Respiratory Research Review™

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Abbreviations used in this issue:

AHI = apnoea-hypopnoea index; **ARDS** = acute respiratory distress syndrome; **aRR** = adjusted risk ratio; **BT** = bronchial thermoplasty; **COPD** = chronic obstructive pulmonary disease; **CPAP** = continuous positive airway pressure; **Fio2** = fraction of inspired oxygen; **HRQoL** = health-related quality of life; **IFN** = interferon; **MRSA** = methicillin-resistant Staphylococcus aureus; **NIV** = noninvasive ventilation; **OHS** = obesity hypoventilation syndrome; **OSA** = obstructive sleep apnoea; **Pao2** = pressure of arterial oxygen; **PImax** = maximal inspiratory pressure; **SF36** = Short Form-36; **Spo2** = oxygen saturation.

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Welcome to the 82nd issue of Respiratory Research Review.

The first article in this issue reports the results of a randomised clinical trial of intravenous interferon β-1a treatment for patients with moderate to severe ARDS. The trial failed to show an improvement in any important clinical outcomes. In addition, treatment was associated with a high number of adverse events. Results from another randomised controlled trial suggest early administration of dexamethasone could reduce duration of mechanical ventilation and overall mortality in patients with moderate-to-severe ARDS. An Australian and New Zealand trial including 1000 patients on mechanical ventilation found the use of conservative oxygen therapy, as compared with usual oxygen therapy, did not significantly affect the number of ventilator-free days. Another study reports early exposure to a conservative-oxygenation strategy compared to liberal oxygen therapy did not increase survival among patients with ARDS.

Researchers assessed the echocardiographic changes with positive airway pressure therapy in obesity hypoventilation syndrome. They found in patients with obesity hypoventilation syndrome who have concomitant severe obstructive sleep apnoea, long-term treatment with noninvasive ventilation and CPAP led to similar degrees of improvement in pulmonary hypertension and left ventricular diastolic dysfunction. The MERGE trial reported CPAP improved the quality of life in patients with mild obstructive sleep apnoea. Other topics reviewed in this issue include bronchial thermoplasty, thoracentesis, COPD, and antibiotic therapy for pneumonia.

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

Kind Regards,

Professor Peter Wark

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Effect of intravenous interferon β-1a on death and days free from mechanical ventilation among patients with moderate to severe acute respiratory distress syndrome: A randomized clinical trial

Authors: Ranieri VM, et al

Summary: The multicentre, randomised, double-blind, parallel-group trial was conducted at 74 intensive care units in 8 European countries between December 2015-December 2017. The cohort of 301 adults with moderate to severe ARDS were randomised to receive an intravenous injection of 10 µg of interferon (IFN) β-1a (n=144) or placebo (n=152) once daily for 6 days. The primary outcome was a score combining death and number of ventilator-free days at day 28. The authors reported the median composite score of death and number of ventilator-free days at day 28 was 10 days in the IFN-β-1a group and 8.5 days in the placebo group (P = .82). In addition, there was no significant difference in 28-day mortality between the IFN-β-1a vs placebo groups (26.4% vs 23.0%). Adverse events considered to be related to treatment were experienced by 28.5% in the IFN-β-1a group and 21.7% in the placebo group.

Comment: There are no effective therapies for ARDS and particularly in the current pandemic where death from COVID-19 is the result of ARDS, intervention trials are needed. This randomised trial of intravenous IFN-β-1a in moderate to severe ARDS however failed to show an improvement in any important clinical outcomes. In addition, treatment was associated with a high number of adverse events. This trial is likely to discount this as a treatment for ARDS.

Reference: JAMA. 2020 Feb 17 [Online ahead of print]

Abstract

Empirical anti-MRSA vs standard antibiotic therapy and risk of 30-day mortality in patients hospitalized for pneumonia

Authors: Jones BE, et al

Summary: This retrospective multicentre cohort study included patients who received either empirical anti-methicillin-resistant Staphylococcus aureus (MRSA) or standard empirical antibiotic regimens for community-onset pneumonia. Among the study cohort of 88 605 patients, empirical anti-MRSA therapy was administered to 38%; 10% died within 30 days. Compared with standard therapy alone, empirical anti-MRSA therapy plus standard therapy was significantly associated with an increased adjusted risk of death (adjusted risk ratio [aRR], 1.4), kidney injury (aRR, 1.4), and secondary C difficile infections (aRR, 1.6), vancomycin-resistant Enterococcus spp infections (aRR, 1.6), and secondary gram-negative rod infections (aRR, 1.5). The researchers reported similar associations between anti-MRSA therapy use and 30-day mortality were found (aRR, 1.6) and among patients admitted to the intensive care unit (aRR, 1.3), those with a high risk for MRSA (aRR, 1.2), and those with MRSA detected on surveillance testing (aRR, 1.6). They also noted no significant favourable association between empirical anti-MRSA therapy and death among patients with MRSA detected on culture (aRR, 1.1).

