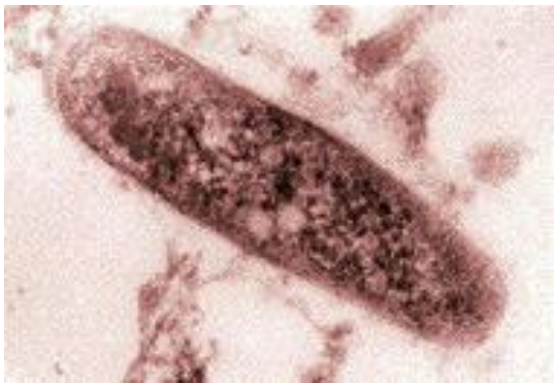
The Australian Tuberculosis Review

June 2016



M. tuberculosis EM Photo

Forthcoming Meetings

47th Union World conference on Lung Health 26-29 October 2016 Liverpool, United Kingdom

6th Conference of The Union Asia Pacific Region 22-25 March 2017
Tokyo International Forum
Tokyo, Japan Coordinating Organisation: Japan Anti-Tuberculosis Association

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Contents:

Research

The association between exaggeration in health related science news and academic press releases: retrospective observational study.

Sumner et al Cardiff, Swansea, UK; Sydney, Wollongong, NSW, Australia.

BMJ 2014;349: g7015

Objective: To identify the source (press releases or news) of distortions, exaggerations or changes to the main conclusions drawn from research that could potentially influence a reader's health-related behavior.
Design: Retrospective quantitative content analysis.
Setting: Journal articles, press releases and related news with accompanying simulations.
Sample: Press releases (n=462) on biomedical and health related science issued by 20 leading UK universities in 2011, alongside their associated peer reviewed research papers and news stories (n=668).
Main outcome measures: Advice to readers to change behavior, causal statements drawn from correlational research, and inferences to humans from animal research that went beyond those in associated peer reviewed papers
Results: 40% (95% CI 33%-46%) of the press releases contained exaggerated advice, 33% (26%-40%) contained exaggerated causal claims, and 36% (28%-46%) contained exaggerated inference to humans from animal research. When press releases contained such exaggeration, 58% (48%-68%), 81% (70%-93%)and 86% (77%-95%)of news stories respectively, contained similar exaggeration, compared with exaggeration rates of 17% (10%-24%), 18% (9%-27%) and 10% (0-19%) in news where the press releases were not exaggerated. Odds ratios for each categories of analysis were 6.5% (95% CI 3.5 to 12), 20 (7.6 to

51) and 56 (15 to 211). At the same time there was little evidence that exaggeration in press releases increased the uptake of news.
Conclusions: Exaggeration in news is strongly associated with exaggeration in press releases. Improving of academic press releases could represent a key opportunity for reducing misleading health related news.
Comment: This study confirms what we have long suspected.

JT

TB and HIV

Tuberculosis-related mortality in people living with HIV in Europe and Latin America: an international cohort study.

Podlekareva et al HIV Study Group Eurocord

The Lancet HIV 2016; March e 120

Background: Tuberculosis in patients with HIV in Eastern Europe is complicated by the high prevalence of drug-resistant tuberculosis, low rates of drug-susceptibility testing and poor access to antiretroviral therapy (ART), We report 1 year mortality estimates from a multi-region Eastern Europe, Western Europe and Latin American prospective cohort study: the TB: HIV Study.
Methods: Consecutive HIV-positive patients aged 16 years or older with a diagnosis of tuberculosis were enrolled from 62 tuberculosis and HIV clinics in 19 countries in Eastern Europe, Western Europe and Latin America, The primary endpoint was death within 12 months after stating anti-tuberculosis treatment; all deaths were classified according to whether or not they were tuberculosis related. Follow-up was until death, the visit or 12 months after baseline, whichever occurred first. Risk factors for all-cause and tuberculosis –related deaths were assessed using Kaplan-Meier estimates and Cox models.
Findings: Of 1406 patients (834 in Eastern Europe, 317 in Western Europe and 255 in Latin America, 264 (19%) died within 12 months. 188 (71%) of these deaths were tuberculosis related. The probability of all cause death was 21%(95% CI 26-32) in Eastern Europe, 4% in Western Europe (95% CI 3-7)and 11% in Latin America (95% CI 8-16) ($p<0.0001$) and the corresponding probabilities of tuberculosis deaths were 23% (20-26), 1% (0-3), and 4% (2-8), respectively ($p<0.0001$). Patients receiving care outside Eastern Europe had a 77% decreased risk of death; adjusted HR 0.23(95% CI 0.16-0.31) compared with patients who started a regimen with at least 3 active anti-tuberculosis drugs, Those who started fewer than 3 anti tuberculosis drugs, were at a higher risk of tuberculosis related death (aHR 3.17; 95% CI 1.83-5.49)(as were those who did not have baseline drug susceptibility tests (2.24; 1.31-3.83). Other prognostic factors for tuberculosis-related mortality were disseminated tuberculosis and a low CD4 cell count. 18% of patients were receiving ART at time of diagnosis in Eastern Europe compared with 44 % in Western Europe and 39% in Latin Europe ($p< 0.0001$) 12 months later the proportions were 67 % in Eastern Europe, 92% in Western Europe and 85% in Latin America ($p< 0.0001$)
Interpretation: Patients with HIV and tuberculosis in Eastern Europe have a risk of death nearly 4 times than that in patients from Western Europe and Latin America. This increased mortality rate is associated with modifiable risk factors such as lack if drug-susceptibility testing and suboptimal initial anti tuberculosis drug treatment in settings with a high proportion of drug resistance. Urgent action is needed to improve tuberculosis care for patients living with HIV in Eastern Europe.
Comment: The fall of Communism may have brought many benefits to the citizens of eastern European countries, but not in the control of contagious diseases such as TB and HIV, especially in their prison systems.

