Respiratory Research Review™

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In this issue:

Abbreviations used in this issue:

AE = adverse event; **ARDS** = acute respiratory distress syndrome; **CF** = cystic fibrosis; **COPD** = chronic obstructive pulmonary disease; **FEV_1** = forced expiratory volume in 1 second; **FVC** = forced vital capacity; **GINA** = Global Initiative for Asthma; **HR** = hazard ratio; **ICU** = intensive care unit; **ICS** = inhaled corticosteroid; **IPF** = idiopathic pulmonary fibrosis; **IV** = intravenous; **OR** = odds ratio; **PaO_2:FiO_2** = ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen; **PEEP** = positive end-expiratory pressure; **RR** = relative risk.

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Welcome to issue 79 of Respiratory Research Review.

The evidence from a couple of studies published recently in *NEJM* and covered in this issue of *Respiratory Research Review* suggests that not all cases of mild asthma need to be treated with continuous ICS therapy. Prescribing in asthma management may change in response to these studies. A couple of other papers suggest that concomitant azithromycin may be problematic when used with IV tobramycin in the treatment of pulmonary exacerbations in adults and paediatric patients with cystic fibrosis. On the topic of air quality, one paper reports the findings of a large Chinese investigation demonstrating that short-term exposure to air pollution is significantly associated with asthma mortality.

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

Kind Regards,

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Effect of pressure support vs T-piece ventilation strategies during spontaneous breathing trials on successful extubation among patients receiving mechanical ventilation

Authors: Subirà C et al.

Summary: This investigation from Spain compared the effects of 30 minutes of pressure support versus 2 hours of T-piece ventilation on successful extubation of mechanical ventilation in a cohort of 1,153 adults (mean age, 62.2 years) deemed ready for weaning after ≥24 hours of mechanical ventilation in the ICU. A total of 1,018 (88.3%) patients completed the trial. The primary outcome of successful extubation (remaining free of mechanical ventilation 72 hours after the first daily spontaneous breathing trial) occurred in 473 patients (82.3%) in the pressure support ventilation group and 428 patients (74.0%) in the T-piece group (p=0.001). Between-group differences were not significant for the pressure support ventilation group vs the T-piece group for reintubation (11.1% vs 11.9%; p=0.63), median ICU length of stay (9 days vs 10 days; p=0.69), or median hospital length of stay (24 days vs 24 days; p=0.45). Hospital mortality rates were 10.4% in the pressure support group and 14.9% in the T-piece group (p=0.02). Mortality at 90 days was significantly lower in the pressure support group than in the T-piece group (13.2% vs 17.3%; HR 0.74; 95% CI, 0.55 to 0.99; p=0.04).

Comment: The timing of extubation for critically ill patients has always been a difficult one, with reintubation a serious complication, increasing morbidity and length of stay. These trials ask an important clinical question, comparing two extubation strategies. The first, a 30-minute trial of spontaneous breathing support with 8 cm of PEEP, and the second, a T-piece trial of spontaneous breathing for 2 hours; the latter a more arduous strategy for the patient. The shorter and simpler spontaneous trial was more successful in leading to a successful extubation; 82% vs 74% (difference, 8.2%; 95% CI, 3.4%-13.0%; p=0.001). There were no differences in ICU or hospital length of stay. This trial would indicate for most ventilated patients that a 30-minute spontaneous breathing trial should be the tool to predict extubation routinely.

Reference: JAMA. 2019;321(22):2175-82

Abstract

Early neuromuscular blockade in the acute respiratory distress syndrome

Authors: National Heart, Lung, and Blood Institute PETAL Clinical Trials Network et al.

