline and Delamanid are administered. Our results add to previous findings showing that the development of drug resistance is a dynamic process involving multiple heterogeneous populations of bacteria within individual patients.

* Known as PAS

Comment: M.tuberculosis seems to do better than humans in the process of natural selection.

JT

Cavitating Pulmonary Tuberculosis (courtesy IUATLD)