Making Education Easy

Issue 102 - 2022

In this issue:

Abbreviations used in this issue:

ARDS = acute respiratory distress syndrome; **BMI** = body mass index; **CLAD** = chronic lung allograft dysfunction; **ELU** = ELISA laboratory units; **FEV1** = forced expiratory volume in 1 second; **FiO2** = fraction of inspired oxygen; **ICU** = intensive care unit; **ILD** = interstitial lung disease; **IL-6** = interleukin-6; **IPF** = idiopathic pulmonary fibrosis; **IQR** = interquartile range; **OR/aOR** = (adjusted) odds ratio; **PaO2** = partial pressure of oxygen; **RCT** = randomised control trial; **UC** = usual care.

Welcome to issue 102 of Respiratory Research Review.

We begin this issue with a post-hoc analysis of a RCT that explores the association between terminal pleural elastance and radiographic lung re-expansion after therapeutic thoracentesis in patients with symptomatic pleural effusion. This is followed by an interesting economic evaluation of an open-label RCT in the UK, which compared the cost-effectiveness of outpatient ambulatory management of primary spontaneous pneumothorax with standard management, showing outpatient treatment accumulated fewer costs than inpatient treatment. The next paper reports the relationship between allograft dysfunction, mortality and depressive symptoms over time in patients who underwent lung transplantation. We conclude this issue with the prospective, longitudinal PHOSP-COVID study, which explored the clinical recovery outcomes for patients hospitalised for COVID-19 at 5 months and 1 year after discharge.

We hope you enjoy this update in Respiratory research, and we look forward to receiving your comments and feedback.

Kind Regards,

Dr Stephen Milne
stephen.milne@researchreview.com.au

Association between terminal pleural elastance and radiographic lung re-expansion after therapeutic thoracentesis in patients with symptomatic pleural effusion

Authors: Lester M et al.

Summary: This post-hoc analysis of a RCT conducted at two university hospitals in the USA evaluated the relationship between lung re-expansion on pleural physiology and post-pleural draining chest imaging, assessing the concordance of radiographic with normal terminal pleural elastance over the final 200mL aspirated. Eligible patients ≥18 years with symptomatic pleural effusions of at least 0.5mL (n=61) allocated to manometry-guided therapeutic thoracentesis were included in the analysis. Successful lung re-expansion was indicated by 69% of post-thoracentesis chest radiographs and 56% of thoracic ultrasounds, however 71% of patients expandable by radiograph and 77% of those expandable by ultrasound had abnormal visceral pleural recoil. Radiographic lung re-expansion for normal visceral pleural recoil had a positive predictive value of 24%, and a sensitivity of 44%.

Comment: Ambulatory pleurodesis (e.g., talc slurry) has low overall success rates. One potential predictor of pleurodesis failure is high pleural elastance caused by recoil of the visceral pleura and underlying lung. This analysis used pleural manometry during fluid drainage to classify participants as having normal or abnormal pleural elastance. The key finding was that full radiographic re-expansion after fluid drainage was a poor surrogate of 'normal' pleural physiology. The authors suggest that using radiographic re-expansion to select patients for pleurodesis may, in part, explain the poor success rate of the procedure. Whether pleural manometry could be used in this way depends on factors such as availability of equipment and training, but ultimately more RCT data are necessary.

Reference: BMJ Open. 2022;12(7):e053606
Abstract

Cost-effectiveness of ambulatory care management of primary spontaneous pneumothorax

Authors: Luengo-Fernandez R et al.

Summary: The cost-effectiveness of outpatient ambulatory management of primary spontaneous pneumothorax was compared with standard management (chest tube insertion and/or aspiration) in this economic evaluation of an open-label RCT in the UK. Eligible patients (n=236) were randomised to be treated with either an ambulatory device (n=117) or standard care (n=119). At a follow-up of 12 months, there were significantly lower National Health Service healthcare costs for patients in the ambulatory care group than for those in the standard care group (–£788; 95% CI difference –1527 to –50; p=0.037). The incremental cost-effectiveness ratio was £799,066 per quality-adjusted life-years gained, and the cost-effectiveness of ambulatory care had a probability of 0.93.