JT

Isoniazid exposure and pyridoxine levels in human immunodeficiency virus associated with distal sensory neuropathy.

Van de Watt Cape Town, South Africa; Miami, Fl, Atlanta. Ga, USA

Int J Tuberc Lung Dis 2015; 19:1312

Setting: Distal sensory polyneuropathy (DSP) may manifest in human immunodeficiency virus (HIV) infected individuals before or after antiretroviral therapy (ART). DSP can also occur in response to isoniazid (INH): this can be prevented by pyridoxine supplementation. N-acetyltransferase 2 (NAT2) polymorphisms influence drug acetylation and possibly the risk for INH-associated DSP.
Objective: To investigate the relationship between previous/current TB, pyridoxine deficiency and DSP in HIV-infected individuals enrolled in a government sponsored HIV programmed.
Design: Neuropathy assessments were performed among 159 adults pre-ART and 12 and 24 weeks thereafter. DSP was defined as >1 neuropathic

symptoms and sign. NAT2 genotypes predicted acetylation phenotype. Serum pyridoxine levels (PLP) were quantified at baseline and week 12.
Results: DSP was present in 16% of individuals pre-ART and was associated with previous/current TB ($p = 0.020$). Over 50% were pyridoxine deficient (PLP <25 nmol/L, despite supplementation with vitamin B complex (2-4 mgs/day pyridoxine). Those with a history of TB and pre-ART were more likely to be pyridoxine deficient ($p = 0.029$) , and slow/intermediate phenotypes impacted on their PLP levels. Incident/worsening DSP after ART developed in 21 % of the participants. PLP levels remained low after ART, particularly in those with prior TB, but without an association between DSP and NAT2 phenotypes.
Conclusion: Adequate pyridoxine supplementation before ART initiation should be prioritized, particularly in those with a history of TB or current TB.
Comment: A study done in Madras (Chennai) in 1963 suggested that the daily dose of pyridoxine should not be less than 6 mg, nor exceed 25mg.

JT

Tuberculosis and HIV co-infection in Vietnam.

Trinh et al Sydney, NSW, Australia; Hanoi, Vietnam; Paris, France.

Int J Infect Dis 2016; 46: 58

Introduction: Tuberculosis (TB) and human immunodeficiency virus (HIV) infection are leading causes of disease and death in Vietnam, but TB/HIV disease trends and the profile of co-infected patients are poorly described.
Methods: We examined national TB and HIV notification data to provide a geographic overview and describe relevant disease trends within Vietnam. We also compared the demographic and clinical profiles of TB patients with and without HIV infection.
Results: During the past 10 years (2005-3015) cumulative HIV case numbers and deaths increased to 298,151 and 71,332 respectively, but access to antiretroviral therapy (ART) improved and new infections and deaths declined. From 2011-2014 routine HIV testing increased from 58.1% to 72.5% and of all TB patients diagnosed with HIV in 2014, 2,803 (72.4%) received ART. The number of multidrug resistant (MDR)-TB cases enrolled for treatment increased almost 3-fold (578 to 1532) from 2011 to 2014. The rate of HIV co-infection in MDR and non-MDR TB cases 51/1532; 3.3% vs 3774/100,555; 3.8%; OR 0.77, 95% CI 0.7-1.2) was similar in 2014.
Conclusions: The care of TB/HIV co-infected patients have shown sustained improvement in Vietnam. Rising numbers of MDR-TB cases is a concern, but this this not driven by HIV co-infection.
Comment: We are not told how many TB isolates are of the Beijing stain and more likely to cause death.

JT

Infection:

Risk of active tuberculosis in the 5 years following infection….15%?

Trauer et al Melbourne, Vic; Townsville, Qld, Australia.

Chest 2016; 149: 516

Background: It is often stated that the lifetime risk of developing active TB after an index infection is 5% to 10%, one half of which accrues in the 2 to 5 years following infection.
Methods: This study included close contacts of individuals with active pulmonary tuberculosis notified in the Australian state of Victoria from January 1 2005 to December 31, 2013, who we deemed to have been infected as a result of their exposure. Survival analysis was first performed on the assumption of complete follow-up through to the end of the study period. The analysis was then repeated with imputation of censorship for migration, death and preventive treatment, using local mortality and migration data combined with programmatic data on the administration of preventive therapy.
Results: Of 613 infected close contacts, 67(10.9%) developed active TB during the study period. Assuming complete follow-up, the 1,650-day cumulative hazard was 11.5% (95% CI, 8.9-14.1). with imputation of censorship for death, migration and preventive therapy, the median 1,650 cumulative hazard over 10,000 simulations was 14.5 (95 % CI, 11.1-17.2). Most risk accrued in the first 5 months after infection and risk was greatest in the group aged less than 5 years, reaching 56% with imputation, but it was also elevated in older children (27.6% in the group 5-15%)
Conclusions: The risk of active TB following infection is several –fold than traditionally accepted estimates, and is particularly high immediately following infection and in children.
Comment: A figure of 50% for infants has been noted before, but not as much as 27.6% for older children. Presumably the vast majority of index cases would have been come from countries where TB and HIV were prevalent., although the numbers

of HIV positive cases introduced to Australia are sill small. However, the tuberculin used in the original studies was very different from that now available, so the accurate diagnosis of infection might be suspect. Finally, an Australia-wide study of this kind, where more subjects can be recruited, is essential.

