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Welcome to this edition of the Respiratory Research Review and thank you for the feedback.

"TB anywhere, TB everywhere" – this was the motto of the last WHO World TB day. It seems timely to review the data on increasing TB drug resistance in the United Kingdom. Researchers from Japan, Canada, America, France and Germany apply themselves to improving our control and early detection programmes, in particular the use of gamma interferon-based systems.

In this edition of the Respiratory Research Review, we also review new evidence in the management of pulmonary embolism and the disappointing outcome of combination therapy for smoking cessation.

Kind regards,

Dr Lutz Beckett

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Serodiagnosis of MAC pulmonary disease using an enzyme immunoassay kit

Authors: Kitada S et al

Summary: The usefulness of an enzyme immunoassay-based serological test for diagnosing *Mycobacterium avium*-complex (MAC) pulmonary disease and distinguishing it from other lung diseases was investigated in this study. Serum IgA glycopeptides core antigen antibodies specific for MAC were measured in samples from healthy subjects (n=76) and patients with MAC pulmonary disease (70), MAC contamination (18), pulmonary tuberculosis (37) and other lung disease (45). Patients with MAC pulmonary disease had significantly higher IgA antibody levels than the other groups ($p < 0.0001$), and with a cut-off of 0.47 U/mL, the test diagnosed MAC pulmonary disease with 84.3% sensitivity and 100% specificity. Among patients with MAC pulmonary disease, those with nodular bronchiectatic disease had significantly higher IgA antibody levels than those with fibrocavitary disease ($p < 0.05$), and their antibody levels also correlated with disease extent on CT scans ($r = 0.43$; $p < 0.05$).

Comment: The diagnosis of MAC requires clinical findings and repeated positive sputa. This group of Japanese researchers reported on the findings of a multi-centre study on the clinical utility of a serum IgA antibody test kit to identify patients with MAC using repeated sputum culture as their reference standard. They describe a sensitivity of 84% and specificity of 100% and have so developed a rapid, non-invasive test for serological diagnosis of MAC. The article and accompanying editorial are worth reading, as they reflect on the state of art of the four clinical phenotypes of MAC infections: 1) pulmonary nodules, 2) fibrocavity lesions, 3) fibronodular bronchiectasis and 4) opportunistic infections.

Reference: *Am J Respir Crit Care Med* 2008; 177(7): 793-7

<http://ajrccm.atsjournals.org/cgi/content/abstract/177/7/793>



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Increasing antituberculosis drug resistance in the UK: analysis of national surveillance data

Authors: Kruijshaar ME et al

Summary: This analysis of 28 620 culture-confirmed cases of tuberculosis (TB) in the UK between 1998 and 2005 matched to drug susceptibility and national strain typing data found increases in resistance to isoniazid (from 5% to 7%) and rifampicin (from 1.0% to 1.2%). Multidrug resistance also increased from 0.8% to 0.9%, but resistance to ethambutol and pyrazinamide remained stable (-0.4% and -0.6%, respectively). Regression analysis revealed that increased isoniazid resistance outside London was associated with changes in age, place of birth and ethnicity, while increases within London were related mainly to an ongoing outbreak. Increases in annualised multidrug and isoniazid resistance were small. Among patients with multidrug-resistant TB in 2004–2005, one fifth had indistinguishable strain types, and one case of extensively drug-resistant TB was identified.

Comment: This paper found a significant increase in isoniazid resistance and also small increases in rifampicin and multidrug resistance. In London, there were more than 300 cases (including health professionals) that were identified as part of one isoniazid-resistant outbreak. This suggests that most UK drug resistance is not caused by failure of previous treatment, but rather, infection with a resistant strain

Reference: *BMJ* 2008; 336(7655): 1231-4
<http://www.bmj.com/cgi/content/abstract/336/7655/1231>

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Predictive value of a whole blood IFN- γ assay for active TB development after recent *M. tuberculosis* infection

