Respiratory Research Review™

Making Education Easy

Issue 159 – 2019

In this issue:

Abbreviations used in this issue
CAP = community-acquired pneumonia
CCPI = culture-positive pleural infection
DNase = deoxyribonuclease
LRTI = lower respiratory tract infection
RCT = randomised controlled trial
tPA = tissue plasminogen activator

Welcome

to this issue of Respiratory Research Review with the focus on pneumonia and infection. As we are producing this review, NZ is in the middle of a measles epidemic. The discussions are certainly stimulating to follow, whether it is an elected council member wearing 'antivaccination' clothing or, the debate, whether unvaccinated children should attend publicly funded schools or kindergartens, a path that Italy has taken. Like with influenza vaccination, we must be mindful of assisting people in accessing vaccinations, as a study from Liverpool highlights.

Last year was the centenary of the 1918 Influenza pandemic, which caused an estimated 90 million deaths. New research suggests that the majority of people died due to bacterial superinfection, probably via the breakdown of the epithelial barrier, impaired activation of the immune system, and immune paresis via increased IL-10. Wendy Barclay and Peter Openshaw published a great review in Lancet Respir Med and highlight the ever-present danger of a new, highly pathogenic avian influenza (H5N1), which has already crossed over into people exposed to poultry in 1997 and again in 2003. The most authoritative review on 'Novel influenza A viruses and pandemic threats' is still by Timothy Uyeki, Jacqueline Katz and Daniel Jernigan from the American CDC.

In this review, we include an article estimating how long a childhood influenza vaccination may last (Lancet Respir Med), articles to assess the global burden of the seasonal influenza (Lancet Respir Med) and the clinical efficacy of a new antiviral medication (N Engl J Med), and evidence that we may have to add aspergillus pneumonia to the complications of an influenza infection (Lancet Respir Med). A great proof-of-concept study from our colleagues in Wellington, using high-flow, high-temperature, humidified air to reduce the symptoms related to the common cold, receives our 'butterfly' in this selection.

Globally, 291.8 million people per year suffer from LRTIs (lower respiratory tract infections), resulting in more than 2.7 million deaths. One of the common causes of this in adults and children is streptococcal pneumonia, with the mortality hardly changed since the introduction of antibiotics in the 1950s. In Respiratory Research Review issue 147, we reviewed evidence of nonrespiratory death following pneumonia, such as increased rates of cardiac events. In this issue, we review the 1-year mortality following an empyema, which again is surprisingly high, at up to 45%. Colleagues in Milan call 'pneumonia a neglected problem' and cite that on ClinicalTrials.gov, only 154 studies are listed involving bacterial pneumonia, versus more than 7000 studies involving HIV infection. One of these studies involving pneumonia is 'Omadacycline for community-acquired bacterial pneumonia', which we will review in this issue.

At this stage, penicillin and β-lactam antibiotics are still the antibiotics of choice for streptococcal infections in NZ. We want to draw attention to the JAMA review and associated video on the 'evaluation and management of penicillin allergy'. In the US, about 10% of the population report an adverse reaction to penicillin; however, 95% of people can tolerate penicillin. The authors give practical hints on how to retake a drug history, when to consider a drug challenge and when to consider skin testing. Their solutions are safe, pragmatic and easy enough to adopt in clinical practice.

We hope you enjoy this selection, and we are looking forward to your feedback, comments and suggestions.

Kind regards

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Mortality, morbidity, and hospitalisations due to influenza lower respiratory tract infections, 2017

Authors: GBD 2017 Influenza Collaborators

Summary: Using data from the Global Burden of Disease Study 2017, LRTI incidences, hospitalisations and mortality attributable to influenza were modelled for every country and selected regions for 1990–2017. Across all ages, influenza LRTIs were responsible for an estimated 145,000 deaths in 2017, with the highest rates for adults aged >70 years (16.4 deaths per 100,000) and for eastern Europeans (5.2 per 100,000). An estimated 9,459,000 hospitalisations covering 81,536,000 hospital days could be attributed to LRTIs. It was also estimated that 11.5% of LRTI episodes were attributable to influenza, corresponding to 54,481,000 episodes, including 8,172,000 severe episodes.

