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Respiratory Bulletin

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Contents

General

Articles

Early-life risk factors for reversible and irreversible airflow limitation in young adults: findings from the BAMSE birth cohort - Wang G, et al. *Thorax* 2021;76:503-507.

We aimed to determine prevalence and early-life risk factors for reversible and irreversible airflow limitation in young adults from the general population. Among young adults in their 20s, the prevalence was 5.3% for reversible airflow limitation and 2.0% for irreversible airflow limitation. While parental asthma was the only risk factor for development of reversible airflow limitation, the risk factors for development of irreversible airflow limitation were current asthma, childhood respiratory tract infections and asthma, and exposure to air pollution.

Evaluation of pulmonary complications and affecting factors in children for repaired esophageal atresia and tracheoesophageal fistula - Tuğcu GD, et al. *Respiratory Medicine*, 2021, 181, 106376.

Introduction: Recurrent pulmonary infections, wheezing and stridor due to swallowing dysfunction, esophageal dysmotility, gastroesophageal reflux, tracheomalacia and bronchomalacia are frequently seen complications after esophageal atresia and tracheo-esophageal fistula (EA-TEF) surgeries. This study aimed to investigate the frequency and causes of respiratory problems and to evaluate the factors that affect respiratory morbidity in patients who had undergone EA-TEF repair in a tertiary referral center.

Journal club - Shiham FF. *Thorax* 2021;76:526.

Rejuvenating old lungs: Ain't no tonic like a drop of retinoic - Gosens R, Ng-Blichfeldt JP. *Thorax* 2021;76:428-429.

One of the main challenges of experimental respiratory medicine today is the development of therapies that could support lung regeneration, leading to restoration of lung structure and function, in chronic lung diseases such as idiopathic pulmonary fibrosis (IPF). Current therapies such as pirfenidone and nintedanib slow down progression of the disease, but are insufficient to modify the underlying disease process to the extent that progression can be halted or that lung regeneration can be achieved.1 Accordingly, new regenerative therapies will need to be developed guided by insights into the mechanistic underpinnings of defective alveolar regeneration. This challenge is on, not just for IPF, but also for other chronic diseases such as chronic obstructive pulmonary disease (COPD), and is complicated by the limited endogenous regenerative capacity of the ageing lung as the background against which these diseases often develop.

Asthma

Articles

An enhanced care package to improve asthma management in Malawian children: a randomised controlled trial - Rylance S, et al. *Thorax* 2021;76:434-440.

Background: Shortages of clinical staff make chronic asthma care challenging in low-income countries. We evaluated an outpatient asthma care package for children, including task-shifting of asthma management roles.

Corticosteroids and bone health in people with asthma: A systematic review and meta-analysis - Chalitsios CV, Shaw DE, McKeever TM. *Respiratory Medicine*, 2021, 181, 106374.

Background: Understanding the potential deleterious effects of corticosteroids on bone health in people with asthma is important when making treatment decisions. There is a need for clearer evidence to better quantify the risk and effect size.

Grandmaternal smoking, asthma and lung function in the offspring: the Lifelines cohort study - Mahon GM, Koppelman GH, Vonk JM. *Thorax* 2021;76:441-447.

Background/objective: Limited research exists regarding the association between grandmaternal smoking during pregnancy and the risk for asthma and altered lung function in grandchildren. This study aimed to investigate this association in a three-generation design.

Nasal High-flow Oxygen Versus Conventional Oxygen Therapy for Acute Severe Asthma Patients: A Pilot Randomized Controlled Trial - Ruangsomboon O, et al. *Academic Emergency Medicine* 2021;28(5):530-541. Nasal high flow reduced the severity of dyspnea and respiratory rate in hypoxemic patients with acute severe asthma in the ED.

Neutrophilic asthma: misconception or misnomer? - Nair P, Surette MG, Virchow JC. *Lancet Respiratory Medicine*, 2021, 9(5), pp.441-443.

Neutrophils are abundant in the circulation. These cells are recruited into the airways in a number of circumstances—eg, following exposure to pollutants and pathogens or in response to a diet rich in fat and carbohydrate. Upon activation in the airways, neutrophils can release their granules, DNA, and proteins, and could contribute to airway damage. Several signalling mechanisms and pathways of egress of neutrophils from the bone marrow, chemotaxis of neutrophils into the airway, and persistence of neutrophils in the airways caused by delayed resolution of inflammatory signals have been elucidated. These signalling mechanisms include, but are not limited to, the following: balanced activity between CXCR2 and CXCR4 signalling; cytokines such as IL-1β, IL-6, IL-8, TNF, GROα, IL-17, IL-23, IFN-γ, phosphoinositide 3-kinase, NLRP3 inflammasome, galectin-10, and dipeptidase-1, and lipid mediators such as leukotriene B4, lipoxins, resolvins; and an intricate network of microRNAs. 1 Neutrophils have been found in sputum, bronchial wash, bronchoalveolar lavage, tracheal aspirates, and bronchial biopsies, in

many cross-sectional studies, with their numbers increasing with disease severity in adults and children with asthma. 2 This increase in neutrophil number is, not surprisingly, associated with the expression of factors that promote neutrophilia and might not necessarily be stable over time. 3 The association between asthma severity and neutrophil number has led to the use of the term neutrophilic asthma, 4 which implies the existence of a specific asthma endotype in which neutrophils are the major cell type mediating pathobiology, severity, and symptoms. However, it is unresolved whether this is indeed the case.

