
Making Education Easy

Issue 74 - 2018

## In this issue:



### Abbreviations used in this issue:

**AE** = adverse event; **ARI** = acute respiratory infection; **AUC** = area under the plasma concentration-time curve; **BMI** = body mass index; **BP** = blood pressure; **COPD** = chronic obstructive pulmonary disease; **CPAP** = continuous positive airway pressure; **ESS** = Epworth Sleepiness Scale; **$FEV_1$** = forced expiratory volume in 1 second; **GP** = general practitioner; **ICU** = intensive care unit; **IFN** = interferon; **IL** = interleukin; **LCI** = lung clearance index; **MDR-TB** = multidrug-resistant tuberculosis; **MIC** = minimum inhibitory concentration; **MIP** = macrophage inflammatory protein; **OR** = odds ratio; **OSA** = obstructive sleep apnoea; **PCR** = polymerase chain reaction; **PHA** = primary health care area; **PJP** = *Pneumocystis jirovecii* pneumonia; **PLHIV** = people living with HIV; **RCT** = randomised controlled trial; **RD** = risk difference; **TB** = tuberculosis.

**Claim CPD/CME points** Click here for more info.

Follow **RESEARCH REVIEW** Australia on Twitter now

@ResearchRevAus

Visit https://twitter.com/ResearchRevAus

# Welcome to issue 74 of Respiratory Research Review.

Evidence in one of the articles included in this issue suggests that high-dose rifampicin may be an appropriate regimen for pulmonary TB. At a dose of 20 mg/kg, rifampicin was not associated with more AEs than those seen with the lower doses (10 and 15 mg/kg). Moreover, the elimination rate of *Mycobacterium tuberculosis* in sputum was cleared more rapidly with the higher doses. Another paper reports promising data on new treatment regimens for pulmonary multidrug-resistant (MDR)-TB. The results of this individual patient data meta-analysis have led the World Health Organization to rewrite its guidelines for MDR-TB, which now recommend all-oral regimens over injectable agents.

Independent commentary was provided by Conjoint Professor Peter Wark, senior staff specialist in Respiratory and Sleep Medicine at John Hunter Hospital, Newcastle, Australia and a conjoint Professor with the University of Newcastle.

I hope you find the papers in this issue useful in your practice and I look forward to your comments and feedback.

Kind Regards,

**Dr Janette Tenne**

**Medical Research Advisor**

janette.tenne@researchreview.com.au

## Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis

**Authors:** Ahmad N et al.

**Summary:** These researchers examined treatment outcomes from 50 observational and experimental studies published between 1 January 2009 and 30 April 2016 performed in 25 countries worldwide and involving 12,030 adults (aged >18 years) treated for MDR-TB. The analysis assessed end of treatment success (defined as cure or completion) compared with failure or relapse, and death from any cause during TB treatment compared with success or failure or relapse. A total of 7,346 (61%) patients were cured or successfully completed treatment, 1,017 (8%) had failure or relapsed, and 1,729 (14%) died. Compared with failure or relapse, treatment success was positively associated with the use of linezolid (adjusted RD 0.15), levofloxacin (0.15), carbapenems (imipenem and meropenem) (0.14), moxifloxacin (0.11), bedaquiline (0.10), and clofazimine (0.06). Significant reductions in mortality were associated with the use of linezolid (adjusted RD −0.20), bedaquiline (−0.14), moxifloxacin (−0.07), or levofloxacin (−0.06). Compared with regimens that did not use injectable drugs, use of amikacin in patients with susceptible isolates was of modest benefit (adjusted RD 0.06), but no difference in death; kanamycin was associated with significantly lower success (−0.07) and no difference in death (0.01), while capreomycin was associated with lower success (−0.03) and more deaths (0.04). The remaining drugs were associated with slight or no improvements in outcomes. Treatment outcomes were significantly worse for most drugs if they were used despite *in vitro* resistance.