Comment: In populations with a high prevalence of MRSA and a high risk of infection, empirical treatments that include antibiotics to cover MRSA are frequently used. This US based large VA cohort study has examined the effect of treatment with regimes that largely contain vancomycin. They found no benefits and in fact the reverse was clearly the case, with empirical vancomycin regimes being associated with increased mortality and acquisition of vancomycin-resistant enterococci. Some of this may be confounded by disease severity. However the findings that increased acute kidney injury and higher rates of Clostridium difficile suggest that broader spectrum antibiotic selection and regimes that are potentially nephrotoxic are more likely to result in side effects in this population.

Reference: JAMA Intern Med. 2020 Feb 17;180(4):552-560
Abstract

Conservative oxygen therapy during mechanical ventilation in the ICU

Authors: Mackle D, et al

Summary: The study cohort of 1000 ICU patients who required mechanical ventilation were randomly assigned to receive conservative or usual oxygen therapy. In the two groups, the default lower limit for oxygen saturation as measured by pulse oximetry (Spo2) was 90%. In the conservative group, the upper limit of the Spo2 alarm was set when the level reached 97%, and the fraction of inspired oxygen (Fio2) was decreased to 0.21 if the Spo2 was above the acceptable lower limit. In the usual-oxygen group, there were no specific measures limiting the Fio2 or the Spo2. The investigators reported number of ventilator-free days did not differ significantly between the conservative-oxygen group and the usual-oxygen group, with a median duration of 21.3 days and 22.1 days, respectively (P = 0.80). The conservative-oxygen group spent more time in the ICU with an Fio2 of 0.21 than the usual-oxygen group, with a median duration of 29 hours and 1 hour, respectively. In addition, the conservative-oxygen group spent less time with an Spo2 exceeding 96%, with a duration of 27 hours and 49 hours, respectively. At 180 days, mortality was 35.7% in the conservative-oxygen group and 34.5% in the usual-oxygen group, for an unadjusted odds ratio of 1.05.

Comment: In people with chronic lung disease and cardiac failure, strategies that titrate or restrict the overuse of oxygen have been shown to be associated with fewer adverse effects and better outcomes. The reasons for this are unclear and probably manifold, however hyperoxia inducing excessive reactive oxidative stress is proposed as a leading mechanism. In this Australian and New Zealand trial 1000 patients on mechanical ventilation were randomised to receive conservative oxygen, where the Fio2 was capped and reduced if Spo2 exceeded 97%, with the lower limits in both arms Spo2 90%. The conservative arm did spend less time with Spo2 >96%. However, no difference was seen in mortality and those in the conservative arm did not have a faster wean from ventilation, with no difference in ventilator free days. There was a small excess in the 180 day mortality in the conservative arm of uncertain significance. It's possible that any effect of hyperoxia in this population is relatively small and less important when compared to other ventilator interventions and/or the overall severity of the clinical conditions. The population described here are also likely heterogeneous in their background and need for ventilation. These results as yet do not put this question to rest. They are interesting though in light of the trial by Barrot et al in ARDS (*Barrot L, et al. N Engl J Med. 2020 Mar 12;382(11):999-1008*).

Reference: N Engl J Med. 2020 Mar 12;382(11):989-998
Abstract

Liberal or conservative oxygen therapy for acute respiratory distress syndrome

Authors: Barrot L, et al

Summary: This multicentre, randomised trial assigned patients with ARDS to receive either conservative oxygen therapy (target Pao2, 55 to 70 mm Hg; Spo2, 88 to 92%) or liberal oxygen therapy (target Pao2, 90 to 105 mm Hg; Spo2, ≥96%) for 7 days. After the enrolment of 205 patients the data and safety monitoring board prematurely stopped the trial due to safety concerns. At day 28, 34.3% in the conservative-oxygen group and 26.5% in the liberal-oxygen group had died. At day 90, 44.4% of the patients in the conservative-oxygen group and 30.4% of the patients in the liberal-oxygen group had died.