Safety and effectiveness of bronchial thermoplasty after 10 years in patients with persistent asthma (BT10+): a follow-up of three randomised controlled trials

Chaudhuri R, et al. *Lancet Respiratory Medicine*, 2021, 9(5), pp.457-466.

Background: Bronchial thermoplasty is an endoscopic treatment for uncontrolled asthma. Previous randomised clinical trials have shown that bronchial thermoplasty reduces severe exacerbations in people with asthma. However, the long-term efficacy and safety of bronchial thermoplasty beyond 5 years is unknown. The BT10+ study aimed to investigate the efficacy and safety of bronchial thermoplasty after 10 or more years of follow-up.

Task shifting: a common-sense approach in children with asthma? - Lenney W. *Thorax* 2021;76:430-431.

Over the last 9 months, the COVID-19 pandemic has been all consuming for virtually every country of the world; destroying lives, overwhelming health services and perplexing governments alike. Other medical disorders have taken a ‘relative’ back seat resulting in research and resources being diverted to best manage the devastating pandemic. Asthma is a good example being the most common disorder seen in children worldwide but with a recent profile lower than previously, despite its continuing and significant morbidity. The Lancet Commission1 has re-enforced our understanding that asthma is a spectrum of airway diseases often poorly diagnosed and frequently inadequately treated. In previous decades, it was believed to be a disease solely of temperate climate countries, but we now know its frequency and particularly its severity have been rapidly climbing in low-income and middle-income countries.

Treatment of mild-to-moderate asthma in childhood and adolescence in 2021 - Abrams EM, et al. *Lancet Respiratory Medicine*, 2021, 9(5), pp.443-445.

In asthma, there is an emerging and much-needed focus on children with mild-to-moderate and episodic symptoms. Although 50–75% of children and adolescents with asthma are classified as having mild disease, approximately 30–40% of all severe exacerbations occur in this group. 1 The burden of illness of mild asthma is significant, but uncertainties remain as to how to manage it, especially in children.

Triple vs Dual Inhaler Therapy and Asthma Outcomes in Moderate to Severe Asthma: A Systematic Review and Meta-analysis. - Lim LHY, et al. *JAMA* 2021;:doi:10.1001/jama.2021.7872.
In this systematic review and meta-analysis that included 20 randomized clinical trials and 11 894 patients,

triple therapy (ICS, LABA, and LAMA), compared with dual therapy (ICS plus LABA), was significantly associated with fewer severe asthma exacerbations (risk ratio, 0.83) and slightly better asthma control, but no significant difference in quality of life or most adverse events.

Reports

Management of chronic asthma in children aged 16 years and under. Healthcare Safety Investigation Branch; 2021.

A HSIB investigation looked at the risks involved in the management of children aged 16 years and under diagnosed with asthma. The investigation was launched after HSIB identified an event involving a 5 year old child. The child had numerous planned and unplanned (emergency) attendances at hospital with respiratory symptoms, before suffering a near fatal asthma attack.

Bronchial diseases

Articles

Chronic bronchitis in the 50-year follow-up of the European cohorts of the Seven Countries Study: prevalence, mortality and association with cardiovascular diseases - Puddu PE, et al. *Respiratory Medicine*, 2021, 181, 106385.

Objectives: To study prevalence of chronic bronchitis (CB) in residential populations and its relationship with mortality in a 50-year follow-up.

Cancers of the respiratory tract

Articles

Effect of exercise on fatigue in patients with lung cancer: a systematic review and meta-analysis of randomized trials. - Zhou L, Chen Q, Zhang J. *Journal of Palliative Medicine* 2021;: http://doi.org/10.1089/jpm.2020.0504.
Conclusion: Exercise demonstrated a moderate effect on fatigue in patients with lung cancer. Exercise also improved depressive symptoms, anxiety, and quality of life; however, its impact on functional capacity was not significant. More clinical trials are warranted to explore the mechanisms underlying the impact of exercise on fatigue. Strategies improving adherence to exercise prescription should be developed to help these patients overcome potential challenges.