**Comment:** This is an important paper that has taken the individual patient data from both observational and experimental treatment trials for patients with MDR-TB. This is an area in which it is extremely difficult to conduct traditional randomised trials, with long treatment periods and in disadvantaged people from multiple health systems. It provides valuable insights then into potentially successful regimes to be considered for first-line, with the use of linezolid, later-generation fluoroquinolones, bedaquiline, clofazimine, and carbapenems. Regimens containing amikacin provided only modest benefits, and kanamycin and capreomycin were associated with worse outcomes. They advise a regime of 5 drugs in the initial phase, then 4 in the continuation phase. However, what is perhaps most important is the continuing high mortality observed at 14%, reinforcing the importance of measures to control transmission and ensure treatment of sensitive TB strains is completed.

***Reference: Lancet. 2018;392(10150):821-34***

Abstract

## Efficacy of an inhaled IL-13 antibody fragment in a model of chronic asthma

**Authors:** Lightwood D et al.

**Summary:** Using cynomolgus macaques sensitive to *Ascaris suum* parasites, which induce bronchial asthma in primates resembling asthma in humans, these researchers examined the efficacy of nebulised CDP7766 (0.1–60 mg/animal) delivered once daily by an eFlow inhaler for 5 days. CDP7766 is an anti-IL-13 monoclonal antibody Fab fragment. Analyses of the aerosol confirmed that it generated a respirable aerosol of CDP7766 with no evidence of degradation, loss of potency, aggregation, or particulate formation. Inhaled CDP7766 showed good tolerability, with no adverse effects related to local irritation. Compared with vehicle, the 60 mg dose of CDP7766 was associated with significant inhibition of BAL allergen-induced cytokine and chemokine upregulation (eotaxin-3, MIP-1β, IL-8 and IFN-γ; p≤0.01 for all comparisons). Moreover, at both 15 minutes and 24 hours after inhaled allergen challenge, CDP7766 significantly inhibited the increase in pulmonary resistance.

**Comment:** IL-13 plays a crucial role in type 2 airway inflammation and airway wall remodelling that is seen in asthma. Specific targeting of the IL-13/IL-4 pathway with systemic monoclonal antibodies has been successful, though IL-13 monoclonal antibodies alone less so. This experimental study is the first to look at the application of an inhaled anti-IL-13 and demonstrate in a primate allergy model of asthma that it can effectively reduce type 2 airway inflammation and airway resistance.

This is a promising proof-of-concept result. As of now, our only inhaled treatment option consists of corticosteroids.

***Reference: Am J Respir Crit Care Med. 2018;198(5):610-9***
Abstract



## Primary care physicians can comprehensively manage sleep apnea patients. A non-inferiority randomized controlled trial

**Authors:** Sánchez-Quiroga MÁ et al.

**Summary:** This multicentre trial in Spain randomised 307 patients at intermediate to high risk of developing OSA to either primary health care area (PHA) or in-laboratory specialised management protocols and followed them for 6 months. As the article explains, simplifying the diagnosis and applying a semiautomatic algorithm for treatment enables the involvement of GPs. Patients in the PHA arm were given a portable monitor with automatic scoring and semiautomatic therapeutic decision-making. Those assigned to the in-laboratory protocol underwent polysomnography and specialised therapeutic decision-making. In both study arms, patients were given CPAP treatment or sleep hygiene and dietary treatment alone. Data were evaluable from 303 patients for the intention-to-treat analysis. Epworth Sleepiness Scale (ESS) scores confirmed noninferiority of the PHA protocol to the in-laboratory protocol. Secondary outcomes included health-related quality of life, BP, incidence of cardiovascular events, use of hospital resources, adherence to CPAP, and within-trial costs; for all variables, outcomes were comparable between the protocols. Cost-effectiveness favoured the PHA arm, with a cost difference of €537.8 per patient.

**Comment:** This trial took adults in primary care with snoring or witnessed apnoeas who were somnolent with an ESS >12 and randomised them to either a simplified 4-channel diagnostic device or standard full polysomnogram and review by a sleep physician. Each group was assigned to CPAP if their AHI was >20 or 10–20 with BMI>35 and age >55 years.

The simplified diagnostic protocol was not inferior and was more cost effective. The primary outcome was improvement in ESS and both groups demonstrated similar compliance when assessed at 6 months.