Authors: Diel R et al

Summary: The prognostic value of a whole-blood interferon- γ assay ('QuantIFERON Gold In-Tube' [QFT] assay) was compared with tuberculin skin testing (TST) in 601 close contacts of *Mycobacterium tuberculosis*-positive source cases. TST tests were positive (with a 5mm cut-off) in 40.4% of the contacts, while QFT assay was positive in only 11%. Within the 2-year follow-up period, 6 contacts progressed to tuberculosis (TB) disease; all were from the QFT-positive group, all declined preventive therapy and one was TST negative. This equated to a significantly greater progression rate of 14.6% among the QFT-positive contacts, compared with 2.3% among untreated TST-positive contacts ($p < 0.003$)

Comment: This paper from a German group addresses some important questions that are associated with the clinical relevance of a positive QuantiFERON-TB Gold (QFT) assay. The researchers follow a group of significant TB contacts (e.g. household, work colleagues and pupils) of smear positive TB cases. Of the 601 contacts, 243 (40%) had a positive TST and 61 (11%) had a positive QFT test. A significant number of TB contacts refused prophylactic treatment, and were followed for two years. 5 of 219 (2.3%) contacts with a positive TST and 6 of 41 (14.6%) contacts with a positive QFT developed active TB within two years. This study suggests that QFT might help to identify people at the greatest risk of developing TB.

Reference: *Am J Respir Crit Care Med* 2008; 177(10): 1164-70
<http://ajrccm.atsjournals.org/cgi/content/abstract/177/10/1164>

Use of an IFN- γ release assay to diagnose latent TB infection in foreign-born patients

Authors: Brodie D et al

Summary: This study compared the interferon- γ release assay 'T-SPOT.TB' with tuberculin skin test (TST) in 96 predominantly foreign-born patients with a high rate of bacille Calmette-Guérin (BCG) vaccination to validate the routine use of T-SPOT.TB in this population. The adjusted odds ratio (OR) for a positive T-SPOT.TB test among close contacts of a case patient with active TB was 2.9 (95% CI 1.1, 7.3; $p = 0.03$). There was a significant association between a positive TST result and being a contact only among patients who had not received BCG vaccination ($p = 0.02$). The T-SPOT.TB test had greater specificity than TST for being a close contact ($p < 0.001$), with specificity among participants who had received BCG vaccination markedly better for T-SPOT.TB than for TST (70% vs. 3%; $p < 0.001$)

Comment: Of the two IFN- γ release assays, T-SPOT.TB and QuantiFERON-TB Gold (QFT), only QFT is licensed for use in the USA. This study investigated the clinical utility of T-SPOT.TB in a population of patients with a high prevalence of BCG vaccinations and therefore frequently positive TSTs. The study group was 'TB contact', which included close (>8h) and non-close (<8h) contacts. The control group were people who were tested for latent TB for 'other reasons'. The authors study design did not allow them to comment on sensitivity. However, they did find improved specificity in identifying close contacts, improved clinical utility and the potential for cost saving compared with TSTs.

Reference: *Chest* 2008; 133(4): 869-74
<http://www.chestjournal.org/cgi/content/abstract/133/4/869>



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Clinical utility of the QuantiFERON TB-2G test for elderly patients with active TB

Authors: Kobashi Y et al

Summary: The feasibility of using the QuantiFERON-TB-2 Gold (QFT-2G) test for diagnosing tuberculosis (TB) infection was evaluated in 30 elderly and 100 younger patients with active TB. Combined and separate responses to culture filtrate protein 10 (CFP-10) and early secretory antigenic target 6-kD (ESAT-6) protein antigens were related to the QFT-2G test results. QFT-2G tests were positive in 77% and 87% of the older and younger patients, respectively ($p=0.185$), compared with positive tuberculin skin tests (TSTs) in 27% and 70%, respectively ($p=0.0.12$). Elderly patients had a significantly lower positive test result rate for both ESAT-6 and CFP-10 antigens than the younger patients (17% vs. 37%; $p = 0.038$). The QTF-2G test result was indeterminate in 5 of the elderly patients, possibly related to lymphopenia, and 2 elderly patients had a negative QTF-2G test, possibly related to severity of active TB.