Comment: In an interesting study to compare with the ICU-ROX trial this trial randomised people specifically with ARDS to a stricter conservative Spo2 regime, aiming for a Pao2 55-70mmHg (the current recommended ARDS net protocol), compared to a much more liberal target of 90 to 105mmHg. In an interesting move the trial was terminated after enrolling 205 patients due to futility and safety, with the development of mesenteric ischaemia in 5 people in the conservative arm and none in the usual care group. A higher heart rate was also observed in the conservative arm. The premature stopping of the trial while understandable, clearly poses questions over the findings. It is likely the lower oxygen target is not clearly superior and it is possible it may be harmful or too low. The investigators admitted that the conservative arm may also have seen more changes in ventilation, as those with lower Fio2 may have allowed investigators to switch from controlled ventilation earlier in the conservative arm.

Interestingly these trials raise more questions than answers. They are unlikely to lead to switching to the very liberal approach used by Barrot et al, (*Barrot L, et al. N Engl J Med. 2020 Mar 12;382(11):999-1008*), but do raise concerns over the current standard of care. In the setting of respiratory failure in the ICU there may well be a higher systemic oxygen requirement than outside of the ICU. The adverse effects of hyperoxia may be less important also in this setting. In either case this question now importantly needs to be examined further in clinical trials.

Reference: N Engl J Med. 2020 Mar 12;382(11):999-1008
Abstract

Continuous positive airway pressure versus standard care for the treatment of people with mild obstructive sleep apnoea (MERGE): A multicentre, randomised controlled trial

Authors: Wimms AJ, et al

Summary: The MERGE trial assessed the clinical effectiveness of continuous positive airway pressure (CPAP) in patients with mild obstructive sleep apnoea (OSA). Patients with mild obstructive sleep apnoea (apnoea-hypopnoea index [AHI] ≥5 to ≤15 events per h) were enrolled from 11 UK sleep centres. Participants were assigned to either 3 months of CPAP plus standard care (n=115), or standard care alone (n=118) with 90% completing the trial. The primary outcome was a change in the score on the Short Form-36 (SF36) questionnaire vitality scale. The investigators found the vitality score significantly increased with a treatment effect of a mean of 10.0 points (p<0.0001) after 3 months of CPAP, compared with standard care alone (9.2 points vs -0.8 points). They noted three serious adverse events occurred (one in the CPAP group) and all were unrelated to the intervention.

Comment: This UK trial assessed the effect of CPAP on people with mild OSA, AHI 5-15. They showed that treatment did improve quality of life, as measured by the SF36 as well as other secondary outcomes. These findings are consistent with previous studies and likely highlight the fact that if people are symptomatic with mild OSA, they derive an improvement in symptoms from CPAP. This is not the same though as clinical benefit in outcomes such as hypertension or cardiovascular disease. The trial also achieved very good adherence, something unlikely to be achieved in a clinical practice setting. The key to treatment would seem to be the presence of symptoms and improvement with treatment.

Reference: Lancet Respir Med. 2020 Apr;8(4):349-358
Abstract

Dexamethasone treatment for the acute respiratory distress syndrome: A multicentre, randomised controlled trial

Authors: Villar J, et al

Summary: The team enrolled patients with established moderate-to-severe ARDS from 17 ICUs across Spain. Patients were randomly assigned to dexamethasone group (n=139) and to control group (n=138). The data safety monitoring board stopped the trial due to low enrolment rate after enrolling more than 88% of the planned sample size. The team reported mean number of ventilator-free days was higher in the dexamethasone group than in the control group (between-group difference 4.8 days; p<0.0001). At 60 days, 21% of patients in the dexamethasone group and 36% of patients in the control group had died (between-group difference -15.3%; p=0.0047). They noted the proportion of adverse events did not differ significantly between groups. The most common adverse events were hyperglycaemia (76% in the dexamethasone group vs 0% in the control group), new infections (24% vs 25%), and barotrauma (10% vs 7%).