For a high-risk population with standard OSA, this simplified diagnostic and management protocol appeared to perform well. Given the increases seen in obesity and the ageing populations in Western countries, simplified diagnostic and management protocols will need to be examined closely.

***Reference: Am J Respir Crit Care Med. 2018 Apr 17. [Epub ahead of print]***
Abstract

## Efficacy and safety of high-dose rifampin in pulmonary tuberculosis. A randomized controlled trial

**Authors:** Velásquez GE et al.

**Summary:** In this phase II trial, 180 adults with smear-positive pulmonary TB susceptible to isoniazid and rifampicin were randomly assigned to daily doses of rifampicin at 10, 15, or 20 mg/kg/day during the 8-week intensive phase. In an analysis of the dose-related differences in change in elimination rate of *Mycobacterium tuberculosis* in sputum, each 5-mg/kg/day increase in dose was associated with differences of −0.011 (p=0.230) and −0.022 (p=0.022) $\log_{10}$ colony-forming units/mL/day in the modified intention-to-treat and per-protocol analyses, respectively. The elimination rate in the per-protocol population increased significantly with rifampicin $AUC_{0-6}$ (p=0.011) but not with $AUC_{0-6}/MIC_{99.9}$ (p=0.053). Grade ≥2 rifampicin-related AEs occurred in similar proportions of patients in each treatment arm: 43.3% in the 10 mg/kg/day cohort, 51.7% in the 15 mg/kg/day cohort and 38.3% in the 20 mg/kg/day cohort had ≥1 event (p=0.7092) up to 4 weeks after the intensive phase. Few patients (6.1%) experienced treatment failure or disease recurrence.

**Comment:** TB remains an important global health issue. The long treatment courses and need to use multiple antibiotics add to its complexity and issues around adherence that then lead to drug resistance. Attempts in the 1970s to shorten treatment duration using intermittent high-dose rifampicin were unsuccessful due to toxicity.

This blinded RCT of 180 adults in Peru gave subjects rifampicin 10 mg/kg, 15 mg/kg, or 20 mg/kg daily during the 8-week intensive therapy phase. In this trial, there were no increases in AEs seen with the higher doses. In addition, the higher doses achieved more rapid clearance of organisms in the sputum. New anti-TB treatment regimens are starting to emerge and high-dose rifampicin appears to be a viable option for further study.

***Reference: Am J Respir Crit Care Med. 2018;198(5):657-66***
Abstract

## Early corticosteroids for *Pneumocystis* pneumonia in adults without HIV are not associated with better outcome

**Authors:** Wieruszewski PM et al.

**Summary:** This retrospective review included 323 hospitalised patients (median age 65 years) admitted to the Mayo Clinic between 2006 and 2016 with non-HIV-related *Pneumocystis jirovecii* pneumonia (PJP) who were either treated early (within 48 h) with oral corticosteroids (n=258) or received no such treatment (n=65). Multivariable logistic regression analysis adjusted for PJP severity and propensity-matched analysis comparing the between-group changes from baseline in the respiratory component of the Sequential Organ Failure Assessment score ($SOFA_{resp}$) at day 5 found that treating patients early with corticosteroids was associated with less improvement in $SOFA_{resp}$ at day 5 compared with no corticosteroids (p≤0.017 for both comparisons). The likelihood of having a ≥1-point improvement from baseline in $SOFA_{resp}$ at day 5 did not differ significantly between the two study groups (adjusted OR 0.76; 95% CI, 0.24 to 2.28; p=0.61). Overall 30-day mortality was 22.9%. There were no between-group differences in mortality, length of stay, ICU admission, or mechanical ventilation requirements.

**Comment:** The use of oral corticosteroids in the treatment of patients with HIV and PJP used to be the established treatment, although now it is rarely seen. Presentations of PJP now are seen in older and more acutely immunosuppressed individuals. The disease presentation also appears to be more acute. The legacy of the use of oral corticosteroids in PJP, however, has lingered. While this is only a retrospective review of 323 cases, the authors found there to be no benefits with the addition of oral corticosteroids, adding further evidence that this should not be considered in the treatment of these cases with non-HIV-related PJP.