JT

Initiation and completion rates for latent tuberculosis infection treatment: a systematic review.

Sandgren et al Stockholm, Sweden; Rotterdam, the Netherlands.

BMC Infect Dis 2016; 16: 204

Background: Control of latent tuberculosis infection (LTBI) is an important step towards tuberculosis admission. Preventive treatment will prevent the the development of disease in most cases of diagnosed with LTBI. However, low initiation and completion rates affect the effectiveness of preventive treatment. The objective was to systematically review data on initiation rates and completion rates for LTBI treatment regimens in the general population and specific populations with LTBI.
Methods: A systematic review of the literature (PubMed, Embase) published up to February 2014 was performed.
Results: Forty-five studies on initiation rates and 83 studies on completion rates of LTB treatment were found. These studies provided initiation rates (IR) and completion rates (CT) in people with LTBI among the general population (IR 26-99%, CR 39-96%),case contacts (IR 34-40-95%,48-82%), healthcare worker (IR47-98%CR 17-79%), the homeless (IR 34-90%, CR 23-71%, people who inject drugs(IR 52-91%, CR 38-89%), HIV-infected individuals (IR 67-92%, CR 55-95%), inmates (IR 7-90%, CR 4-100 %), Immigrants (IR 23-97%, CR 7-86%) and patients with comorbidities (IR 82-93, CR75-92%). Generally, completion rates were higher for short than for long LTBI treatment regimens.
Conclusion: Initiation and completion rates for LTBI treatment regimens were frequently suboptimal and varied greatly within and across different populations.
Comment: No great surprises here, but how some studies reached 90+% CR, (one, even 100%) needs further analysis .

JT

Population Studies

Mortality among tuberculosis cases in Victoria, 2002-2013: case fatality and factors associated with death.

Dale et al Melbourne, Vic., Australia

Int J Tuberc Lung Dis 2016; 20: 515

Setting: The state of Victoria, Australia, is an industrialized setting with low tuberculosis (TB) incidence, universal health care and high levels of migration.
Objective: To assess case fatality rates (CFRs) and factors associated with death in a cohort of TB cases notified between 2002 and 2013.
Design: Retrospective cohort study. Cases who died untreated or during treatment were reviewed to determine whether TB was a primary cause of, contributed to, or was unrelated to death. Descriptive and multivariate analyses were used to compare demographic, clinical and pathological characteristics.
Results: Of 3056 cases, 198 (5.0%) died of any cause. TB was the primary cause of death in 99 cases (50.3%) and contributed to death in a further 34 cases, giving a TB-related (CFR) of 3.4%. In multivariate analysis, TB-related mortality reduced over time, and was positively associated with male sex, older age, history of substance abuse and disseminated or meningeal TB. Factors associated with survival included having a history of past travel to or residence in a high TB risk country, lymph node TB or extrapulmonary TB manifestations, excluding meningeal, genitourinary, pleural and lymph node TB.
Conclusions: TB CFRs in this setting are among the lowest reported globally. TB mortality steadily decreased from 2002 to 2013.
Comment: I assume the reference to lymph node TB on two occasions referred to intrathoracic and extrathoracic node TB. There was a time when having your scrofula touched by a monarch was associated with survival.

JT

Causes of death in Vanuatu

Carter et al Noumea, New Caledonia; Port Vila, Vanuatu; Canberra, Brisbane, Melbourne, Sydney, Australia

Popul Health Metr 2016; 14:7

Background: The population of the Pacific Melanesian country of Vanuatu was 234,000 at the

2009 census. Apart from subsistence activities, economic activity includes tourism and agriculture. Current completeness of vital registration is considered too low to be useable for national statistics; mortality and life expectancy (LE) are derived from indirect demographic estimates from censuses/surveys. Some cause of death (CoD) data are available to provide information on major causes of premature death.
Methods: Deaths 2001-2007 were coded for cause (ICDv10) for ages 0-59 years from hospital separations (HS) (n=636), hospital medical certificates (MC) of death and monthly reports from community health facilities (CHF) (n=1,169). Ill-defined causes were 3% for hospital deaths and 20% from CHF. Proportional mortality was calculated by cause (excluding ill-defined) and age 0-4,5-14 years and also by sex for 15-59 years. From total deaths by broad age group and sex from 1999 and 2009 census analyses, community deaths were estimated.by a weighted average of MC and CHF deaths..
Results: National estimates indicate main causes of death <5 years perinatal disorders (45%) and malaria, diarrhea and pneumonia (27%). For 15-59 years, main causes of male deaths were circulatory disease 27%, neoplasms 13%, injury 13%, liver disease 19%, infection 18%, diabetes 7% and chronic respiratory disease 7%; and for females: neoplasms 29%, circulatory disease 15%, diabetes10%, infection 9% and maternal deaths 8%. Infection included **tuberculosis,** malaria and viral hepatitis. Liver disease (including hepatitis and cancer) accounted for 18% of deaths in adult males and 9% in females. Non-communicable disease (NCD) including circulatory disease and chronic respiratory disease accounted for 52% of premature deaths in adult males and 60 % in adult females. Injuries accounted for 13 % in adult males 6% in adult females. Maternal deaths translate into
an annual maternal mortality ratio of 130/100.000 for the period.
Conclusion: Vanuatu manifests a double burden of disease with significant proportional mortality from perinatal disorders and infection/pneumonia <5 years and maternal mortality, coupled with significant proportional mortality in adults (15-59 years) from cardiovascular disease (CVD), neoplasms and diabetes.
Comment: It would appear that tuberculosis is seriously underreported.