Comment: Treatment of ARDS remains problematic. The use of high dose or pulse methylprednisone is thought to be harmful, though lower doses of corticosteroids may offer protection. This Spanish RCT used moderate dose of dexamethasone 20 mg daily for 5 days then 10 mg daily for 5 days. Dexamethasone led to a small but significant reduction of 4.8 ventilator free days. Dexamethasone was not associated with any significant adverse outcomes.

Reference: Lancet Respir Med. 2020 Mar;8(3):267-276
Abstract

Prevalence, characteristics, and prognosis of early chronic obstructive pulmonary disease. The Copenhagen general population study

Authors: Çolak Y, et al

Summary: This Danish population-based cohort included 105 630 randomly chosen adults. The group defined early chronic obstructive pulmonary disease (COPD) as FEV1/FVC less than the lower limit of normal in individuals under 50 years of age with 10 pack-years or greater of tobacco consumption. Among 8064 individuals under 50 years of age with 10 pack-years or greater of tobacco consumption, 15% had early COPD, of whom 58% were current smokers. Individuals with early COPD more often had chronic respiratory symptoms, severe lung function impairment, asthma, and a history with bronchitis/pneumonia. Furthermore, compared with individuals without COPD, those with early COPD had adjusted hazard ratios of 6.42 for acute obstructive lung disease hospitalisations, 2.03 for acute pneumonia hospitalisations, and 1.79 for all-cause mortality.

Comment: This Danish study examined the outcomes for a group of young people with early COPD, as determined by age less 50 years. Certainly, some of these people will have early evolving disease, especially the smokers or former smokers. The remainder may have COPD from reduced childhood disease or other birth factors. Nonetheless despite their relatively young age over the next 14 years they had a surprising burden of illness, including hospitalisation pneumonia and increased death. Disease in this group, in a usually productive age of the population is clearly highly significant. While efforts to screen for people with COPD has lost some momentum, maybe some further thought should be put to this in younger age groups.

Reference: Am J Respir Crit Care Med. 2020 Mar 15;201(6):671-680
Abstract

Echocardiographic changes with positive airway pressure therapy in obesity hypoventilation syndrome. Long-term Pickwick randomized controlled clinical trial

Authors: Masa JF, et al

Summary: The researchers compared the effectiveness of noninvasive ventilation (NIV) and CPAP on structural and functional echocardiographic changes in patients with obesity hypoventilation syndrome (OHS). At baseline and annually during three years, patients underwent transthoracic two-dimensional and Doppler echocardiography. The study cohort included 102 patients treated with CPAP and 94 were treated with NIV. The authors observed the systolic pulmonary artery pressure decreased from 40.5 ± 1.47 mm Hg at baseline to 35.3 ± 1.33 mm Hg at three years with CPAP, and from 41.5 ± 1.56 mm Hg to 35.5 ± 1.42 with NIV ($P < 0.0001$). However, there were no significant differences between groups. In addition, NIV and CPAP therapies improved left ventricular diastolic dysfunction, reduced left atrial diameter and improved respiratory function and dyspnoea.

Comment: Obesity hypoventilation syndrome is an important complication, leading to severe morbidity and mortality. Untreated OHS has been associated with cardiac dysfunction, especially the development of pulmonary hypertension and right heart failure. The "Pickwick" programme followed 221 people with OHS, treated with either CPAP or NIV over 3 years. Pulmonary hypertension was diagnosed and assessed by echocardiography. Treatment with either CPAP/NIV when reversing sleep disordered breathing led to a significant reduction in pulmonary arterial pressures. This was also associated with improvements in lung function and dyspnoea. This confirms the importance of treatment and the substantial disease modification that can occur at least over the medium term for people with OHS.

Reference: Am J Respir Crit Care Med. 2020 Mar 1;201(5):586-597
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.

Safety and effectiveness of bronchial thermoplasty when FEV_1 is less than 50

Authors: Langton D, et al

Summary: The investigators grouped patients with severe asthma from the Australian Bronchial Thermoplasty Registry into: those with a baseline prebronchodilator FEV1 % predicted < 50% (n = 32); or those with an FEV1 ≥ 50% (n = 36). They concluded more severely obstructed patients were no more likely to have experienced any adverse event. Furthermore, significant improvements in Asthma Control Questionnaire score, exacerbation frequency, reliever medication use, and requirement for daily oral steroids were observed in both groups.