Summary: In this study, 1,006 patients with moderate-to-severe ARDS (i.e. PaO_2:FiO_2 of <150 mm Hg with a PEEP of ≥8 cm of water) were randomised within 7.6 hours after the onset of a 48-hour continuous infusion of cisatracurium with concomitant deep sedation (intervention group; n=501) or to a usual-care approach without routine neuromuscular blockade and with lighter sedation targets (controls; n=505). All patients received the same mechanical ventilation strategies, including a high PEEP strategy. During the first 48 hours after randomisation, 488 (97.4%) patients in the intervention group started a continuous infusion of cisatracurium (median duration of infusion, 47.8 hours; median dose, 1,807 mg), and 86 (17.0%) controls received a neuromuscular blocking agent (median dose, 38 mg). The primary endpoint was in-hospital death from any cause at 90 days. The trial was stopped at the second interim analysis for futility. At 90 days, in-hospital death from any cause had occurred in 213 patients (42.5%) in the intervention group and 216 (42.8%) in the control group (p=0.93). In-hospital levels of physical activity were higher among controls compared with patients in the intervention group and fewer adverse cardiovascular events occurred in the control group. Assessments of study endpoints were similar between the groups at 3, 6 and 12 months.

Comment: This was another large collaborative trial performed by the National Heart, Lung, and Blood Institute that is systematically determining effective ICU management strategies for ARDS. In this trial, 1,006 subjects with moderate-to-severe ARDS were randomised to usual care or continuous infusion of a neuromuscular blocking agent (cisatracurium). The trial was prematurely ceased during a planned futility analysis, with no advantages likely to be seen between the groups and a concerning trend of less physical activity and more cardiovascular AEs with cisatracurium than those with lighter sedation. As a strategy, this will not be pursued further for ARDS. Such early analysis is a sensible approach in clinical trials abandoning futile treatments early, reducing expense and determining a clinically negative outcome early.

Reference: N Engl J Med. 2019;380(21):1997-2008
Abstract

Mometasone or tiotropium in mild asthma with a low sputum eosinophil level

Authors: Lazarus SC et al.

Summary: This study compared the use of inhaled mometasone (a glucocorticoid) and tiotropium (a long-acting muscarinic antagonist) in 295 patients with mild, persistent asthma, categorised according to sputum eosinophil level (low, <2% or high, ≥2%). They were randomised to receive mometasone, tiotropium, or placebo in a crossover design. Of the 73% of the patients with a low eosinophil level, 59% had a differential response to a trial agent. However, there was no significant difference overall in the response to mometasone or tiotropium compared with placebo. Among patients with a high eosinophil level, the response to mometasone was significantly better than the response to placebo, but the response to tiotropium was not.

Comment: This is a very interesting trial that may herald an important change in the way we consider mild asthma and should be seen in the context of the major changes that have occurred with the GINA 2019 update. Low-dose ICS regularly are now recommended for mild asthma in preference to the use of short-acting β2-agonists (SABAs) alone with as-needed ICS long-acting formoterol a second-line alternative for all adolescents and adults. ICS in this setting reduces exacerbations, including severe exacerbations, and leads to better symptom control compared to SABAs alone. There remains some concern about the need to use regular ICS in everyone with mild asthma, especially younger adolescents. Monotherapy with long-acting beta agonists is contraindicated in asthma due to serious AEs.

In this pilot study, 295 patients aged ≥12 years with mild asthma were assigned to low-dose ICS (mometasone) or tiotropium. The study assessed how many had elevated sputum eosinophils and determined whether this would predict response. Interestingly, 73% did not have elevated sputum eosinophils (>2%). In those with elevated eosinophils, the response to ICS was significantly better. In the low eosinophil group, the response to ICS was better than placebo, but tiotropium performed equally as well in this group and possibly better when compared to the difference seen with placebo. Unlike long-acting beta agonists, tiotropium may be a safe and effective alternative treatment, at least in mild, non-type 2 inflammatory asthma. However, how these results will be integrated into clinical practice are not clear, at least with the current definitions for asthma assessment and diagnosis.

Reference: N Engl J Med. 2019;380:2009-19
Abstract

Controlled trial of budesonide-formoterol as needed for mild asthma

Authors: Beasley R et al.