JT

The burden of drug-resistant tuberculosis in Papua New Guinea: results of a large population – based survey.

Aia et al Port Moresby, New Guinea; Brisbane, Qld, Australia; London, UK; Geneva, Switzerland; Manila, Philippines.

PLoS One 2016; 11: e0149806

Background: Reliable estimates of the burden of multidrug-resistant tuberculosis (MDR-TB) are crucial for effective control and prevention of tuberculosis (TB). Papua New Guinea is a high TB burden country with limited information on the magnitude of the MDR-TB problem.
Methods: A cross-sectional study was conducted in four PNG provinces: Madang, Morobe, National Capital District and Western Province. Patient sputum samples were tested for rifampicin resistance by the Xpert MTB/RIF and those showing the presence of resistance underwent phenotypic susceptibility to first and second –line anti-TB drugs including streptomycin, isoniazid, rifampicin, ethambutol, pyrazinamide, ofloxacin, amikacin, kanamycin and capreomycin.
Results: Among 1182 TB patients enrolled in the study, MDR-TB was detected in 20 new cases (2.7%:95%CI 1.1-4.3) and 24 previously treated (19.1; 95% CI 8.5-29.5%) TB cases. No case of extremely drug-resistant TB (XDR-TB was detected. Thirty percent (6/20) of new and 33.3% (8/24) of previously treated with MDR-TB were detected in a single cluster in Western Province.
Conclusion: In PNG the proportion of MDR-TB in new cases is slightly lower than the regional average of 4.4% (95%CI 2.6-6.3%). A large proportion of MDR-TB cases were identified from a single hospital in Western Province, suggesting that the prevalence of MDR-TB across the country is heterogeneous. Future surveys surveys should further explore this finding. The survey also helped strengthen the use of smear microscopy and Xpert MTB/RIF testing as diagnostic tools for TB in the country.
Comment: From the experience of Papuans in the Western Province who flocked to the Torres Straits to have their drug –sensitive TB treated, this region of PNG had a TB control program which was one of the worst in the country. Let's hope the injection of Australian money and resources into Daru and the Western Province for TB control will prove useful.

Drug Reactions

Baseline abnormal liver function tests are more important than age in the development of isoniazid-induced hepatoxicity for patients receiving preventive therapy for latent tuberculosis infection.

Gray et al Sydney, NSW, Australia

Int Med J 2016; 46: 281

Background: One of the cornerstones of Australia's public health programs to eliminate tuberculosis (TB) is the identification and treatment of latent tuberculosis infection (LTBI)
Aims: the aim of this study is to determine demographics, compliance, completion rates and adverse events of patients on preventive therapy (PT) for LTBI at our institution. The secondary aim is to determine he rates of isoniazid hepatoxicity and identify any contributory factors.
Methods: The method used was an audit using medical records of 120 consecutive patients. (2010-2014) treated with PT for LTBI.
Results: Seventy two patients with confirmed with LTBI started 9 months of INH and 22 started 4 months on rifampicin (RIF). The median age was 30 years. Half the patients were born in high TB prevalence countries. Fifty six percent were contacts of index cases with confirmed TB, and 26% were pre-immunosuppression. Seventy seven percent completed therapy with adequate compliance. Thirty three per cent on isoniazid and twenty three percent on RIF experienced some liver function test abnormality while on treatment. INH was ceased in 3 % due to asymptomatic hepatitis (transaminases > 5times upper limit of normal). No patients had permanent liver damage. Significant risk factors for liver dysfunction were risks for liver disease (p=0.03) or abnormal pre-therapy LFT (P<0.001), No patients developed active TB.
Conclusion: The completion rate of 77% and rate of INH induced hepatic dysfunction of 3% is compatible with the literature. We found no age association with the risk of INH-induced hepatic dysfunction, however, there was a significant and linear association with the degree of liver dysfunction during INH therapy and the presence of abnormal baseline LFT. Routine LFT monitoring allowed early cessation of INH in those with significant but asymptomatic hepatitis who did not meet criteria for ATS/ CDC LFT monitoring.
Comment: If base line LFTs are abnormal should we be treating with INH anyway? In those circumstances it seems illogical to continue serial liver function tests, particularly as we know that most who develop abnormal LFTs during treatment will see them return to normal even if the drug is continued.

Molecular Studies

Mycobacterium tuberculosis whole genome sequencing and protein structure modelling provides insights into anti-tuberculosis drug resistance.

Phelan et al Sydney, NSW, Australia; London, Cambridge, UK; Cape Town, South Africa; Belo Horizonte, Brazil; Antwerp, Belgium; Thuwal, Saudi Arabia; Geneva, Switzerland
BMC Med 2016; 14: 31