Comment: This was a cost-benefit analysis of a previous trial which showed that outpatient management of primary spontaneous pneumothorax was safe and effective. This analysis showed that outpatient treatment accumulated fewer costs than inpatient treatment. Importantly, this included the costs in the lead up to emergency presentation, ambulatory treatments/visits, and any subsequent complications. A major limitation was that there were quite a lot of missing data, which required multiple imputations. Nevertheless, this is further evidence of the benefits of outpatient management of primary spontaneous pneumothorax, the uptake of which remains low according to most available data.

Reference: Thorax. 2022;77(9):913-8
Abstract

Depressive symptoms in lung transplant recipients

Authors: Kolaitis N A et al.

Summary: This study examined the relationship between allograft dysfunction, mortality and depressive symptoms over time in 266 participants who underwent lung transplantation, using the Geriatric Depression Scale. Overall, transplantation was associated with an improvement in depressive symptoms while a worsening of depressive symptoms following transplant was associated with decreased FEV1 (–1.62% change; 95% CI –2.49 to –0.76) and an increased risk of mortality (HR 1.25; 95% CI 1.05—1.50). Visual analyses indicated that CLAD could be preceded by worsening depressive symptoms.

Comment: Approximately half of the participants in this study experienced at least mild depressive symptoms prior to lung transplantation, most of whom showed improvement or resolution of their depression soon after transplantation. However, a number of patients who developed CLAD showed signs of depression prior to the onset of CLAD: among these patients, three quarters showed factors that may have contributed to CLAD such as missed appointments and poor medication adherence. The novel time-dependent analysis suggests that at least some of the association between CLAD and post-transplant depression could be explained by changes in FEV1: however this analysis cannot answer the question of which comes first – depression leading to behaviours predisposing to CLAD, or vice versa. This is important to understand since post-transplant depression may be a modifiable risk factor for CLAD.

Reference: Thorax. 2022;77(9):891-9
Abstract

Impact of concomitant medication burden on tolerability of disease-targeted therapy and survival in interstitial lung disease

Authors: Khor Y H et al.

Summary: These researchers explored the correlations between the survival and tolerability of ILD-targeted medications and concomitant medication burden in patients with IPF and non-IPF ILD. Two Canadian and Australian registries provided data for patients with IPF treated with nintedanib or pirfenidone (n=645) and patients with non-IPF ILD treated with mycophenolate or azathioprine (n=1255). Within 6 months of commencing treatment, 43% of patients with IPF had adverse reactions which prompted dose reduction, temporary dose interruption or permanent cessation, and intolerance was significantly associated with medication regimen complexity index (p=0.04), polypharmacy (p=0.006) and medication count (p=0.005), however there was no such association observed in patients with non-IPF ILD on immunosuppressive medications. At 1 year, there was no association between the permanent cessation of immunosuppressive or antifibrotic medications with concomitant medication burden. Transplant-free survival was associated with the medication regimen complexity index in both groups (both p<0.01).

Comment: Drug-related adverse effects are important considerations when treating ILD. Critically, they are also an important cause of treatment discontinuation, and being able to predict which patients are most likely to suffer adverse effects may improve management plans. In this study, intolerance of anti-fibrotic therapy was observed in almost half of patients with IPF, and the number and complexity of concomitant medications before treatment were predictors of intolerance at 6 months. These observations did not apply to immunosuppressive therapy in non-IPF ILD, but we can't be sure if this is due to drug or patient/disease factors. Reducing concomitant medication complexity prior to initiating anti-fibrotic therapy in IPF may lead to improved tolerance, but this remains to be tested.

Reference: Ann Am Thorac Soc. 2022;19(6):962-70
Abstract

Risk factors for developing COVID-19

Authors: Holt H et al.

