

Respiratory Research Review™

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Issue 81 - 2020

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Abbreviations used in this issue:

ARDS = acute respiratory distress syndrome; **BPAP** = bilevel positive airway pressure; **CFR** = case fatality rate; **COPD** = chronic obstructive pulmonary disease; **COVID-19** = coronavirus disease 2019; **ECMO** = extracorporeal membrane oxygenation; **DLco** = carbon monoxide diffusing capacity; **FVC** = forced vital capacity; **hIVIG** = hyperimmune intravenous immunoglobulin; **HMV** = home mechanical ventilator; **IPF** = idiopathic pulmonary fibrosis; **ILD** = interstitial lung disease; **6MWD** = 6-min walk distance; **NIPPV** = noninvasive positive pressure ventilation; **NIV** = noninvasive ventilation; **NK-1** = neurokinin-1; **RCT** = randomised clinical trial; **SOFA** = Sequential Organ Failure Assessment; **TLD** = targeted lung denervation.

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Welcome to the 81st issue of Respiratory Research Review.

A number of articles in this issue focus on COVID-19; assessing the clinical course, risk factors for mortality and estimated risk of death in China. The first study included a cohort of 1099 patients with COVID-19 from 552 hospitals in mainland China through to January 29, 2020. The authors concluded COVID-19 spread rapidly and caused varying degrees of illness. Patients often presented without fever, and many did not have abnormal radiologic findings. A retrospective cohort study of inpatients with COVID-19 in Wuhan, China found 48% of patients had a comorbidity, with hypertension being the most common (30%), followed by diabetes (19%) and coronary heart disease (8%). Older age, high SOFA score, and d-dimer greater than 1 µg/mL at admission were associated with increased odds of death. Another interesting study explored the epidemiology of COVID-19 in China. The investigators estimated the time-delay adjusted risk for death from COVID-19 in Wuhan, in the Hubei Province of China, reached values as high as 12% in the epicentre of the epidemic and ≈1% in other, more mildly affected areas. They suggest the elevated death risk estimates may be associated with a breakdown of the healthcare system.

Other topics reviewed in this issue include COPD, interstitial lung disease, influenza and pleural TB. We hope you find the research useful in your practice and look forward to your comments and feedback.

Dr Janette Tenne

Medical Research Advisor

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Clinical characteristics of coronavirus disease 2019 in China

Authors: Guan WJ, et al

Summary: The study cohort included 1099 patients with laboratory-confirmed coronavirus disease 2019 (COVID-19) from 552 hospitals in mainland China through to January 29, 2020. Among nonresidents of Wuhan, 72.3% had contact with residents of Wuhan and only 1.9% of the patients had a history of direct contact with wildlife. The most common symptoms were fever (43.8% on admission and 88.7% during hospitalisation) and cough (67.8%). Lymphocytopenia was present in 83.2% of the patients on admission. The authors reported 5.0% of patients were admitted to ICU, 2.3% underwent invasive mechanical ventilation and 1.4% died.

Comment: The study included patients from hospital and outpatient settings with confirmed COVID-19 between December 11, 2019, and January 29, 2020. 7736 patients were confirmed with COVID-19 during this period of which 1099 had data available for analysis. The largest cohort of patients was from Wuhan Jinyintan Hospital. 3.5% of cases were in health care workers. The median incubation period was 4 days and median age of the patients was 47 years. 0.9% of the patients were younger than 15 years of age. Fever was the most common symptom with cough being the second most common symptom. 15.7% of patients had severe disease and were likely to be older and with more co-morbidities. They also were more likely to have laboratory abnormalities including lymphopaenia, leucopaenia and thrombocytopenia. 86.2% of patients who had CT chest had evidence of abnormalities although 2.9% of severe cases had no evidence of CT abnormality on admission. Among those with severe disease, the risk of ICU admission, mechanical ventilation or death was 20.6%. Mean duration from symptom onset to ventilator support was 9.3 days. Overall case fatality in this study was 1.4%, which is lower than that of SARS-CoV and MERS-CoV.