***Reference: Chest. 2018;154(3):636-44***
Abstract

## Ventilation inhomogeneity in infants with recurrent wheezing

**Authors:** Lu Z et al.

**Summary:** This case-control study included data from 37 infants with recurrent wheezing presenting to outpatient clinics and 113 healthy infants from the Canadian Healthy Infant Longitudinal Development birth cohort study. All infants were subjected to multiple breath washout, forced expiratory flow and body plethysmography measurements when they were clinically stable, in order to obtain lung clearance index (LCI) scores as a measure of ventilation inhomogeneity. The mean LCI z-score for the infants with recurrent wheezing was significantly higher (by 0.84 units) than that for the healthy infants (0.26 vs −0.58; p<0.001). Approximately one-fifth (19%) of the infants with recurrent wheeze had LCI values that exceeded the upper limit of normal (>1.64 z-scores). A significant association was observed between abnormal LCI scores and elevated nitric oxide in the infants with recurrent wheeze (p=0.05); no such association was seen between LCI scores and symptoms.

**Comment:** This is an interesting observational study assessing ventilation inhomogeneity in infants with recurring wheeze, utilising the nitrogen multi-breath washout test. In this study, the authors established with a small cohort of healthy controls what the normal range should be in terms of the lung clearance index (LCI). They then determined that as a group, wheezing infants had abnormal LCI, though only 19% of them had values above the normal range. It was interesting that this correlated with elevated exhaled nitric oxide, known to be associated with type 2 airway inflammation in older children. The study demonstrates the heterogeneity of this group, but also implies that the majority of these children, at least between episodes, may have normal lung function. It will be interesting to apply this measure in other cohorts and in longitudinal studies to see how it associates with or predicts the later development of asthma and spirometric values such as $FEV_1$.

***Reference: Thorax. 2018;73:936-41***
Abstract


**Independent commentary by Conjoint Professor Peter Wark**

Prof Peter Wark is a senior staff specialist in Respiratory and Sleep Medicine at John Hunter Hospital, Newcastle, Australia and a conjoint Professor with the University of Newcastle. In addition, he is a senior investigator with the Priority Research Centre for Healthy Lungs and the Vaccines Immunology Viruses and Asthma research group at the Hunter Medical Research Institute. He is also a chief investigator in the National Health and Medical Research Council Centre of Excellence in Severe Asthma. His research interests are in the area of infection and the impact this has on inflammatory airways disease, with a particular interest in viral respiratory infections and acute exacerbations of chronic airways disease.

## Viruses causing lower respiratory symptoms in young children: findings from the ORChID birth cohort

**Authors:** Sarna M et al.

**Summary:** The Observational Research in Childhood Infectious Diseases (ORChID) study, a community-based birth cohort study of acute respiratory illness in children in the first 2 years of life, was conducted in Brisbane, Australia, between September 2010 and October 2014. This article describes disease-pathogen associations of respiratory viruses and 'quantifies virus-specific attributable risk for 158 term newborn infants in ORChID. Parents completed daily diaries recording predefined respiratory symptoms or diagnoses for their children until they were 2 years old. Weekly parent-collected nasal swabs were batch-tested by PCR assays for 17 respiratory viruses: human rhinovirus (HRV), influenza A and B (IFV-A, IFV-B), respiratory syncytial virus A and B (RSV-A, RSV-B), parainfluenza viruses 1–3 (PIV-1, PIV-2, PIV-3), human coronaviruses (HCoV) OC43, NL63, 229E and HKU1, human metapneumovirus (HMPV), adenovirus (AdV), human polyomaviruses WU (WU-PyV) and KI (KI-PyV) and human bocavirus-1 (HBoV-1). PCR testing provided information about the attributable fraction in the exposed (AFE) and enabled the researchers to determine the proportion of virus-positive children whose acute respiratory infection (ARI) symptoms could be attributed to that particular virus. The analysis included 8,100 nasal swabs; one-third (32.7%) were positive for respiratory viruses and 3.4% of the specimens were found to have ≥1 virus. The most commonly detected virus was HRV (77.8% of all positive detections). A total of 1,530 ARIs had swabs submitted during the ARI episode, including swabs taken 7 days prior to or 7 days after the last day of the illness; 1,154 (75.4%) of ARIs had ≥1 swab with a virus detected during this period. Of 4,308 swabs taken during asymptomatic periods, around one-fifth (984; 22.8%) were virus-positive. RSV (AFE: 68%) and HMPV (AFE: 69%) were strongly associated with ARIs and lower respiratory symptoms.