Summary: This open-label trial evaluated the effects of inhaled budesonide-formoterol when used on an as-needed basis for mild asthma. 668 patients with mild asthma were randomised to receive inhaled albuterol as needed, regular inhaled budesonide plus albuterol as needed, or inhaled budesonide-formoterol as needed. The annualised exacerbation rate in the budesonide-formoterol as needed group was lower than that in the albuterol as needed group (absolute rate, 0.195 vs 0.400; relative rate, 0.49; 95% CI, 0.33 to 0.72; p<0.001) and did not differ significantly from that in the regular budesonide group (0.195 vs 0.175; 1.12; 95% CI, 0.70 to 1.79; p=0.65). The number of severe exacerbations was lower in the budesonide-formoterol as needed group than in both the albuterol as needed group (9 vs 23; RR 0.40; 95% CI, 0.18 to 0.86) and the regular budesonide group (9 vs 21; 0.44; 0.20 to 0.96). The mean dose of inhaled budesonide was 107 µg/day in the budesonide-formoterol as needed group and 222 µg/day in the regular budesonide group.

Comment: This is the third prospective randomised trial to assess the effect of as-needed ICS/formoterol in mild asthma, compared to as-needed SABA alone and regular ICS plus as-needed SABA. In contrast to the previous Sygma trials this was more "real world", accepting a doctor's diagnosis of asthma and open-label treatment. This trial again demonstrated that as-needed SABA was a clearly inferior treatment, associated with higher rates of exacerbations, compared to ICS/formoterol and ICS maintenance. This trial also showed that despite as-needed use, the ICS/formoterol group had a lower overall use of budesonide. In contrast to the Sygma trials, the reduction in exacerbations was better with ICS/formoterol compared to regular ICS. The latter finding it was proposed may reflect the reduced regular adherence that is known to occur in those with mild asthma treated with regular ICS. This confirms in adolescents and adults that ICS/formoterol is a viable alternative to regular ICS and clearly superior to SABA as needed.

Reference: N Engl J Med. 2019;380(21):2020-30
Abstract

Clinical effectiveness of antifibrotic medications for idiopathic pulmonary fibrosis

Authors: Dempsey TM et al.

Summary: These researchers analysed data from a propensity score-matched cohort of 2,510 patients with idiopathic pulmonary fibrosis (IPF) registered with a large US insurance database: 1,255 were treated with antifibrotic medications pirfenidone and nintedanib and 1,255 were not. For the primary outcome of all-cause mortality, antifibrotic treatment was associated with significantly reduced all-cause mortality (HR 0.77; 95% CI, 0.62 to 0.98; p=0.034), although this benefit was only apparent through the first 2 years of treatment. Acute hospitalisations were also significantly reduced by treatment (HR 0.70; 95% CI, 0.61 to 0.80; p<0.001). Subgroup analysis revealed no significant difference in all-cause mortality between pirfenidone and nintedanib (HR 1.14; 95% CI, 0.79 to 1.65; p=0.471).

Comment: This was a real-world effectiveness study of the antifibrotic agents pirfenidone and nintedanib using a large US insurance database for the treatment of IPF. The investigators demonstrated that both agents reduced mortality in the first 2 years of use and reduced hospitalisations. This data is helpful in confirming these agents have a meaningful effect for those with IPF. Demonstrating a survival benefit beyond 2 years though may have been too much to expect in this elderly population, or may reflect the fact theses agents only slow disease progression as opposed to arrest the process.

Reference: Am J Respir Crit Care Med. 2019;200(2):168-74
Abstract

Short-term exposure to ambient air pollution and asthma mortality

Authors: Liu Y et al.

Summary: This Chinese investigation into short-term exposure to air pollution and asthma mortality examined data from 4,454 individuals who lived in Hubei province and died from asthma between 2013 and 2018. The study researchers applied inverse distance weighting to estimate exposures to particulate matter ≤2.5 µm in aerodynamic diameter ($PM_{2.5}$), particulate matter ≤10 µm in aerodynamic diameter (PM_{10}), sulphur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO) and ozone (O_3); all measurements were obtained from monitoring stations within 50 km of each study participant's home address. Conditional logistic regression analyses revealed positive associations between asthma mortality and each interquartile range (IQR) increase of $PM_{2.5}$ (lag 3; IQR, 47.1 µg/m^3; OR 1.07; 1.01 to 1.12), NO_2 (lag 03; 26.3 µg/m^3; 1.11; 1.01 to 1.22) and O_3 (lag 3; 52.9 µg/m^3; 1.09; 1.01 to 1.18). These associations showed consistent linearity and were not changed materially by further analyses that adjusted for other pollutants. There were no significant associations between PM_{10}, SO_2, and CO exposures and asthma mortality. The results were similar in sensitivity analyses.