Reference: *N Engl J Med.* 2020 February 28 [Epub ahead of print]

[Abstract](#)

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References: 1. Galie N, et al. *Eur Heart J* 2016; 37:67-119. 2. Strange G, et al. *Pulm Circ* 2013; 3(1):89-94. 3. D'Alonzo GE, et al. *Ann Intern Med* 1991; 115(5):343-9. Actelion, a business unit of Janssen-Cilag Pty Ltd. CAN 000 129 975, 1-5 Khartoum Rd, Macquarie Park, NSW 2113, Australia. Telephone: 1800 226 334 <http://www.janssen.com/australia> Date of Preparation: February 2020. CP-140273. ACTECH1533/RRR/01.

Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study

Authors: Zhou F, et al

Summary: The study included 135 patients from Jinyintan Hospital and 56 from Wuhan Pulmonary Hospital (Wuhan, China) with laboratory-confirmed COVID-19, of whom 137 were discharged and 54 died in hospital by Jan 31, 2020. The researchers found 48% of patients had a comorbidity, with hypertension being the most common (30%), followed by diabetes (19%) and coronary heart disease (8%). They also reported increasing odds of in-hospital death associated with older age (OR 1.10, 95% CI 1.03-1.17, per year increase; $p=0.0043$), higher Sequential Organ Failure Assessment (SOFA) score (5.65, 2.61-12.23; $p<0.0001$), and d-dimer greater than 1 $\mu\text{g/mL}$ (18.42, 2.64-128.55; $p=0.0033$) on admission.

Comment: The study is a retrospective study of adult patients with confirmed COVID-19 from Jinyintan Hospital and Wuhan Pulmonary Hospital. Total of 191 patients were analysed with age ranging from 18-87 years and median age of 56. More than half had associated co-morbidities most commonly hypertension, diabetes mellitus and coronary artery disease. Median time to discharge was 22 days but median time to death was 18.5 days. 16.7% of patients required mechanical ventilation, of whom 97% died. Extracorporeal membrane oxygenation (ECMO) was used in 3 patients but none survived. Sepsis was the most frequent complication, followed by respiratory failure, acute respiratory distress syndrome (ARDS), heart failure, and septic shock. Half of non-survivors experienced a secondary infection. 21% were treated with antivirals (lopinavir/ritonavir) but in this study no benefit was seen in viral shedding times or outcomes. Older age, higher SOFA score, and d-dimer greater than 1 $\mu\text{g/mL}$ at admission were associated with increased odds of death.

Reference: *Lancet*. 2020 Mar 28;395(10229):1054-1062

[Abstract](#)

Estimating risk for death from 2019 novel coronavirus disease, China, January-February 2020

Authors: Mizumoto K, et al

Summary: The investigators estimated the time-delay adjusted risk for death from COVID-19 in Wuhan, in the Hubei Province of China, reached values as high as 12% in the epicentre of the epidemic and $\approx 1\%$ in other, more mildly affected areas. They suggest the elevated death risk estimates may be associated with a breakdown of the healthcare system.

Comment: This is an interesting study that looked at the epidemiology of COVID-19 in China. The study highlights the importance of containment with enhanced public health interventions (including social distancing measures, quarantine, enhanced infection control in healthcare settings, and movement restrictions), enhanced public hygiene measures and increased healthcare capacity. As of February 11, 2020, a total of 44,795 cases of COVID-19 had been reported in China, 1,117 of which had resulted in death. 73.4% of deaths occurred in Wuhan, 22.2% occurred in Hubei Province excluding Wuhan, and 4.4% occurred in China excluding Hubei Province. The delay-adjusted case fatality rate (CFR) in Wuhan reach values as high as 12.2%, an estimate that is 3-fold higher than our estimate for Hubei Province excluding Wuhan and ≈ 14 -fold higher than our estimate for China excluding Hubei Province. The upward trend of CFR indicates that the temporal disease burden exceeded the capacity of healthcare facilities. Evidence exists for the high transmissibility of COVID-19 in enclosed spaces. The difference in case fatality rates between epicentres and areas less affected suggest a breakdown in health care systems.