Background: Combating the spread of drug resistant tuberculosis is a global health priority. Whole genome association are being applied to identify genetic determinants of resistance to anti-tuberculosis drugs. Protein structure and interaction modelling are used to understand the functional effects of putative mutative mutations and provide insight into the molecular mechanisms leading to resistance.
Methods: To investigate the potential utility of these approaches, we analysed the genomes of 144 Mycobacterium tuberculosis clinical isolates from the Special Programme for Research and Training in Tropical Diseases (TDR) collection sourced from 20 countries in four continents. A genome-wide approach was applied to 127 isolates was applied to to identify polymorphisms associated with MICs for first –line anti-tuberculosis drugs. In addition, the effect of identified candidate mutations on protein stability and interactions were assessed quantitatively with established computational methods.
Results: The analysis revealed thar mutations in the genes rpoB (rifampicin), katG (isoniazid), inhA-promotor (isoniazid) rpsL (streptomycin) and embB (ethambutol) were responsible for the majority of resistance observed. A subset of the mutations identified in rpoB and katG were predicted to affect protein stability. Further, a strong correlation was observed between the MIC values and the distance of the mutated residues in the three-dimensional structures of rpoB and katG to their respective drugs binding sites.
Conclusions: Using the TDR resource, we demonstrate the usefulness of whole genome association and convergent evolution approaches to detect known and potentially novel mutations

associated with drug resistance. Further, protein structural modelling could provide a means of predicting the impact of polymorphisms on drug efficacy in the absence of phenotypic data. These approaches could ultimately lead to novel resistance mutations to improve the design of tuberculosis control measures, such as diagnostics, and inform patient management.
Comment: Provided the cost of new diagnostics falls within the budget of those countries that need them most.

JT

Children

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

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

Med J Aust 2015; 203: 440

Objective: To describe the burden and trends in paediatric tuberculosis (TB) in Australia between 2003 and 2012.
Design: A retrospective analysis of TB data from the the National Notifiable Diseases Surveillance System (NNDSS) on TB in children (under 15 years of age) during the 10-year period, 2003-2012.
Results: TB notifications in Australia during the study period included 538 children (range, 37-66 cases per year), representing a 4.6% of the total case load during the period (range 3.8%-5.8% each year). Place of birth was recorded for 524 (97.4%); of these 230 (43.9%) were born in Australia, 294 (56.1%) overseas. The average annual notification rate was 1.31 (95% CI 1.20-1.43) cases per 100,000 child population. The rate was highest for overseas-born than for Australian-born children, (9.57 [95% CI 8.51-10.73] v 0.61[95% CI 0.53-0.69]) cases per 100,000 children. The overall rate was highest among those aged 0-4 years. The annual notification was three times higher for Indigenous children than for nonindigenous Australia 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, 8.78% by post-arrival immigration screening and 54.3% by passive case detection. Pulmonary tuberculosis 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; 89.4% 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: At least this should involve clinical assessment and concurrent blood and intradermal screenings.

JT

Dilemma of managing asymptomatic children referred with "culture-confirmed" drug-resistant tuberculosis.

Loveday et al Tygerberg, Durban, South Africa; Sydney, NSW, Australia; Bronx, NY, USA

Arch Dis Child 2016; April: pii

Background: The diagnosis of drug-resistant tuberculosis (DR-TB) in children is challenging and treatment is associated with many adverse effects.
Objective: We aimed to assess if careful observation, without initiation of second-line treatment is safe in asymptomatic children referred with "culture –confirmed ".DR-TB
Setting: KwaZulu-Natal, South Africa, an area with high burdens of HIV, TB and DR-TB.
Design, Intervention and Main Outcome Measures: We performed an outcome review of children with "culture-confirmed" DR-TB who were not initiated on second-line TB treatment, as they were asymptomatic with normal chest radiographs on examination at our specialist referral hospital. Children were followed up every other month for the first year, with a final outcome assessment at the end of the study.
Results: In total, 43 asymptomatic children with normal chest radiographs were reviewed. The median length of follow-up until final evaluation was 549 days (IQR 259-722days); most (34; 83%) children were HIV uninfected. Resistance patterns included 9 (21%) monoresistant and 34 (79%) multidrug-resistant (MDR) strains. Fifteen children (35%) had been treated with first-line TB treatment, prior to presentation to our referral hospital. At the final evaluation, 34 (80%) children were well. 7(16%) were lost to follow- up. 1 (2%) received MDR-TB treatment and 1 (2%) died of unknown causes. The child who received MDR-TB treatment developed new symptoms at the 12 – month review and responded well to second line-treatment.

Conclusions: Bacteriological evaluation should not be performed in the absence of any clinical indication. If drug-resistance Mycobacterium tuberculosis is detected in an asymptomatic child with a normal chest radiograph, close observation may be appropriate strategy, especially in settings where potential laboratory error and poor record keeping are constant challenges.
Comment: Before nuclear studies were available, false positive cultures were not rare, but a trip to the laboratory concerned usually resolved the problem without subjecting the patient to prolonged follow-up.

JT

Treatment:

Dry powder inhalable formulations for anti-tubercular therapy.

Parumasivum et al Sydney, NSW, Australia; Amman, Jordan

Adv Drug Deliv Rev 2016; May 17: pii S0169

Abstract: Tuberculosis (TB) is an intracellular infectious disease caused by the airborne bacterium, Mycobacterium tuberculosis. Despite considerable research efforts, the treatment of TB continues to be a great challenge in part due to the requirement of prolonged therapy with multiple high-dose drugs and associated side effects. The delivery of pharmacological agents directly to the respiratory system, following the natural route of infection, represents a logical therapeutic approach for treatment or vaccination against TB. Pulmonary delivery is non-invasive, avoids first–pass metabolism in the liver and enables targeting of therapeutic agents to the infection site. Inhaled delivery also potentially reduces the dose requirement and the accompanying side-effects.. Dry powder is a stable formulation of drug that can be stored without refrigeration compared to liquids and suspensions. The dry powder inhalers are easy to use and suitable for high-dose formulations. This review focuses on the current innovations of inhalable dry powder formulations of drug and vaccine delivery for TB, including the powder production method, preclinical and clinical evaluations of inhaled dry powder over the last decade. Finally the risks associated with pulmonary therapy are addressed. A novel dry powder formulation with high percentages of respirable particles coupled with a cost effective inhaler device is an appealing platform for a TB drug delivery.