**Comment:** This was a study of a healthy community birth cohort to determine the prevalence of viral infections over 4 years, using nasal swabs. It found that 75% of acute respiratory tract infections were associated with viral infections. The most common virus isolated was rhinovirus, but respiratory viruses were also seen during times when the children were asymptomatic. Both respiratory syncytial and human metapneumovirus were seen frequently and more likely to be associated with more severe symptoms. In both cases, the development of a vaccine strategy against these two viruses would have a major impact.

***Reference: Thorax. 2018;73(10):969-79***
Abstract



## Increasing burden of noninfectious lung disease in persons living with HIV: a 7-year study using the French nationwide hospital administrative database

**Authors:** Maitre T et al.

**Summary:** These researchers analysed data from the French nationwide hospital medical information database for a total of 52,091 PLHIV hospitalised in France between 2007 and 2013. In those who were hospitalised with lung disease, the analysis identified a significant increase in non-infectious lung diseases (from 45.6% in 2007 to 54.7% by 2013), whereas there was a significant decline in the proportion of patients with ≥1 infectious lung disease between 2007 and 2013. In 2010, 10,067 prevalent hospitalised PLHIV were compared with 8,244,682 hospitalised non-PLHIV. After adjusting for smoking status, analyses of 30–49-year-olds determined associations between HIV infection and COPD, chronic respiratory failure, emphysema, lung fibrosis and pulmonary arterial hypertension.

**Comment:** The experience of HIV illness has dramatically changed in the last 25 years for the better, turning this illness from an acute fatal disorder to a chronic outpatient-based disease, albeit with a persistently high burden of treatment morbidity. This article provides insight into the progression of the disorder and highlights what appears to be a problem of emerging chronic non-infectious disease in this cohort. The review of the French national database demonstrates a fall between 2010 and 2013 in hospitalisations with infectious lung disease, largely pneumonia. However, there was an increase in chronic respiratory disease, especially COPD. This appears to occur at a greatly accelerated rate, causing disease that leads to hospitalisation in a relatively younger cohort than would be seen in people without HIV. This finding was also independent of smoking. For people with HIV, chronic lung disease remains an important co-morbid illness and should be considered in this population in regard to smoking and also in relation to identifying disease as well as ensuring that treatment is optimised.

***Reference: Eur Respir J. 2018;52(3)pii:1800359***
Abstract

## Patterns of healthcare utilisation for respiratory complications of adults with neuromuscular disease: a population study

**Authors:** Rose L et al.

**Summary:** This Canadian population-based study analysed health service utilisation, including the monitoring and treatment of respiratory complications, in a cohort of 185,586 adults (mean age, 52 years) with neuromuscular disease between 2003 and 2015. Approximately one-fifth (22%) presented to the emergency department for respiratory complications on average 1.6 times every 3 years; 8% were admitted to hospital 1.4 times every 3 years. One-third (35%) received outpatient respiratory specialist visits, with 4 visits every 3 years, although visit frequency varied substantially amongst this group. A large proportion (85%) presented to the emergency department (all-cause) almost 4 times every 3 years and over half (54%) of the entire study cohort were admitted to hospital. Emergency department visits were much more frequent for those with amyotrophic lateral sclerosis/motor neurone disease than for adults with any other neuromuscular disease ($p<0.0001$).