Summary: The risk factors for developing COVID-19 were explored in this prospective, population-based longitudinal study (COVIDENCE UK). In a total of 15,227 participants <16 years, 446 cases of COVID-19 were identified. Baseline information from online questionnaires revealed that risk factors associated with increased odds of developing COVID-19 included raised BMI (aOR 1.50; 95% CI 1.19—1.89 for BMI 25.0–30.0 kg/m^2 and 1.39; 95% CI 1.06—1.84 for BMI >30.0 kg/m^2 vs. BMI <25.0 kg/m^2), household overcrowding (aOR per additional 0.5 people per bedroom 1.26; 95% CI 1.11—1.43), visits to or from other households within one week prior vs. no visits (aOR 1.31; 95% CI 1.06—1.62), frontline work excluding health or social care vs. no frontline work (aOR 1.49; 95% CI 1.12—1.98) and Asian vs. white ethnicity (aOR 2.28; 95% CI 1.33—3.91). Those participants who had atopic disease had decreased odds of developing COVID-19 (aOR 0.75; 95% CI 0.59—0.97), and factors including age, sex, diet, micronutrient supplement use and other medical conditions did not have any independent associations.

Comment: The exciting thing about this analysis is that the investigators captured detailed information on lifestyle and behaviour such that the risk factors for COVID-19 could be determined independent of these potential confounders. The only independent 'biological' risk factor for SARS-CoV-2 infection was increased BMI, but the other independent risk factors included household overcrowding, visiting other households, and 'frontline' work outside of health care. The 'dose dependence' of social contact reaffirms the strategy of social distancing for COVID-19 prevention. Interestingly, Asian race was associated with increased risk of infection which confirms previous findings, but this was independent of the social/behavioural factors that may explain this increased risk. This exposes ethnic disparities that deserve extra attention as the pandemic progresses.

Reference: Thorax. 2022;77(9):900-12
Abstract

Safety, immunogenicity, and reactogenicity of BNT162b2 and mRNA-1273 COVID-19 vaccines given as fourth-dose boosters following two doses of ChAdOx1 nCoV-19 or BNT162b2 and a third dose of BNT162b2 (COV-BOOST)

Authors: Munro A P S et al.

Summary: This sub-study of the phase 2, multicentre, blinded RCT, COV-BOOST conducted across 18 locations in the UK evaluated the immunogenicity, reactogenicity and safety of a fourth-dose booster of COVID-19 vaccines. Eligible patients (n=166; 48% male; median age 70.1 years) who had received the Pfizer-BioNTech BNT162b2 as their third booster were randomised 1:1 to be administered either full-dose BNT162b2 (30µg in 0.30mL; n=83) or half-dose Moderna mRNA-1273 (50µg in 0.25mL; n=83), at a median of 208.5 days after their third dose. The fourth-dose booster vaccines were well tolerated: the most common local solicited adverse event was mild-moderate pain, and the most common systemic solicited adverse events were fatigue, headache, muscle ache and malaise. The geometric mean anti-spike protein IgG concentration increased significantly between Day 28 after the third dose and Day 14 after the fourth dose in both the BNT162b2 and mRNA-1273 groups, respectively ([23,325 ELU/mL; 95% CI 20,030—27,162 to 37,460 ELU/mL; 95% CI 31 996—43 857; geometric mean 1.59; 95% CI 1.41—1.78] and [25 317 ELU/mL; 95% CI 20,996—30,528 to 54,936 ELU/mL; 95% CI 46,826—64,452; geometric mean fold change of 2.19; 95% CI 1.90—2.52]). From before Day 0 to after Day 14, both BNT162b2 and mRNA-1273 groups experienced respective anti-spike protein IgG titre fold changes of 12.19 (95% CI 10.37—14.32) and 15.90 (12.92—19.58), and boosted T-cell responses of 7.32 (95% CI 3.24—16.54) and 6.22 (95% CI 3.90—9.92).

Comment: Although this was a small sub-study nested within a larger RCT, it raised some interesting points. First, the largest immune responses (anti-spike IgG) were seen in those with the lowest baseline antibody levels while people with high baseline levels or recent SARS-CoV-2 infection had smaller increases. This suggests there may be a 'ceiling' for antibody responses which may need to be taken into account when timing or prioritising booster shots. Second, mixed schedules of COVID-19 vaccines (i.e., mixing of different vaccine types/brands) were well-tolerated with no safety signals. Third, mixed booster (Pfizer-BioNTech third dose followed by Moderna fourth dose) may produce a stronger antibody response than homologous dosing – this agrees with other observational data but needs further testing.

Reference: Lancet Infect Dis. 2022;22(8):1131-41
Abstract

Defibrotide Therapy for SARS-CoV-2 ARDS

Authors: Frame D et al.