Reference: *Emerg Infect Dis*. 2020 Mar 13;26(6)

[Abstract](#)

Association of home noninvasive positive pressure ventilation with clinical outcomes in chronic obstructive pulmonary disease: A systematic review and meta-analysis

Authors: Wilson ME, et al

Summary: This meta-analysis evaluated home noninvasive positive pressure ventilation (NIPPV) via bilevel positive airway pressure (BPAP) devices and noninvasive home mechanical ventilator (HMV) devices in patients with chronic obstructive pulmonary disease (COPD) and hypercapnia. A total of 21 randomised clinical trials (RCTs) and 12 observational studies were included ($n = 51,085$). There were 434 deaths and 27 patients underwent intubation. BPAP compared with no device was significantly associated with lower risk of mortality (22.31% vs 28.57%; 13 studies; 1,423 patients), fewer patients with all-cause hospital admissions (39.74% vs 75.00%; 1 study; 166 patients), and lower need for intubation (5.34% vs 14.71; 3 studies; 267 patients). Noninvasive HMV use compared with no device was significantly associated with fewer all-cause hospital admissions (rate ratio, 0.50; 1 study; 93 patients), but not mortality (21.84% vs 34.09%; 2 studies; 175 patients). There was no statistically significant difference in the total number of adverse events in patients using NIPPV compared with no device (0.18 vs 0.17 per patient; 6 studies; 414 patients). There was no significant difference in the total number of all-cause hospital admissions or quality of life.

Comment: This is a review of the latest evidence on the benefits of home NIV (noninvasive ventilation) in COPD patients. 31 studies were included of which 21 were RCTs. BPAP compared with no device was shown to improve mortality, all cause hospital admissions and risk of intubation but did not show any effect on quality of life. Home mechanical ventilation reduced hospital admissions but did not show a mortality benefit. There is still a need to clarify the benefits of NIV in improving quality of life although some studies have shown improvement in dyspnoea and shuttle distance. There were no significant adverse events. Most common adverse events were skin, eye and gastrointestinal symptoms. The evidence was of low-moderate quality and this was predominantly due to great heterogeneity in types of NIV settings used with unclear clinical targets for the use of NIV. This makes it challenging to make decisions on appropriateness of initiating home NIV, settings to use and clinical parameters to target.

Reference: *JAMA*. 2020 Feb 4;323(5):455-465

[Abstract](#)

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References: 1. Galie N, et al. *Eur Heart J* 2016; 37:67-119.
2. Kamani NG, et al. *Am Fam Physician* 2005; 71(8):1529-37.
3. Strange G, et al. *Pulm Circ* 2013; 3(1):89-94. 4. Humbert M, et al. *Circulation* 2010; 122:156-63.

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Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: A double-blind, randomised, placebo-controlled, phase 2 trial

Authors: Maher TM, et al

Summary: The phase 2 trial at 70 centres randomly assigned patients with progressive fibrosing unclassifiable interstitial lung disease (ILD) to receive 2403 mg pirfenidone (n=127) or placebo (n=126). The primary endpoint was mean predicted change in forced vital capacity (FVC) from baseline over 24 weeks, measured by daily home spirometry. The authors note the analysis of the primary endpoint was affected by intraindividual variability in home spirometry values. Over 24 weeks, predicted median change in FVC measured by home spirometry was -87.7 mL in the pirfenidone group versus -157.1 mL in the placebo group. Over 24 weeks, predicted mean change in FVC measured by site spirometry was lower in patients given pirfenidone than placebo (treatment difference 95.3 mL [95% CI 35.9 to 154.6], p=0.002). Patients in the pirfenidone group were less likely to have a decline in FVC of more than 5% (OR 0.42 [95% CI 0.25 to 0.69], p=0.001) or more than 10% (OR 0.44 [0.23 to 0.84], p=0.011). At week 24, mean change in carbon monoxide diffusing capacity (DLco) from baseline was -0.7% (SD 7.1) for the pirfenidone group and -2.5% (8.8) for the placebo group, and mean change in 6-min walk distance (6MWD) from baseline was -2.0 m (68.1) for the pirfenidone group and -26.7 m (79.3) for the placebo group. No differences in progression-free survival were identified between the pirfenidone and placebo groups. Treatment-emergent adverse events were reported in 94% of patients in the pirfenidone group and 81% of patients in the placebo group. Serious treatment-emergent adverse events were reported in 14% patients in the pirfenidone group and 16% patients in the placebo group. The most common treatment-related treatment-emergent adverse events were gastrointestinal disorders (47% in the pirfenidone group vs 26% in the placebo group), fatigue (13% vs 10%), and rash (10% vs 7%).