Comment: Air pollution, especially exposure to dangerous levels of particulates (in this case $PM_{2.5}$, SO_2, NO_2, CO, and O_3) are known to affect asthma and are linked with increased symptoms and exacerbations. These Chinese researchers however have been able to demonstrate using a large population database a link between asthma mortality and levels of increased pollutants. This study builds on accumulating evidence of the serious health effects of air pollution in susceptible persons, such as those with asthma.

Reference: Am J Respir Crit Care Med. 2019 Jul 1;200(1):24-32
Abstract

Oral azithromycin use and the recovery of lung function from pulmonary exacerbations treated with intravenous tobramycin or colistimethate in adults with cystic fibrosis

Authors: Somayaji R et al.

Summary: These researchers retrospectively examined the impact of concomitant azithromycin on the degree of lung function recovery in adult patients with cystic fibrosis (CF) treated for a pulmonary exacerbation with IV tobramycin or IV colistimethate (colistin). The tobramycin group consisted of 121 patients who had a total of 220 pulmonary exacerbation events (47% were on azithromycin at time of first event); the colistin group consisted of 86 patients who had 207 exacerbation events (59% were on azithromycin at time of first event). The primary outcome was relative lung function recovery (FEV_1) following pulmonary exacerbation treatment. Azithromycin use in the tobramycin cohort was associated with a lower relative and absolute recovery of FEV_1% (–3% relative FEV_1% recovery and –2.64% absolute FEV_1% change). Azithromycin use in the colistin cohort was associated with a greater relative and absolute recovery of FEV_1% (+3% relative FEV_1% recovery and 2.00% absolute improvement in FEV_1%). The odds of 90% or 100% recovery to baseline FEV_1% were lower with azithromycin use in the tobramycin cohort and higher with azithromycin use in the colistin cohort, but were not statistically significant.

Comment: See next paper.

Reference: Ann Am Thorac Soc. 2019;16(7):853-60
Abstract

Oral azithromycin and response to pulmonary exacerbations treated with intravenous tobramycin in children with cystic fibrosis

Authors: Klingel M et al.

Summary: These researchers sought to determine whether oral azithromycin use is associated with worse lung function response to IV tobramycin in the treatment of pulmonary exacerbations in 33 paediatric CF patients with chronic *Pseudomonas aeruginosa* infection. A total of 67 exacerbations were treated. Similar proportions of patients using and not using azithromycin recovered lung function (i.e. returned to ≥90% of baseline FEV_1; 69% and 61%, respectively). However, in an analysis that accounted for the fact that azithromycin users had worse lung function at baseline than azithromycin nonusers and that factored in baseline FEV_1 as both a confounder and mediator, the azithromycin users had a smaller relative improvement in FEV_1 (9.5% lower) compared with azithromycin nonusers.

Comment: Azithromycin has been used extensively in patients with CF to reduce the risk of exacerbations. Recent concerns have been raised that it may interact with inhaled tobramycin to reduce the effectiveness of this agent in reducing its effect on airway infection. Two retrospective studies from registry data examine this issue following the treatment of exacerbations. Firstly, in adults, Somayaji et al. examines this question, again in the context of assessing responses following exacerbations treated with either IV tobramycin or IV colistin. Those who received azithromycin post-IV colistin were more likely to demonstrate an FEV_1 that returned to baseline compared to those who received tobramycin, where it appeared to be detrimental. In children, the impact was not as clear cut. When the investigators controlled for baseline FEV_1, the relative improvement in FEV_1 was less in those who had received IV tobramycin for an exacerbation and were on azithromycin. These studies add more evidence to the concern that azithromycin may interact with tobramycin negatively and raises concerns that these agents should not be co-administered in CF.

Reference: Ann Am Thorac Soc. 2019;16(7):861-7
Abstract

Occupational exposure to solvents and lung function decline: a population based study

Authors: Alif SM et al.