Pembrolizumab with or without radiotherapy for metastatic non-small-cell lung cancer: a pooled analysis of two randomised trials - Theelen WSME, et al. *Lancet Respiratory Medicine*, 2021, 9(5), pp.467-475.

Background: Radiotherapy might augment systemic antitumoral responses to immunotherapy. In the PEMBRO-RT (phase 2) and MDACC (phase 1/2) trials, patients with metastatic non-small-cell lung cancer were randomly allocated immunotherapy (pembrolizumab) with or without radiotherapy. When the trials were analysed individually, a potential benefit was noted in the combination treatment arm. However, owing to the small sample size of each trial, differences in response rates and outcomes were not statistically significant but remained clinically notable. We therefore did a pooled analysis to infer whether

radiotherapy improves responses to immunotherapy in patients with metastatic non-small-cell lung cancer.

COPD

Articles

COPD-derived fibroblasts secrete higher levels of senescence-associated secretory phenotype proteins - Woldhuis RR, et al. *Thorax* 2021;76:508-511.

COPD-derived fibroblasts have increased cellular senescence. Senescent cell accumulation can induce tissue dysfunction by their senescence-associated secretory phenotype (SASP). We aimed to determine the SASP of senescent fibroblasts and COPD-derived lung fibroblasts, including severe, early-onset (SEO)-COPD. SASP protein secretion was measured after paraquat-induced senescence in lung fibroblasts using Olink Proteomics and compared between (SEO-)COPD-derived and control-derived fibroblasts. We identified 124 SASP proteins of senescent lung fibroblasts, of which 42 were secreted at higher levels by COPD-derived fibroblasts and 35 by SEO-COPD-derived fibroblasts compared with controls. Interestingly, the (SEO-)COPD-associated SASP included proteins involved in chronic inflammation, which may contribute to (SEO-)COPD pathogenesis.

COVID-19 and 'basal' exacerbation frequency in COPD - Cheng DO, Hurst JR. *Thorax* 2021;76:432-433.

The 2020 coronavirus pandemic has been particularly difficult for people living with chronic respiratory diseases, including chronic obstructive pulmonary disease (COPD). COPD is associated with greater severity of COVID-19 infection and increased mortality.1 Interventions such as social distancing, face coverings, hand hygiene and closure of public spaces have been implemented across the world, although with significant local variations. It remains unclear whether patients with COPD have altered risk of acquiring COVID-19, and 'shielding' (maximum avoidance of interpersonal interaction for those at highest risk) was intended to limit this risk. However, shielding also significantly limits physical activity, social interactions and access to healthcare, all of which may adversely impact physical and mental health.

COVID-19 public health measures: a reduction in hospital admissions for COPD exacerbations - Tan JY, et al. *Thorax* 2021;76:512-513.

Hospitalisations for acute exacerbations of COPD (AECOPD) carry significant morbidity and mortality. Respiratory viral infections (RVIs) are the most common cause of AECOPD and are associated with worse clinical outcomes. During the COVID-19 pandemic, public health measures, such as social distancing and universal masking, were originally implemented to reduce transmission of SARS-CoV-2; these public health measures were subsequently also observed to reduce transmission of other common circulating RVIs. In this study, we report a significant and sustained decrease in hospital admissions for all AECOPD as well as RVI-associated AECOPD, which coincided with the introduction of public health measures during the COVID-19 pandemic.

DNA methylation is associated with airflow obstruction in patients living with HIV - Cordero AIH, et al. *Thorax* 2021;76:448-455.

Introduction: People living with HIV (PLWH) suffer from age-related comorbidities such as COPD. The processes responsible for reduced lung function in PLWH are largely unknown. We performed an epigenome-wide association study to investigate whether blood DNA methylation is associated with impaired lung function in PLWH.

Efficacy of unsupervised exercise in adults with obstructive lung disease: a systematic review and meta-analysis. - Taylor D, et al. *Thorax* 2021;:doi: 10.1136/thoraxjnl-2020-216007.
The aim of this systematic review was to synthesise evidence regarding the efficacy of unsupervised exercise versus non-exercise-based usual care in patients with obstructive lung disease. The benefits of unsupervised exercise programmes in obstructive lung disease are unclear. The aim of this systematic review was to synthesise evidence regarding the efficacy of unsupervised exercise versus non-exercise-based usual care in patients with obstructive lung disease.

Noninvasive ventilation acutely improves endothelial function in exacerbated COPD patients - Heubel AD, et al. *Respiratory Medicine*, 2021, 181, 106389.

Purpose: Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is associated with an elevated risk of cardiovascular events, which can be linked to endothelial dysfunction. In this study, we aimed to investigate whether noninvasive ventilation (NIV) acutely changes endothelial function in hospitalized AECOPD patients.

Sedentary time in people with obstructive airway diseases - Cordova-Rivera L, et al. *Respiratory Medicine*, 2021, 181, 106367.