Comment: Pirfenidone has been shown to be beneficial in the treatment of idiopathic pulmonary fibrosis (IPF). This study evaluates its role in treatment of unclassifiable fibrosing ILDs. This was a double blind, randomised controlled study and enrolled 253 patients in total. Fewer patients treated with pirfenidone showed an absolute or relative decline in percent predicted FVC of more than 5%. No new safety signals were noted. The effects on secondary end points such as 6MWD and DL_{CO} were less defined. This is, however, an important study as to date evidence on how best to treat unclassifiable ILDs has been lacking. There also appears to be similarities in behaviour between unclassifiable ILDs and IPF, which may reflect similar pathological processes, which could respond to treatment with pirfenidone.

Reference: *Lancet Respir Med.* 2020 Feb;8(2):147-157

[Abstract](#)

Anti-influenza hyperimmune intravenous immunoglobulin for adults with influenza A or B infection (FLU-IVIG): A double-blind, randomised, placebo-controlled trial

Authors: Davey RT Jr, et al

Summary: The study evaluated the safety and efficacy of hyperimmune intravenous immunoglobulin (hIVIG) in patients with influenza A or B infection. Patients were randomly assigned to receive standard care (most commonly oseltamivir), plus either a single 500-mL infusion of high-titre hIVIG (n= 156) or saline placebo (n=152). The primary endpoint was a six-category outcome of clinical status at day 7, ranging in severity from death to resumption of normal activities after discharge. An odds ratio greater than 1 indicated that, for a given category, patients in the hIVIG group were more likely to be in a better category than those in the placebo group. The authors concluded OR on day 7 was 1.25 (95% CI 0.79-1.97; p=0.33). The OR in patients with influenza A was 0.94 (0.55-1.59) and was 3.19 (1.21-8.42) for those with influenza B (interaction p=0.023). They observed hIVIG treatment produced a robust rise in haemagglutination inhibition titres against influenza A and smaller rises in influenza B titres.

Comment: This study was a multicentre, double-blind, randomised, placebo-controlled study. Patients confirmed with Influenza A or B that were randomised to the treatment arm received a single 500-mL infusion of high-titre hIVIG. Most (95%) of patients in both treatment and placebo arm were treated with oseltamivir. The study did not show any significant benefit with treatment on clinical status at Day 7, which was the predefined primary endpoint. A more favourable outcome for the hIVIG group was seen in patients with influenza B than influenza A infection. The OR in favour of a clinical benefit on the primary outcome for hIVIG use in patients with influenza B was 3.19. Haemagglutination inhibition antibody titres were used to measure the humoral response to infection but better biomarkers to measure antibody mediated response may be needed. The study was not powered to measure mortality benefit of treatment.

Reference: *Lancet Respir Med.* 2019 Nov;7(11):951-963

[Abstract](#)

Safety and adverse events after targeted lung denervation for symptomatic moderate to severe chronic obstructive pulmonary disease (AIRFLOW): A multicenter randomized controlled clinical trial

Authors: Slebos DJ, et al

Summary: Patients with symptomatic COPD (n=82) were randomised 1:1 to the targeted lung denervation (TLD) group or the sham group. During the 3- to 6.5-month window, patients in the TLD group experienced significantly fewer respiratory adverse events than those in the sham group (32% vs. 71%); this was also the case during the 0 and 12.5 months window (83% vs. 90%). Furthermore, there was no statistical difference in the time to first moderate or severe COPD exacerbation or patient-reported symptoms over the 12.5 months of follow-up.

Comment: Targeted lung denervation is a novel bronchoscopic therapy that disrupts parasympathetic pulmonary nerve input to the lung to reduce the clinical consequences of cholinergic hyperactivity. 82 patients were randomised to receive TLD or sham procedure. Respiratory adverse events between 3 and 6.5 months after the procedure was 71% in the sham arm and 32% in the TLD arm (P = 0.0008). There were no increased adverse events in the treatment arm in the first 3 months. The treatment arm also had reduced risk of exacerbation requiring hospitalisation at 1 year follow up. There was a trend of increased gastrointestinal side effects in the treatment arm but overall the procedure was well tolerated.

Reference: *Am J Respir Crit Care Med.* 2019 Dec 15;200(12):1477-1486

[Abstract](#)

The neurokinin-1 receptor antagonist orvepitant is a novel antitussive therapy for chronic refractory cough: Results from a phase 2 pilot study (VOLCANO-1)

Authors: Smith J, et al

Summary: This phase 2, unblinded trial treated 13 patients with chronic refractory cough with a neurokinin-1 (NK-1) antagonist, orvepitant (30 mg once daily for 4 weeks). The authors concluded a significant improvement in objective daytime cough frequency was observed at week 4; with a 26% reduction from baseline. This effect was apparent at week 1 (38% reduction in coughs from baseline) and sustained after drug discontinuation at week 8 (29% reduction in coughs from baseline). They also noted statistically significant improvements for severity visual analog scale score and quality of life.