Comment: This group of Japanese researchers investigated the role of QFT-2G in elderly patients with active TB and compared the results to culture results (gold standard), TST and outcome in young patients. Two patients with culture-positive TB had a negative QFT-2G test. Both patients with a negative QFT-2G and also three of the patients with undetermined QFT-2G results had mild lymphopenia. The specificity and sensitivity was better than TST. Bottom line: As shown previously in other study populations, QFT-2G has a sensitivity of approximately 80% in detecting active TB.

Reference: *Chest* 2008; 133(5): 1196-1202

<http://www.chestjournal.org/cgi/content/abstract/133/5/1196>

Evaluation of a model for efficient screening of TB contact subjects

Authors: Aissa K et al

Summary: Standardised data from 325 index cases of tuberculosis (TB) and 2009 of their contacts were analysed in this study to develop an efficient model for selecting contacts for TB screening. The following independent risk factors were identified: 1) age 6–14 years (OR 3.6; 95% CI 1.6, 8.0), 15–29 years (3.7; 1.8, 7.7) to ≥ 30 years (4.1; 2.0, 8.5); 2) cavitation on the index case's chest x-ray (1.6; 1.1, 2.2); 3) index case sputum smear with ≥ 100 acid-fast bacilli per field (1.8; 1.2, 2.8); 4) first-degree relative of index case (2.1; 1.3, 3.3); 5) household contact at night (2.1; 1.3, 3.2); 6) free healthcare (2.0; 1.2, 3.2); 7) active smoking by the contact (1.6; 1.1, 2.4); and 8) birth in a country with TB incidence rate >25 per 100,000 (2.2; 1.5, 3.2). The investigators reported that this approach resulted in a 26% reduction in the number of contacts that need to be screened while maintaining a false-negative rate of 8% (lower than the estimated background TB infection).

Comment: This group of French researchers published a standardised, contact-tracing protocol to identify groups at risk of TB. The researchers used a 15mm TST as their gold standard, quoting a specificity of 36% using a 5mm cut-off, but a specificity of 98% when using a 15mm cut-off (comparable with the interferon- γ release assays). Using a Paris-based TB service, the researchers identified eight independent risk factors increasing the odds ratio from 0.033 for none to 0.92 probability for eight risk factors. The authors concluded that in the hand of experienced TB field workers, TST testing can be reduced by 26% (and overtreatment can be avoided) with the same low 8% false-negative rate.

Reference: *Am J Respir Crit Care Med* 2008; 177(9): 1041-7

<http://ajrccm.atsjournals.org/cgi/content/abstract/177/9/1041>

Nortriptyline plus nicotine replacement versus placebo plus nicotine replacement for smoking cessation

Authors: Aveyard P et al

Summary: This pragmatic RCT was designed to see if adding nortriptyline to nicotine replacement therapy (NRT) increased smoking cessation rates. Smokers interested in quitting received an NRT of their choice and behavioural support either with 8 weeks of nortriptyline 25 mg/day increased to a maximum of 75 mg/day over 1 week ($n=445$) or placebo (456) started 2 weeks before quit day. Of the participants who stopped smoking and maintained abstinence for 6 months, 16% were from the nortriptyline group compared with 12% from the placebo group (relative risk 1.34; 95% CI 0.97, 1.86), and at 12 months 11% and 9% had maintained abstinence, respectively (1.26; 0.84, 1.87). The severity of dry mouth, constipation, shakiness and sweating was greater among the nortriptyline recipients, but the urge to smoke and withdrawal symptoms scores were similar between the groups, and nortriptyline users had less depression and anxiety.

Comment: This British study investigated the possibility that the combination of nortriptyline and NRT may have a complementary effect on smoking cessation rates. Both agents when used alone double the rate of smoking cessation. If this effect was additive, this drug combination would be more effective than varenicline. In their trial of 901 smokers wishing to quit, they found only a slight (although not statistically significant) advantage of adding nortriptyline to nicotine replacement therapy. Bottom line: In routine practice both nortriptyline and nicotine replacement used alone may aid smoking cessation. Combination therapy should not be used routinely.