Comment: If inhalable rifampicin was used, it would obviate the need to ingest it on an empty stomach.

JT

A pharmacokinetic evaluation of sulfamethoxazole 800 mgs once daily in the the treatment of tuberculosis.

Alsaad et al Groningen, Nijmegen, Bilthoven, The Netherlands.

Antimicrob Agents Chemother 2016; Apr 11.

Abstract: For treatment of multidrug-resistant tuberculosis (MDR-TB) there is a scarcity of antituberculosis drugs. Co-trimoxazole is one of the available drug candidates and already frequently co-prescribed in TB-HIV co-infected patients. However, only limited data are available on pharmacokinetic (PK) and pharmacokinetic (PD) parameters of co-trimoxazole in TB patients. The objective of this study was to evaluate PK parameters and in vitro PD data of the effective part of co-trimoxazole; sulfamethoxazole. In a prospective PK study in patients with drug-susceptible TB (age>18), SXTwas administered in a dose of 960 mg daily. One-compartment population
Pharmacokinetic modelling was performed using Mw (pound) harm3.81 (Mediware Groningen, the Netherlands). The *f*AUC/MIC ratio and the and the timeperiod in which the free concentration exceeded the MIC (T>MIC) were calculated. Twelve patients received 960 mgs co-trimoxazole on top of first line drugs. The pharmacokinetic parameters of the population model were as follows (geometric mean+/- SD: metabolic clearance (CLm) 1.57+/- L/h, volume of distribution (Vd) 0.03+/_0.13, gamma distribution rate constant (Ktr_po 2.18+/- 1.143, gamma distribution shape factor (n__po) 2.15 +/- 0.39. Free fraction of sulfamethoxazole was 0.3, but ranged between 0.2-0.4. The median value of the MICs was 9.5 mg/L (IQR 4.75-9.5) and of *f* AUC/MIC was 14.3(IQR 13.0-17.5). The percentage of *f* T> MIC ranged between 43 and 100% of the dosing interval, The PK and PD data from this study are useful to explore a future dosing regimen of cotrimoxazole for MDR-TB treatment.
Comment: There seems to be some confusion over what dose of sulfamethoxazole the patients were given. The standard dose is 800 mg daily.

JT

WHO recommends rapid test, shorter drug regimen for MDR-TB

Brooks M Geneva

Medscape.com 2016; 19 May

The World Health Organisation (WHO) today issued new recommendations designed to speed up detection and improve treatment of multidrug-resistant tuberculosis (MDR-TB), The recommendations call for use of a novel rapid diagnostic to rule out resistance to second-line drugs and a shorter cheaper regimen for MDR-TB. The new treatment regimen can be completed in 9 to 12 months, rather than the typical 18 to 24 months, and is less expensive than current regimens.

The shorter regimen is recommended for patients with uncomplicated MDR-TB; for example, those individuals whose MDR-TB is not resistant to the more important second-line drugs used to treat MDR-TB (fluoroquinolones and injectables). The shorter regimen is also recommended for people who have not yet been treated with second-line drugs.

The shorter regimen includes an intensive treatment phase, lasting 4 to 6 months and consisting of four second –line drugs, and a continuation phase lasting 5 months and composed of two drugs. The seven recommended drugs are kanamycin, moxifloxacin, prothionamide, clofazamine, pyrazinamide, high dose isoniazid and ethambutol. The recommendations on the shorter regimens are based of initial studies involving 1200 patients with uncomplicated MDR-TB in 10 countries, and are expected to benefit the majority with MDR-TB worldwide. However, there are serious risks for worsening resistance if the shorter regimen is used inappropriately (ie in patients with extensively drug-resistant (XDR-TB).

The WHO also recommends national TB reference laboratories now use a novel rapid diagnostic to rule out resistance to to second-line drugs. The DNA-based test called MTBDRs1 identifies genetic mutations in MDR-TB strains, rendering them resistant to fluoroquinolones and injectable second-line drugs. This test yields results in just 24-48 hours down from the 3 months or longer as currently required. The much faster turnaround time means that MDR-TB patients with additional resistance are not only diagnosed more quickly, but can be placed on appropriate second-line regimens. The MTBDRsI test is also a critical prerequisite for identifying patients with MDR-TB eligible for the new shorter treatment regimen, while avoiding putting patients who have resistance to second-line drugs on the shorter regimen which could contribute to the development of XDR-TB.

Comment: Presumably one would administer the Xpert RIF test first.

JT

Comparison of effectiveness and safety of imipenin/clavulanate versus meropenem/clavulanate containing regimens in the treatment of MDR-and XDR-TB.

Tiberi et al Sassari, Rome, Brescia, Varese, Italy; London, UK;Lugano, Switzerland; Sao Paulo, Brazil; Paris, France; Lima, Peru; Groningen, Hague, The Netherlands; Las Palmas, Spain; Athens, Greece; Minsk, Belarus; Ruzomberok,Slovakia; Guayaquil, Ecuador; Brussels, Belgium.