Comment: About 150,000 deaths secondary to LRTIs or about 5% of all deaths due to LRTIs are secondary to influenza, according to the Global Burden of Disease influenza collaborators. People above the age of 70 years have the highest infection rate and the highest mortality. However, Sheena Sullivan and Benjamin Cowling from the WHO Collaborating Centre for Reference and Research on Influenza argue in their accompanying editorial that this number is far too low, because of methodological weaknesses and by restricting the death due to LRTIs. **Bottom line: influenza has a considerable death toll even outside pandemics.**

Reference: Lancet Respir Med 2019;7:69–89
Abstract

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Independent commentary by Professor Lutz Beckert.
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Baloxavir marboxil for uncomplicated influenza in adults and adolescents

Authors: Hayden FG et al., for the Baloxavir Marboxil Investigators Group

Summary: Outpatients aged 12–64 years with acute uncomplicated influenza received baloxavir marboxil 10–40mg in a dose-ranging, placebo-controlled trial, after which 1064 (84.8–88.1% with influenza A [H3N2] infection) were randomised to receive baloxavir 40mg or 80mg according to bodyweight, oseltamivir 75mg twice daily or placebo during the 2016–2017 influenza season. In the phase 2 trial, alleviation of influenza symptoms was seen a median of 23.4–28.2 hours faster with baloxavir than with placebo ($p<0.05$). In the phase 3 trial, baloxavir recipients had a quicker time to alleviation of symptoms than placebo recipients (53.7 vs. 80.2 hours [$p<0.001$]) with a similar time to symptom alleviation as oseltamivir recipients. Baloxavir recipients also experienced greater reductions in viral load the day after starting treatment compared with placebo and oseltamivir recipients. The respective adverse event rates in the baloxavir, oseltamivir and placebo arms were 20.7%, 24.8% and 24.6%.

Comment: In October 2018, the US FDA-approved a new class of antiviral agent, baloxavir, which is given as a single dose and inhibits the endonuclease within the viral polymerase acid protein subunit. In this international trial, the investigators randomised around 1400 participants with influenza symptoms within 48 hours to baloxavir, oseltamivir or placebo. Baloxavir was well tolerated and led to earlier resolution of symptoms and earlier viral load clearance when compared with placebo. **Bottom line: baloxavir is a step forward in antiviral therapy and has the potential to be combined with oseltamivir.**

Reference: N Engl J Med 2018;379:913–23
Abstract

Effectiveness of influenza vaccination on influenza-associated hospitalisations over time among children in Hong Kong

Authors: Feng S et al.

Summary: Influenza vaccine effectiveness was investigated in children admitted to hospital for respiratory infections during 2012–2017, comparing those who tested positive for influenza A or B (cases; n=2500) with those who tested negative (n=13,195; controls). For the influenza-positive and -negative groups, the respective vaccination rates were 6.4% and 11.0%. Influenza-related admissions peaked in January–March over 2012–2017 with a large summer peak in 2016. The respective pooled vaccine effectiveness rates were 79%, 67% and 43% for September–December, January–April and May–August, with estimated rates of 79%, 60%, 57% and 45% within 0.5–2, 2–4, 4–6 and 6–9 months of vaccination, respectively. Analyses by type and subtype showed that vaccine effectiveness rates fell by 2–5 percentage points each month.