Reference: *BMJ* 2008; 336(7655): 1223-7

<http://www.bmj.com/cgi/content/abstract/336/7655/1223>

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Safety of long-acting β -agonists in stable COPD

Authors: Rodrigo GJ et al

Summary: The safety and efficacy of long-acting β 2-adrenoceptor agonists (LABAs) in patients with stable reversible and poorly reversible COPD were reviewed in this paper. A meta-analysis of 27 published RCTs comparing LABAs with placebo or anticholinergics in such patients showed that LABAs significantly reduced exacerbations compared with placebo (relative risk [RR] 0.78; 95% CI 0.67, 0.91), but tiotropium resulted in fewer severe exacerbations than LABA therapy (0.52; 0.31, 0.87). Moreover, respiratory-related death did not differ between LABA and placebo recipients (RR 1.09; 95% CI 0.45, 2.64), while adding inhaled corticosteroid therapy to LABA therapy did reduce respiratory-related death compared with LABA therapy alone (0.35; 0.14, 0.93).

Comment: This review from a Spanish group addressed the important topic of the safety of LABAs in the management of COPD. Some previous studies have suggested an increased risk of adverse events and even respiratory death in asthma and COPD patients. This meta-analysis included 27 RCTs with populations aged >35 years who fulfilled the ERS/ATS or GOLD criteria for COPD, and were using LABAs and were followed up for at least four weeks. It is very reassuring that this study did not confirm previous data about an increased risk of respiratory death while using LABAs.

Reference: Chest 2008; 133(5): 1079-87

<http://www.chestjournal.org/cgi/content/abstract/133/5/1079>

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Pneumonia in elderly patients with COPD

Authors: Ernst P et al

Summary: The potential role of inhaled corticosteroids (ICS) in the development of pneumonia in elderly patients with COPD was investigated in this large observational case-control study. Using information on hospitalisation and medication use in patients aged >65 years obtained from a Quebec healthcare administrative database, the investigators reported an excess of hospitalisation due to pneumonia, and an excess of fatal pneumonia among hospitalised patients, among patients receiving ICS, particularly with high-dose therapy.

Comment: This Canadian study by two epidemiologists investigated the possible relationship between ICS use and development of pneumonia in patients with COPD. The authors used a database of 23,492 patients admitted with pneumonia and four aged-matched controls (95,768) being treated at the same time but not developing pneumonia. After adjustment, the risk of developing pneumonia during ICS therapy showed a dose-dependent risk between 1.7 and 2.25 fold. The authors speculate that this effect could be caused by: 1) blunted physiological stress response, 2) blunted local immune response to bacterial invasion or 3) an adaptive immune response in the peripheral lung.

Reference: Curr Infect Dis Rep 2008; 10(3): 223-8

http://www.current-reports.com/article_frame.cfm?PubID=IR10-3-2-02&Type=Abstract

Diagnosis of PE by multidetector CT alone or combined with venous ultrasonography of the leg

Authors: Righini M et al

Summary: In this noninferiority study, 1819 consecutive outpatients with clinically suspected pulmonary embolism (PE) were randomised to undergo clinical probability assessment and multislice CT (MSCT) combined with D-dimer measurement either on their own (DD-CT group) or with venous compression ultrasonography of the leg (DD-US-CT group). The prevalence of PE did not differ between the two groups, and there was no between-group difference in the 3-month risk of thromboembolism (0.3%; 95% CI 0.1, 1.2 vs. 0.3%; 0.1, 1.1 for the DD-CT group [n=838] and DD-US-CT group [855], respectively). MSCT was not performed in 53/574 patients (9%) in the DD-US-CT group due to the presence of deep vein thrombosis on ultrasonography.

Comment: This well-designed RCT by the Geneva group investigated the clinical question, 'Does venous compression ultrasonography add value when investigating patients with possible PE?' Based on 1819 patients with the main endpoint of PE recurrence or death, the researchers came to the conclusion that an ultrasound is not needed to rule out PE when MSCT is used. This article and accompanying editorial are recommended reading because the article contains a modified, validated Geneva score using objective observations. However, arterial blood gas results or chest x-ray are not included. The editorial contains a clinically relevant, evidence-based treatment protocol for managing PE.

Reference: Lancet 2008; 371(9621): 1343-52

<http://www.thelancet.com/journals/lancet/article/PIIS0140673608605942/abstract>

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