Summary: The tolerability and safety of defibrotide in patients with severe COVID-19 infections and COVID-related ARDS was explored in this prospective, open-label single-centre safety trial. Eligible patients ≥18 years (n=12; median age 63.0 years; 10 receiving mechanical ventilation; 6 receiving vasopressor support) were administered defibrotide 6.25mg/kg four times daily for a median of 7 days. During therapy, there were no thrombotic or haemorrhagic complications and no adverse events attributable to defibrotide. Within the first 72 hours of therapy, all four patients who met the Day 7 pulmonary response parameter showed a decrease in serum D-Dimer levels. After 11, 17 and 34 days of study initiation, three patients died, and the 30-day all-cause mortality rate was 17% (95% CI 0—35). After 64-174 days of beginning defibrotide treatment, nine patients (75%) remained alive. All three patients who had a baseline PaO_2 to FiO_2 ratio of <125 mmHg died, and all of those with a baseline ratio of ≥125 mmHg survived.

Comment: This was a really interesting feasibility study for the use of defibrotide in critically ill COVID-19 patients. This drug is used for the treatment of hepatic venoocclusive disease in stem cell transplant recipients (TGA-approved in Australia for this indication only) and has both antifibrotic and anti-inflammatory properties. None of the 12 patients treated in this open-label study experienced bleeding or thrombotic complications, even those who also received prophylactic anticoagulation with heparin. The study was not designed to assess efficacy, but the clinical improvements and mortality compare favourably to other critical COVID-19 patients. There are at least two ongoing trials of defibrotide treatment in COVID-19, which should provide more data.

Reference: Chest. 2022;162(2):346-55
Abstract

Effect of interleukin-6 receptor antagonists in critically ill adult patients with COVID-19 pneumonia

Authors: Hermine O et al., on behalf of the CORIMUNO-19 collaborative group

Summary: In these two multicentre, open-label RCTs, researchers examined whether anti-IL-6 receptors improved the outcomes of patients critically ill with COVID-19 pneumonia. In the TOCI-2 trial, eligible patients were randomly assigned to receive either usual care (UC; n=46) or UC + intravenous tocilizumab 8mg/kg (n=51) on Day 1 and 3 if needed. There were no significant between-group differences in the proportions of patients alive without any non-invasive ventilation or mechanical ventilation by Day 14 (47% vs. 42%; HR 1.19; 90% CI 0.71—2.04). Eligible patients in the SARI-2 trial were randomised to receive either UC (n=41) or UC + intravenous sarilumab 200mg (n=50) on Day 1 and 3 if needed. Similarly, there were no significant between-group differences in the proportions of patients alive without any non-invasive ventilation or mechanical ventilation by Day 14 (38% vs. 33%; HR 1.05; 90% CI 0.55—2.07). Up to 90 days, the risk of death for UC vs. UC + tocilizumab was 30% vs. 24% (HR 0.67), and the risk of death for UC vs. UC + sarilumab was 39% vs. 29% (HR 0.74).

Comment: Overall, this was a negative study in that treatment with either anti-IL-6 receptor antibody did not significantly improve survival in critically ill COVID-19 patients. This conflicts with other studies including the large RECOVERY trial. The discordance may be explained by the fact that the present trial was conducted very early in the pandemic, and none of the patients received dexamethasone. Additionally, most of the patients were treated with the anti-IL-6R antibodies at a relatively late stage (>24 hours after arrival in ICU). One potentially important factor that has not been considered is patient selection: previous data suggest that patients with IL-6-driven inflammation and the highest IL-6 levels at baseline may derive the most benefit from anti-IL-6 treatments.

Reference: Eur Respir J. 2022;60(2):2102523
Abstract

Effect of high versus low dose of dexamethasone on clinical worsening in patients hospitalised with moderate or severe COVID-19 pneumonia: an open-label, randomised clinical trial

Authors: Taboada M et al.