Comment: NZ is just running through its cycle of influenza vaccinations, targeting in particular children aged 6 months to 3 years, adults above the age of 65 years and special groups (Influenza: Immunisation Handbook 2017; pdf, 784KB). Hong-Kong offers vaccinations for children aged 6 months to 12 years. These Chinese/Australian researchers report on the protection conferred by the seasonal influenza vaccination. The efficacy varied a little from year to year, and the effectiveness against influenza A (H3N2) appears to be the lowest. **Bottom line: a protective effect was available within 2 weeks; however, this effect was less than 50% after 6 months. Currently, annual vaccination is the most effective strategy to protect from influenza.**

Reference: Lancet Respir Med 2018;6:925–34
Abstract

Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza

Authors: Schauwvlieghe AFAD et al., on behalf of the Dutch-Belgian Mycosis study group

Summary: The incidence of invasive pulmonary aspergillosis was investigated over several influenza seasons for a retrospective cohort of 432 adults admitted to an ICU with influenza, with assessment of whether influenza was an independent risk factor for those who were diagnosed with invasive pulmonary aspergillosis a median of 3 days after ICU admission (n=83). Compared with nonimmunocompromised patients (n=315), those who were immunocompromised (n=117) had a higher incidence of invasive pulmonary aspergillosis (32% vs. 14%). Compared with patients who did not develop invasive pulmonary aspergillosis, those who did had a higher 90-day mortality rate (51% vs. 28% [p=0.0001]). Influenza was found to be a significant independent predictor for invasive pulmonary aspergillosis (adjusted odds ratio 5.19 [95% CI 2.63, 10.26], as were higher APACHE II score, male sex and corticosteroid use.

Comment: It has been suspected that the primary cause of death during the influenza pandemic was a secondary bacterial infection. This is a fascinating study from the Dutch-Belgian Mycosis study group, who systematically investigated 432 patients admitted to ICUs with severe influenza. An influenza superinfection occurred in almost 20% of the patients, and once infected, the mortality in this group was 45%. Prior treatment with corticosteroids increased the risk of invasive aspergillosis by about 50%. The accompanying editorial gives us the **bottom line: we need to add invasive pulmonary aspergillosis to the list of influenza complications.**

Reference: Lancet Respir Med 2018;6:782–92
Abstract

Randomised controlled trial of rhinothermy for treatment of the common cold

Authors: van de Hei S et al.

Summary: Adult participants presenting within 48 hours of developing symptoms of a common cold were randomised 2:1 to receive rhinothermy with 35 L/min of 100% humidified air at 41°C via high-flow nasal cannulae, 2 hours per day for ≤5 days, or vitamin C (ascorbic acid) 250 mg/day for 5 days as a control in this feasibility trial from NZ. Thirty of 79 potential participants (38%) screened for eligibility were randomised (primary outcome), all of whom completed the study. Compared with vitamin C, rhinothermy was associated with greater reductions from baseline in modified Jackson score at days 2–6, with the maximum difference of –6.4 points seen at day 4; a 5-point change was designated the threshold for substantial clinical benefit.

Comment: In this proof of concept study, our colleagues in Wellington used hot (41°C), humidified air at 35 L/min to treat the common cold. Adults contract about 2–4 'colds' per year, with an estimated loss of productivity of US$40 billion a year in the US alone. In this feasibility study, our colleagues randomised patients to rhinothermy at 41°C for 2 hours versus low-dose vitamin C. Rhinothermy was well tolerated without mucosa burns. Although not a primary endpoint, the modified Jackson score showed considerable improvement in the rhinothermy group. **Bottom line: it is feasible to perform an RCT to explore rhinothermy for the common cold.**

Reference: BMJ Open 2018;8:e019350
Abstract

Omadacycline for community-acquired bacterial pneumonia

Authors: Stets R et al.