**Comment:** This is an important observational trial that highlights the increasing burden of respiratory illness being seen amongst people with neuromuscular disease and the need for respiratory support. The assessment included people with acute rapidly progressing diseases, mostly motor neurone disease, but also those with chronic neuromuscular disease in Ontario, Canada. The striking observation is that 85% were hospitalised or presented to the emergency room for respiratory complications. This was particularly common in those with motor neurone disease. In contrast, only 35% were seen in outpatient respiratory services, fewer than 5% of all subjects received a positive pressure ventilator device.

This paints a picture of a substantial and likely rising burden of illness from those with neuromuscular disease. It also suggests that evidence-based treatments such as ventilatory support are underutilised and access is fragmentary. The high rate of acute presentations may also reflect a lack of support and plans being put in place that require equipment and coordinated care.

***Reference: Eur Respir J. 2018;52(3)pii:1800754.***
Abstract

## Recurrence rates in primary spontaneous pneumothorax: a systematic review and meta-analysis

**Authors:** Walker SP et al.

**Summary:** This systematic review of English language publications of randomised trials and observational studies included 29 studies reporting primary spontaneous pneumothorax (PSP) recurrence rates in a total of 13,548 adults who underwent conservative management, pleural aspiration or chest drainage. The pooled 1-year recurrence rate was 29.0%; the overall recurrence rate was 32.1%. The risk was 3-fold higher for females (OR 3.03; 95% CI, 1.24 to 7.41); quitting smoking reduced the risk (OR 0.26; 95% CI, 0.10 to 0.63). There was substantial heterogeneity amongst the studies, according to the results of a random effects meta-analysis ($I^2$ 94%; p<0.0001).

**Comment:** This is a systematic review of over thirteen thousand patients with primary spontaneous pneumothorax. It demonstrated a 32% recurrence rate after the first event. Interestingly, it also demonstrates the heightened risk for women, although also in this group without lung disease a marked reduction occurs with smoking cessation. The value of smoking cessation in this context needs to be emphasised for patients with a primary pneumothorax, to reduce the risk of recurrence.

***Reference: Eur Respir J. 2018;52(3)pii:1800864***
Abstract

RESEARCH REVIEW — The Australian Perspective Since 2007

## 30-year trends in asthma and the trends in relation to hospitalization and mortality

**Authors:** Pelkonen MK et al.

**Summary:** These researchers examined trends in asthma prevalence during the 30-year period from 1982 to 2012 in Finland and they also assessed concurrent hospitalisations and mortality. Data were obtained from 7 cross-sectional risk factor population surveys conducted every 5 years, involving a total of 54,320 subjects aged 25–74 years. Each survey required participants to complete a standardised questionnaire on self-reported asthma, smoking habits and other risk factors, as well as clinical measurements. Asthma prevalence increased during the 30-year study period, particularly amongst women. Compared with non-asthmatics, asthmatics had significantly higher all-cause hospitalisations, respiratory causes, cardiovascular causes and lung cancer. Mean yearly hospital days decreased in the 5-year periods after each survey, particularly amongst asthmatics: yearly all-cause hospital days decreased in the asthmatics from 4.45 (between 1982 and 1987) to 1.11 (between 2012 and 2015); the corresponding decrease in non-asthmatics was from 1.77 to 0.60 (p<0.001). Similarly, between 1982 and 2015, COPD hospitalisations fell by a greater extent amongst asthmatics than amongst non-asthmatics. Generally, all-cause mortality decreased between 1982 and 2015, although asthmatics had higher all-cause mortality, respiratory mortality and lung cancer mortality, compared with non-asthmatics.

**Comment:** This is an interesting observational study of adult asthmatic cohorts examined between 1982 and 2015. Despite the increase seen in asthma prevalence, there has been a very clear improvement in outcomes; with reduced hospitalisations and reduced mortality. It reflects the success seen with asthma treatments, especially in these important epidemiological outcomes. Unfortunately, despite our ability to effectively manage the majority of asthmatics, we are still unable to reduce its prevalence.

***Reference: Respir Med. 2018;142:29-35***
Abstract



**Australian Research Review subscribers can claim CPD/CME points** for time spent reading our reviews from a wide range of local medical and nursing colleges. Find out more on our CPD page.





 