Summary: These researchers compared the efficacy of low- vs. high-dose dexamethasone in patients hospitalised with COVID-19 requiring oxygen therapy for respiratory failure in this open-label, parallel-group RCT. Eligible patients aged ≥18 years (n=200; mean age 64.3 years; 62% male) were randomised 1:1 to receive standard care plus 6mg dexamethasone once daily for 10 days (low-dose; n=102) or 20mg dexamethasone twice daily for 5 days, before 10mg once daily for 5 days (high-dose; n=98). At the discretion of the medical team, patients could receive additional clinical intervention including anticoagulants, antibiotics, antiviral agents and other immunomodulators, and a high dose of dexamethasone as a rescue therapy. Within 11 days of randomisation, a higher proportion of patients in the low-dose group experienced clinical worsening compared to those in the high-dose group (31.4% vs. 16.3%; 95% CI 0.216—0.842; p=0.014; primary outcome). There were no significant between-group differences in the secondary outcomes of 28-day mortality, time to recovery or clinical status at days 5, 11, 14 and 28.

Comment: There is little information available as to what is the optimum dose of corticosteroid in critically ill COVID-19 patients and in particular, whether there is any benefit in less severe patients. This study specifically addressed this issue by comparing the 'RECOVERY' trial dose (dexamethasone 6mg x 10 days) to a higher dose in patients requiring oxygen therapy but not high-flow or mechanical ventilation. The higher dose had improved time to clinical improvement, but not mortality. Note that patients in the low-dose arm were allowed 'rescue therapy' with the higher dose if they deteriorated, which may have diluted any effect on mortality. More studies are necessary before this approach could be considered standard-of-care, but it is a further reminder that the treatment landscape in COVID-19 is always changing.

Reference: Eur Respir J. 2022;60(2):2102518
Abstract

Independent commentary by Dr Stephen Milne

Dr Milne is a respiratory physician and Postdoctoral Research Fellow at University of British Columbia Centre for Heart Lung Innovation, and Postdoctoral Senior Research Fellow at University of Sydney. His current research programme is on the genomics of COPD and the discovery of novel biomarkers.

RACP MyCPD Program participants can claim **one credit per hour** (maximum of 60 credits per year in Category One – Educational Activities) **for reading and evaluating Research Reviews.**

Please CLICK HERE to download CPD Information

Clinical characteristics with inflammation profiling of long COVID and association with 1-year recovery following hospitalisation in the UK

Authors: Evans R A et al., on behalf of the PHOSP-COVID Collaborative Group

Summary: The clinical recovery outcomes for patients hospitalised for COVID-19 were explored in this prospective, longitudinal observational Post-Hospitalisation COVID-19 study (PHOSP-COVID). Researchers examined the self-reported outcome measures, organ function and physical performance of eligible patients aged ≥18 years (n=807; 64.4% male; mean age 58.7 years; 27.8% had received mechanical intervention) who were discharged from hospital between March 2020 and April 2021 at both 5 months and 1 year following discharge. Between these points of follow-up, there was no change in the proportion of patients who reported full recovery (25.5% vs. 28.9%), and patients with factors including female sex, obesity and invasive mechanical ventilation were less likely to report full recovery at 1 year (ORs 0.68; 0.50; 0.42; respectively). Both clusters with "Very Severe" and "Moderate" physical health, mental health and cognitive impairment at 5 months had increased inflammatory mediators of tissue damage and repair, and increased IL-6 concentrations. At 1 year after discharge, there were minimal improvements across all outcome measures for all patients, and the median EQ-5D-5L utility index (mobility, self-care, usual activities, pain & discomfort, anxiety & depression) was also substantially decreased from before COVID-19 (retrospective assessment; 0.88; IQR 0.74-1.00) to both 5 months (0.74; IQR 0.64–0.88) and 1 year after discharge (0.75; IQR 0.62–0.88).

Comment: The primary outcome for this study was the response to a very simple question: "Do you feel fully recovered?". The prevalence of self-perceived non-recovery was quite high at 1 year (over 70% answered "No" or "Not sure"). However, this was supported by validated instruments measuring anxiety/depression, quality of life, functional capacity, dyspnoea, and exercise capacity. Interestingly the top plasma protein correlated with non-recovery, TFF2, is associated with airway epithelial dysfunction, suggesting there may be ongoing mucosal abnormalities in the lungs. It must be noted however, that this patient cohort was infected and treated in late 2020. The results may therefore not be generalisable to the "modern era" of COVID with newer variants and widespread vaccination.

Reference: Lancet Respir Med. 2022;60(2):2102518
Abstract