Summary: Intent-to-treat data were reported for adults with CAP who were treated with intravenous omadacycline 100mg every 12 hours for two doses then 100mg every 24 hours (n=386) or intravenous moxifloxacin 400mg every 24 hours (n=388). Participants could transition to oral omadacycline 300mg every 24 hours or moxifloxacin 400mg every 24 hours after 3 days; the total treatment duration was 7–14 days. Omadacycline was noninferior to moxifloxacin for the primary endpoint of early clinical response (survival with improvements in ≥2 of cough, sputum production, pleuritic chest pain and dyspnoea, and no worsening of symptoms at 76–120 hours, without any rescue antibacterial therapy), with rates of 81.1% and 82.7%, respectively; the corresponding rates of investigator-assessed clinical response at 5–10 days after the last dose were 87.6% and 85.1%. After commencing treatment, adverse events were reported by 41.1% of the omadacycline arm and 48.5% of the moxifloxacin arm; the most commonly reported events were gastrointestinal (10.2% and 18.0%, respectively), with diarrhoea affecting fewer omadacycline recipients than moxifloxacin recipients (1.0% vs. 8.0%).

Comment: This RCT introduces a new antibiotic, derived from the tetracycline class, that overcomes the mechanism of tetracycline resistance. The research team, with the first three authors from Zaporizhzhia, Bucharest and Manila, co-ordinated 86 centres in Europa, North America, South America, Middle East, Africa and Asia to randomise patients with severe CAP to moxifloxacin or omadacycline. Overall, omadacycline was well tolerated with only minor side effects. **Bottom line: once-daily omadacycline was noninferior to moxifloxacin for the treatment of adults hospitalised for CAP.**

Reference: N Engl J Med 2019;380:517–27
Abstract

Mortality in patients with community-onset pneumonia at low risk of drug-resistant pathogens: impact of β-lactam plus macrolide combination therapy

Authors: Okumura J et al., on behalf of the Central Japan Lung Study Group

Summary: This *post hoc* analysis of data from a prospective cohort of patients with CAP (community-acquired pneumonia) at low risk of a drug-resistant pathogen evaluated 30-day differences in mortality between those treated with non-antipseudomonal β-lactam monotherapy (n=369) and those who additionally received a macrolide (n=225). Compared with monotherapy recipients, those who received a non-antipseudomonal β-lactam plus a macrolide had a significantly lower 30-day mortality rate (1.8% vs. 13.8%; adjusted odds ratio 0.28 [95% CI 0.09, 0.87]). Factors significantly, independently associated with 30-day mortality included $PaCO_2$ >50mm Hg, leucocyte count <4000 cells/mm^3, nonambulatory status, albumin level <3.0 g/dL, haematocrit <30%, age ≥80 years, respiratory rate >25 breaths per minute and body temperature <36°C.

Comment: A group of Japanese researchers from Nagoya retrospectively reviewed the 30-day mortality of around 600 patients with CAP. Around 350 were treated with a β-lactam antibiotic alone, and around 250 were treated with a combination of β-lactam/macrolide antibiotics. The mortality rate in the first group was 18%, compared with less than 2% in the combination group. Grant Waterer wrote the editorial, reviewing other evidence for early treatment and combination therapy with a macrolide. In case he would ever be admitted with CAP, his **bottom line is: *"a macrolide followed a short time later by a third generation cephalosporin please, preferably getting both within 2 h of presenting".***

Reference: Respirology 2018;23:526–34
Abstract

Bacteriology and clinical outcomes of patients with culture-positive pleural infection in Western Australia

Authors: Brims F et al.

Summary: These authors presented a 6-year analysis of the bacteriology and clinical outcomes of 601 Western Australian adults with CCPI (culture-positive pleural infection); 894 bacterial isolates were identified. Hospital- and community-acquired CPPI was documented for 66.2% and 27.3% of the patients, respectively, with the remainder classified as oesophageal rupture/leak. The proportion of patients with comorbidities was 65.2%, mostly cancer. There was radiological evidence of pneumonia in 43.8% and 27.3% of patients with community- and hospital-acquired CPPI, respectively. *Streptococcus* spp. (32.9%), particularly viridans streptococci group, were the most frequently occurring of the 153 bacterial strains cultured among patients with community-acquired CPPI, whereas *Staphylococcus aureus* (11.6%) and Gram-negative (31.9%) infections were the most frequent among patients with hospital-acquired CCPI. The respective in-hospital mortality rates were similar for patients with community- versus hospital-acquired CCPI (13.4% vs. 16.6% [p=0.417]), but a significant difference was seen for 1-year mortality (32.4% vs. 45.5% [p=0.006]).