Comment: The role of bronchial thermoplasty (BT) in the treatment of asthma remains unclear. Its use is now being considered in individuals with more severe disease, many of whom would not have been eligible to take part in the only RCT of this therapy. In those with more severe asthma, lung function is much likely to be lower. This was a non-randomised comparison of outcomes for people with BT, comparing those with severe fixed airway obstruction (FEV1<50%) to those without. Importantly those with more severe obstruction were no more likely to suffer complications or adverse events.

Reference: Chest. 2020 Mar;157(3):509-515
Abstract

The impact of gravity vs suction-driven therapeutic thoracentesis on pressure-related complications: The GRAVITAS multicenter randomized controlled trial

Authors: Lentz RJ, et al

Summary: This prospective, multicentre, single-blind, randomised controlled trial allocated 142 patients with large free-flowing effusions estimated ≥ 500 mL 1:1 to undergo active aspiration or gravity drainage. Patients rated chest discomfort on 100-mm visual analog scales prior to, during, and following drainage. The primary outcome was overall procedural chest discomfort scored 5 min following the procedure, and secondary outcomes included measures of discomfort and breathlessness through 48 hours postprocedure. The team reported groups did not differ for the primary outcome (mean visual analog scale score difference, 5.3 mm; P = .17). Discomfort and dyspnoea did not differ between groups. Comparable volumes were drained in both groups, however, the procedure duration was significantly longer in the gravity arm (mean difference, 7.4 min; P < .001). They noted there were no serious complications.

Comment: There have been few randomised trials to determine the best approach to managing pleural effusions and thoracentesis. Large effusions have generally been managed by insertion of an intercostal drain and then gradual drainage. This study compared acute outcomes between people who had large free flowing effusions drained by thoracocentesis or drainage and gravity. Adverse events were equivalent. Thoracocentesis was faster with comparable patient comfort. In regards to efficiency this probably should be the intervention of choice.

Reference: Chest. 2020 Mar;157(3):702-711
Abstract

Home initiation of chronic non-invasive ventilation in COPD patients with chronic hypercapnic respiratory failure: A randomised controlled trial

Authors: Duiverman ML, et al

Summary: The study cohort of 67 stable hypercapnic COPD patients were randomised to initiation of NIV in the hospital or at home using telemedicine. Primary outcome was daytime PaCO2 reduction after 6 months NIV, with a non-inferiority margin of 0.4 kPa. Home NIV initiation was non-inferior to in-hospital initiation (adjusted mean difference in PaCO2 change home vs in-hospital: 0.04 kPa), with both groups showing a PaCO2 reduction at 6 months compared with baseline (home: from 7.3±0.9 to 6.4±0.8 kPa (p<0.001) and in-hospital: from 7.4±1.0 to 6.4±0.6 kPa (p<0.001)). In both groups, health-related quality of life (HRQoL) improved without a difference in change between groups. In addition, home NIV initiation was significantly cheaper with cost reductions over 50%.

Comment: NIV is an effective treatment for a subgroup with COPD and chronic hypercapnoeic respiratory failure. Initiating and adjusting NIV in these people can be difficult and has often involved inpatient stays. This trial shows that treatment can be commenced in the outpatient setting with telehealth support. This was just as effective as with hospitalisation and not surprisingly cheaper.

Reference: Thorax. 2020 Mar;75(3):244-252
Abstract

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Impact of respiratory muscle training on respiratory muscle strength, respiratory function and quality of life in individuals with tetraplegia: A randomised clinical trial

Authors: Boswell-Ruys CL, et al

Summary: Sixty-two adults with tetraplegia were randomised to active or sham respiratory muscle training twice daily for 6 weeks. The investigators observed a greater improvement in maximal inspiratory pressure (PImax) in the active group than in the sham group (mean difference 11.5 cmH_2O, p<0.001) at 6 weeks. They also found respiratory symptoms were reduced and significant improvements in quality of life and perceived breathlessness.

Comment: Respiratory muscle weakness is an important complication of people with spinal cord disease and tetraplegia. This is the first randomised trial of inspiratory muscle training. A 6 week programme was effective in improving both objective measures, PIMax as well as symptoms and quality of life and to an extent that should be clinically meaningful. These effects have been assessed only in the short term and longer term studies will be needed to see how long the effects last. Inspiratory muscle training should be considered now as intervention in those with tetraplegia. Longer term effects on clinical outcomes need also to be assessed.

Reference: Thorax. 2020 Mar;75(3):279-288
Abstract

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