Eur Respir J 2016; Apr 13

Abstract: No large study to date has ever evaluated the effectiveness, safety and tolerability of imipenim/clavulanate versus meropenem/ clavulanate to treat multidrug –and extensively drug-resistant tuberculosis (MDR-TB and XDR-TB. The aim of this observational study was to compare the therapeutic contribution of imipenin/clavanulute versus meropenem/ clavanulate added to back-ground regimens to treat MDR-and XDR-TB.\ cases. 84 patients treated with imipenem/clavulanate containing regimens showed a similar median number of antibiotic resistances (8 versus 8) but more fluoroquinolone resistance (79% versus 48.9%, p, 0.0001) and higher XDR-TB prevalence (67.9% versus 49.0 %, P=0.01) in comparison with 96 patients exposed to meropenem/clavulanate containing regimens. Patients were treated with imipenem/clavulanate and meropenem/clavulanate= containing regimens for a median (interquartile range (of 187 (60-428) versus 85 (49-156) days, respectively. Statistically significantly differences were observed on sputum smear and culture conversion rates (79.7% versus 94.8%, p= 0.03) and 71.9% versus 94.8 % p< 0.0001, respectively) and on success rates (59.7% versus77.5%, p=0.03. Adverse events to imipenem/clavulanate and meropenem/clavulanate were reported in 5.4% and 6.5% of cases only. Our study suggests that meropenem/clavulanate is more effective than imipenem/clavulanate in treating M/XDR –TB patients.

Comment : It would be reassuring to compare the results from individual centers.

JT

Propensity score-based approaches to confounding by indication in individual patients data meta-analysis: non-standardised treatment for multidrug resistant tuberculosis.

Fox et al Sydney, NSW, Australia; Montreal, Canada.

PLOS one 2016; March 29

Background: In the absence of randomized clinical trials, meta-analysis of individual patient data (IPD) from observational studies may provide the most accurate effect estimates for an intervention. However, confounding by indication remains an important concern that can be addressed by incorporating individual patient covariates in different ways. We compared different analytic approaches to account for confounding in IPD from patients for multidrug-resistant tuberculosis.
Methods: Two antibiotic classes were evaluated; fluoroquinolones-considered the cornerstone of effective MDR-TB treatment.- and macrolides, which are known to be safe, yet are ineffective in vitro. The primary outcome was treatment success against treatment failure failure, relapse or death. Effect estimates were obtained using multivariate and propensity-score- based approaches.
Results: Fluoroquinolone antibiotics were used in 28 included studies, within which 6612 patients received a fluoroquinolone and 723 patients did not. Macrolides were used in 15 included studies, within which 459 patients received this class of antibiotic 3670 did not. Both standard multivariable regression and propensity score–based methods resulted in similar effect estimates for early and late generation fluoroquinolone, while macrolide antibiotics use was associated with reduced treatment success.
Conclusions: In the individual patient data meta-analysis, standard multivariate and propensity – score based methods of adjusting for individual patient covariates for observational studies yielded produced similar estimates. Even when such adjustment is made for potential confounding, interpretation of adjusted estimates must still consider the potential for residual bias.
Comment: We ae reminded that statistical analysis has not yet reached perfection.

JT

Extrapulmonary tuberculosis

High rate of drug resistance among tuberculous meningitis cases in Shaanxi province, China.

Wang et al Xi'an, Shaanxi, Kunming, Yunnan, Beijing, PR China; Sydney, NSW, Australia.

Sci Rep 2016; 6: 25251

Abstract: The clinical and mycobacterial features of tuberculous meningitis (TBM) cases in China are not well described, especially in western provinces with poor tuberculosis control. We prospectively enrolled patients in whom TBM was considered in Shaanxi province, northwestern China, over a two-year period (September 2010 to December 2012). Cerebrospinal fluid specimens were cultured for Mycobacterium tuberculosis, with phenotypic and genotypic drug susceptibility testing (DST), as well as genotyping of all positive cultures. Among 350 patients included in the study, 27(7.7%) had culture confirmed TBM; 84 (24.0%) had probable and 239 (68.4%) had possible TBM. DST was performed on 25/27 (92.3%) culture positive ; 12/25 (48.0%) had "any resistance" detected and 3 (12.0 %) were multidrug resistant (MDR). Demographic and clinical features of drug resistant and drug susceptible TBM were similar. Beijing was the most common (20/25; 80.0%) with 9/20 (45%)exhibiting drug drug resistance; including all 3 MDR strains. All (4/4) isoniazid resistant strains had mutations in the katG gene. 75% (3/4) of strains with phenotypic rifampin resistance had mutations in the rpoB gene detected by Xprt MTB/RIF. High rates of drug resistance were found among culture- confirmed TBM cases; most were Beijing strains.
Comment: The absolute numbers of those resistant seem rather small. How many of the probable and possible responded to treatment.

JT

Safety and efficacy of additional levofloxacin in tuberculous meningitis: a randomized controlled pilot study.

Kalita et al Lucknow, Uttar Pradesh, India.

Tuberculosis (Edin) 2016; 98: 1

Background: Levofloxacin is an effective bactericidal category 111 antitubercular drug. There is paucity of studies comparing the role of additional levofloxacin to standard antitubercular regimen in the patients with tuberculous meningitis (TBM).
Aims: To compare the safety and efficacy of adding levofloxacin to standard four drug ATT regimen (RHZE)
Subjects and Methods: The patients with TBM diagnosed on the basis of clinical, cerebrospinal (CSF) and MRI criteria were included. Children below 15 years, patients with pregnancy, seizures, liver failure, kidney failure and malignancy were excluded. The baseline clinical, CSF and MRI characteristics were noted and consciousness was evaluated by Glasgow Coma Scale (GCS). The patients were randomized to RHZE (rifampicin, isoniazid, pyrazinamide and ethambutol) RHZEL (RHZE and levofloxacin) groups. Outcome was defined at 6 months. Primary outcome was death and secondary outcomes were disability as assessed by Barthel Index score and adverse events.
Results: Out of 110 TBM patients screened, 57 fulfilled the inclusion criteria. Their median age was 35 (15-75) years. 29 patients received RHZEL and 28 RHZE. The baseline clinical , biochemical and MRI characteristics were similar in both groups. At 6 months, 11 (19.3%) patients died, 38 (66.76%) had good and 7 (12.3%) poor outcome. There was insignificant survival benefit in RHZEL group compared to RHZE (HR- 2.61, 95%CI 0.73-9.36, P=0.14, 25% patients died in RHZE whereas 13.8% in RHZEL group. The disability was not significantly different between the two groups. The composite side effects were also similar between the two groups except for a higher frequency of seizures
In RHZEL group (5 vs 0) which resulted in withdrawal of levofloxacin.
Conclusion: There was insignificant survival benefit in RHZEL which was associated with high frequency of seizures.
Comment: A disappointing result, although larger number may have shown a difference. I am pleased to see the authors using the long authorized abbreviations for antituberculosis drugs, now generally neglected.