Comment: Our colleagues from Perth followed more than 600 cases of patients with culture-positive empyema. Given that about half of the 4 million patients with pneumonia develop an effusion, it is surprising how little we know about empyema. The Perth group found evidence of pneumonia in only about 40% of the community-acquired culture-positive effusions and in less than 30% of hospital-acquired ones. Pyng Lee provides context in the accompanying editorial, as well as linking back to Hippocrates. **Bottom line: patients with a community-acquired infection have a more than 30% and patients with a hospital-acquired pleural infection have a 45% 1-year mortality.**

Reference: Respirology 2019;24:171–8
Abstract

A pilot feasibility study in establishing the role of ultrasound-guided pleural biopsies in pleural infection

Authors: Psallidas I et al.

Summary: The AUDIO study recruited 20 patients with pleural infection to evaluate the feasibility of using ultrasound-guided pleural biopsy culture to increase microbiological yield. Exploratory analyses used the 16S ribosomal RNA technique to assess its utility for increasing microbiological diagnosis speed and accuracy. There were no adverse events associated with ultrasound-guided pleural biopsy, which increased microbiological yield compared with pleural fluid and blood culture samples (45% vs. 20% and 10%, respectively). The 16S ribosomal RNA technique was successfully applied to pleural biopsy samples, with sensitivity and specificity values of 93% and 89.5%, respectively.

Comment: This is an intriguing proof-of-concept study exploring pleural infections, which, according to the authors, occur in the US and UK in 80,000 people per year, with 220 new cases per day. Making a microbiological diagnosis using standard techniques is often surprisingly difficult. These researchers used ultrasound guidance to avoid the intercostal arteries, the biopsy 'guns' used for lung fine needle aspirates, and DNA extraction tuning into the bacterial ribosomal DNA. **Bottom line: pleural biopsies were safe in patients with pleural infections and increased the microbiological yield to confirm a diagnosis.**

Reference: Chest 2018;154:766–72
Abstract

Predictive variables for failure in administration of intrapleural tissue plasminogen activator/deoxyribonuclease in patients with complicated parapneumonic effusions/empyema

Authors: Khemasuwan D et al.

Summary: This retrospective analysis included the medical charts of 84 patients receiving chest tube drainage and combined intrapleural therapy with tPA (tissue plasminogen activator) and DNase (deoxyribonuclease) for complicated pleural effusion/empyema. The study researchers sought to determine which clinical and radiological features indicate failure of combined intrapleural therapy. Two-thirds of the patients achieved resolution of complicated pleural effusion/empyema with intrapleural tPA/DNase. The researchers coupled an ensemble machine learning method with decision trees and hyperparameter tuning to mitigate overfitting to rank the importance of 19 candidate clinical variables with respect to their ability to predict failure of tPA/DNase therapy. Of all candidate predictors, the presence of pleural thickening was the most important (48% relative importance), followed by the presence of an abscess or necrotising pneumonia (24%), the pleural protein level (6%) and the presence of loculated effusion (4%).

Comment: In this retrospective study of 84 patients, the North American authors explored factors reducing the success rate of tPA/DNase in patients with a complicated pleural effusion or empyema. Their overall success rate seemed low at 68% and 27 patients required surgical intervention. The authors don't comment on the timing of installing fibrinolytic therapy and are tough on their expectation of (near) complete resolution. They used a machine learning algorithm and identified features suggesting a low success rate of fibrinolysis (Chest). **Bottom line: pleural thickening, lung abscess and necrotising pneumonia are risk factors for failure of fibrinolytic therapy.**

Reference: Chest 2018;154:550–6
Abstract