Comment: Orvepitant is a brain-penetrant NK-1 antagonist. Neurokinin-1 receptor is implicated in chronic refractory cough pathophysiology. This study had 13 patients treated with orvepitant and a statistical and clinically significant improvement in daytime cough frequency was noted. The benefits were noted as early as week 1 and sustained after drug discontinuation. It also improved quality of life scores. It was well tolerated and appeared safe. A promising study which brings hope for a number of patients who suffer with chronic refractory cough.

Reference: *Chest.* 2020 Jan;157(1):111-118

[Abstract](#)



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Accuracy of Xpert MTB/RIF ultra for the diagnosis of pleural TB in a multicenter cohort study

Authors: Wang G, et al

Summary: This study evaluated the performance of the Xpert MTB/RIF Ultra (Xpert Ultra) for pleural TB diagnosis. In total, 317 individuals with suspected pleural TB were recruited; 208 of them were diagnosed with pleural TB. Comparison for Mycobacterium tuberculosis detection showed that Xpert Ultra (44.23%) produced a higher sensitivity than culture (26.44%, $P < .001$), Xpert (19.23%, $P < .001$) and smear (1.44%, $P < .001$). In addition, when Xpert Ultra outcomes were integrated, the percentage of definite pleural TB cases increased from 56.25% to 64.90%. The specificities of smear, culture, Xpert, and Xpert Ultra were 100% (84 of 84), 100% (84 of 84), 98.67% (83 of 84), and 98.67% (83 of 84), respectively.

Comment: The Xpert MTB/RIF (Xpert) assay, a point-of-care technique, was a major step toward improved diagnosis of TB and resistance to rifampicin globally. The assay has previously had poor sensitivity in paucibacillary specimens such as pleural fluid. This study looked at the efficacy of the next generation assay Xpert MTB/RIF Ultra (Xpert Ultra). Xpert Ultra (44.23%) demonstrated higher sensitivity than both culture and Xpert for pleural TB diagnosis. The test had 100% specificity and the integration of the Xpert Ultra outcomes increase the rate of definitive diagnosis from 56.25% to 64.9%. The study shows that Xpert Ultra can be a very useful tool, aiding in quick diagnosis and treatment in pleural TB.

Reference: *Chest.* 2020 Feb;157(2):268-275

[Abstract](#)

Metoprolol for the prevention of acute exacerbations of COPD

Authors: Dransfield MT, et al

Summary: This prospective, randomised trial assigned 532 patients with COPD to receive either metoprolol or placebo. The trial was stopped early because of primary end point futility and safety concerns. The team reported no significant between-group difference in the median time until the first exacerbation; 202 days in the metoprolol group and 222 days in the placebo group. Metoprolol was associated with a higher risk of exacerbation leading to hospitalisation (HR 1.91).

Comment: Observational studies have shown that beta-blockers in COPD patients can reduce risk of exacerbations and mortality. This study evaluated metoprolol in moderate to severe COPD patients with a history of exacerbation. 40% of the cohort had chronic respiratory failure and were on home oxygen therapy. The study did not show any difference between the treatment and placebo groups in time to first exacerbation but metoprolol resulted in more dyspnoea and COPD symptoms even though there was no difference in lung function or 6MWD. The treatment arm had higher risk of severe and very severe exacerbations. There was higher drop out rate in the treatment arm and more deaths were also noted resulting in the study being terminated early. It is important to highlight that this population is very different from those in previous studies where patients with COPD were prescribed beta-blockers for cardiovascular indications primarily. The use of beta-blockers without cardiovascular indications may be more harmful than beneficial.

Reference: *N Engl J Med.* 2019 Dec 12;381(24):2304-2314

[Abstract](#)

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Independent commentary by Dr Alpana Marissa Antony, MBBS, MRCP, FRACP.
Dr Antony is a Respiratory and Sleep Physician currently working at St. George Hospital, Sydney as a Staff Specialist in General Medicine. Her areas of clinical interest include respiratory infections, interventional pulmonology and respiratory failure.

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