JT

Risk Factors

Risk of tuberculosis after lung transplantation: the value of pretransplant chest computed tomography and the impact of m TOR inhibitors and azathioprine use.

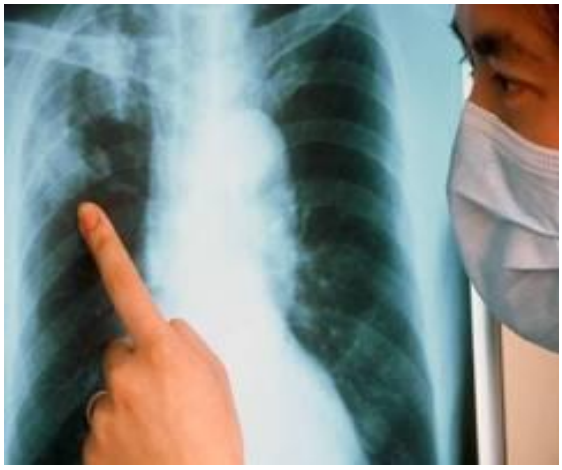
Guirao-Arrabal et al Cordoba, Spain

Transpl Infect Dis 2016; May 25

Background: It is necessary to determine the incidence and risk factors for tuberculosis (TB), as well as strategies to assess and treat latent tuberculosis infection (LTBI) in lung transplant recipients.
Methods: A retrospective cohort study of 398 lung transplant recipients was performed. Episodes of TB were studied and the incidence rate was calculated. Logistic regression analysis was used to analyzed specific variables as potential risk factors for TB.
Results: Median follow-up was 558 days (1-6636). Six cases (1.5%) of TB were documented in 398 transplant patients The incidence density was 406.3 cases/100,000 patient years (95% CI 154.7-845), which is higher than in the general population (13.1cases/100,000 person years). All cases occurred in the period 1993-2006 when the tuberculin skin test (TST) and treatment of LTBI in positive TST were not part of the protocol. Pretransplant computed tomography(CT) showed residual lesions in 50% of patients who developed TB, although the TST was negative and the chest radiograph was inconclusive. Multivariate analysis identified the presence of residual lesions in the pretransplant chest CT (OR 11.5, 85%CI 1.9-69.1, P=0.008), use of azathioprine (OR 10.6, 95% CI 1.1-99, P= 0.038), and use of everolimus (OR 6.7, 95% CI1.1-39.8, P=0.036) as independent risk factors
Conclusions: Residual lesions in the pretransplant chest CTs and the use of azathioprine and nTOR inhibitors are associated with the risk of TB.
Comment: It is not clear that the authors have made a case for routine CT chest scan of candidates for organ transplant, particularly in countries with a low TB incidence.

JT

Laboratory Studies



Thermostability of IFN-Gamma and IP-10 release assays for latent infection with Mycobacterium tuberculosis: A Tbnet study.

Blauenfeldt et al Copenhagen,Hillerod, Roskild, Denmark; Freiburg, Borstel, Lubeck, Germany; Windhoek, Namibia; Stockholm, Sweden; Porto, Portugal; St Gallen, Switzerland; Badalona, Spain.

Tuberculosis (Edin) 2016; 98: 7

Introduction: Interferon-gamma (INF-gamma inducible protein 10kD (IP-10) and IFN-gamma release assays (IGRAs) are immunodiagnostic tests aiming to identify the presense of specific cellilar immune responses, interpreted as markers for latent infection with Mycobacterium tuberculosis. Incubation at higher temperatures could affectIFN-gamma and IP-10 responsiveness in order to Improve the performance of IP-10 release assays ans IGRAs.
Aim; The aim of this study was to assess the robstmess of whole blood based IP-10 release assay and IGRAs and the effet of hyperthermic incubation (39 C) on the diagnostic accuracyof IP-10 release assay and IGRAs.
Results: We included 65 patients with confirmed pulmonary tuberculosis and 160 healthy controls from 8 European countries collaborating in the Tbnet. In patients, IP=10 responses increased 1.07 (IQR 0.90-1.36) fold and IFN-gamma decreased 0.88 (IQR0.57-1.02(fold with 39 C compared to 37 C incubation temperature. At 37 C IGRA sensitivity was 85% and IP-10 sensitivity was 82%, whereas specificity was 97% for both tests ($p>0.8$). These minor changes observed as a result of hyperthermic incubation were not sufficient to impact IGRA and IP-10 release assay test performance.
Conclusion: The performance of IGRA and IP-10 release assays is robust despite variations in the incubation temperature between 37 C and 39 C.
Comment: Are we to conclude that if these tests ever became available in the primary health care center , room temperature would not matter.

JT

Cavitating PTB- courtesy IUATLD