Summary: Using data from 767 individuals aged 45–50 years enrolled in the population-based Tasmanian Longitudinal Health Study, these researchers examined the associations between occupational exposures and longitudinal lung function decline. Occupational exposures were assessed from lifetime work history calendars and used to identify and calculate ever exposure and cumulative exposure using a job exposure matrix. The researchers also investigated whether the relationships were modified by sex, smoking and asthma status. Compared with those without exposure, ever exposures to aromatic solvents and metals were associated with a greater decline in FEV_1 (aromatic solvents 15.5 mL/year; metals 11.3 mL/year) and FVC (aromatic solvents 14.1 mL/year; metals 17.5 mL/year). Cumulative exposure (unit years) to aromatic solvents was also associated with greater decline in FEV_1 and FVC. While women had less cumulative exposure to aromatic solvents than men (mean, 9.6 years vs 16.6 years), women had a greater lung function decline than men. The analyses also identified associations between ever exposures to gases/fumes or mineral dust and greater decline in lung function.

Comment: Occupational causes of decline in lung function are often forgotten but are thought to be an important cause of COPD in those who have not smoked. Using the Tasmanian longitudinal health study, investigators have demonstrated that exposure to aromatic solvents over a period of even just 5 years led to a greater loss in lung function, with this effect most pronounced in women. This data should be used to take steps to limit the exposure to these agents in the workplace.

Reference: Thorax. 2019;74(7):650-8
Abstract

Combined impact of healthy lifestyle factors on risk of asthma, rhinoconjunctivitis and eczema in school children: ISAAC phase III

Authors: Morales E et al.

Summary: These investigators used data from the International Study of Asthma and Allergies in Childhood (ISAAC) phase III study to develop a Healthy Lifestyle Index (HLI) to examine the combined impact of modifiable lifestyle factors on asthma, rhinoconjunctivitis and eczema in schoolchildren. The HLI combined 5 factors: no parental smoking, child's adherence to a Mediterranean diet, child's healthy BMI, high physical activity and non-sedentary behaviour. Data were analysed from written questionnaires on asthma symptoms, rhinoconjunctivitis, eczema and lifestyle factors for 70,795 children aged 6–7 years in 19 countries. Each additional healthy lifestyle factor was associated with a reduced risk of current wheeze (OR 0.87), asthma ever (OR 0.89), current symptoms of rhinoconjunctivitis (OR 0.95) and current symptoms of eczema (OR 0.92).

Comment: Asthma and allergic disease is not considered a modifiable disease, though the increased prevalence that has been seen in Westernised countries suggests there is a strong environmental component. Data taken from over 70,000 children aged 6–7 years show that if five lifestyle factors could be modified (no parenteral smoking, a Mediterranean diet, a healthy BMI, and increased physical activity with reduced sedentary behaviour) then a 16% reduction in asthma cases could be seen, with some variability according to global region.

Reference: Thorax. 2019;74:531-8
Abstract

Tiotropium add-on therapy is safe and reduces seasonal worsening in paediatric asthma patients

Authors: Vogelberg C et al.

Summary: This was an analysis of a large safety database including 5 randomised, placebo-controlled studies, in which 1,691 patients aged 1–17 years with symptomatic asthma received tiotropium 5 or 2.5 µg (n=1,119) or placebo (n=572) as add-on therapy. Throughout the studies and for 30 days following treatment, reporting of AEs was low and comparable across the study groups: tiotropium 5 µg (51%), tiotropium 2.5 µg (51%) and placebo (54%). Similarly, reporting of drug-related AEs, those leading to discontinuation and serious AEs was also low and did not differ significantly between treatment groups, regardless of age, disease severity or sex. Compared with placebo, tiotropium 5 µg was associated with fewer AEs relating to asthma symptoms and exacerbations, particularly during the seasonal peaks of these AEs.

Comment: Tiotropium has been shown to be effective in adults and adolescents with asthma. Its use in younger children with asthma, a group where regular ICS are either not as effective or of no proven benefit depending upon age, means alternative treatments are needed. This pooled meta-analysis looks at the safety of tiotropium in children aged 1–17 years, and shows there is no signal that suggests worsened AEs and in reference to asthma-related events, there appears to be an improvement. Tiotropium appears quite safe in children aged 1–17 years with asthma.

Reference: Eur Respir J. 2019;53(6):1801824
Abstract

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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.

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