Sedentary time (ST) and light-intensity physical activity (LIPA) are movement behaviours associated with important health outcomes, but are not widely explored in respiratory diseases. We aimed to describe their volume and/or accumulation patterns in moderate-severe COPD, bronchiectasis and severe asthma using the accurate postural-based accelerometer activPAL, contrasting these values with a non-respiratory population. We also sought to test the cross-sectional associations of these behaviours with disease characteristics by diagnostic group, and as a combined label-free disease group.

The role of FeNO in stable COPD patients with eosinophilic airway inflammation - Vincken S, et al. *Respiratory Medicine*, 2021, 181, 106377.

Chronic obstructive pulmonary disease (COPD) is a chronic and progressive inflammatory disease of the airways and alveoli, characterized by persistent respiratory symptoms and airflow limitation. The course of COPD is complicated by acute exacerbations, which are defined as an acute worsening of respiratory symptoms that result in additional therapy. An important goal in the management of COPD is prevention of these acute exacerbations, as they have a negative impact on health status, (re)admission rates, disease progression and mortality 1. While most patients with COPD have a predominantly neutrophilic airway inflammation, a non-negligible portion of COPD patients shows evidence of eosinophilic airway

inflammation 2 with high sputum and blood eosinophils. In these patients high blood eosinophil counts (≥300 cells/mcL) 3 are associated with increased risk of acute exacerbations 4. Blood eosinophil counts also appear to predict responsiveness to the addition of inhaled corticosteroids (ICS) to maintenance treatment with long-acting bronchodilators in preventing acute exacerbations, in patients with a history of acute exacerbations 5. Since ICS can cause significant side-effects, and increases the risk of pneumonia in patients with COPD, there is a need for guidance by a biomarker that can identify those COPD patients who are most likely to benefit from ICS with an acceptable risk of potential side effects 1.

Infections (including COVID-19)

General

Antimicrobial prescribing: nebulised liposomal amikacin. - National Institute for Health and Care Excellence (NICE); 2021.
Nebulised liposomal amikacin (amikacin liposomal nebuliser dispersion, Arikayce, Insmed) is an aminoglycoside antibiotic that is given by oral nebulisation once daily. It has a marketing authorisation for the treatment of non-tuberculous mycobacterial (NTM) lung infections caused by Mycobacterium avium complex in adults with limited treatment options, who do not have cystic fibrosis.

Assessing the impact of the 13 valent pneumococcal vaccine on childhood empyema in Australia - Strachan R, et al. *Thorax* 2021;76:487-493.

Background: Empyema is a serious complication of pneumonia frequently caused by Streptococcus pneumoniae (SP). We assessed the impact of the 13-valent pneumococcal conjugate vaccine (13vPCV) on childhood pneumonia and empyema after inclusion in the Australian National Immunisation Program.

Breathomics for the clinician: the use of volatile organic compounds in respiratory diseases - Ibrahim W, et al. *Thorax* 2021;76:514-521.

Exhaled breath analysis has the potential to provide valuable insight on the status of various metabolic pathways taking place in the lungs locally and other vital organs, via systemic circulation. For years, volatile organic compounds (VOCs) have been proposed as feasible alternative diagnostic and prognostic biomarkers for different respiratory pathologies. We reviewed the currently published literature on the discovery of exhaled breath VOCs and their utilisation in various respiratory diseases Key barriers in the development of clinical breath tests include the lack of unified consensus for breath collection and analysis and the complexity of understanding the relationship between the exhaled VOCs and the underlying metabolic pathways. We present a comprehensive overview, in light of published literature and our experience from coordinating a national breathomics centre, of the progress made to date and some of the key challenges in the field and ways to overcome them. We particularly focus on the relevance of breathomics to clinicians and the valuable insights it adds to diagnostics and disease monitoring. Breathomics holds great promise and our findings merit further large-scale multicentre diagnostic studies using standardised protocols to help position this novel technology at the centre of respiratory disease diagnostics.

Female patient with recurrent chest infections and non-resolving consolidation - Bedawi EO, et al. *Thorax* 2021;76:522-524.

A 45-year-old Caucasian woman was referred for investigation of recurrent chest infections. She had been treated over the previous 9 months for recurrent symptoms characterised by intermittent episodes of dyspnoea, cough productive of green sputum and pleuritic chest pain. Systemic enquiry was unremarkable; specifically, she had not experienced any weight loss or anorexia. On each episode, oxygen saturations were >94% and heart rate was <100 beats/min, with a single occurrence of a low-grade fever (37.8°C). The white cell count peaked at 10.59×108 (neutrophils 8.82, eosinophils 0.18, lymphocytes 0.89), and her C reactive protein remained consistently within normal lab ranges. She was not anaemic. Liver, kidney and bone profiles were all within normal limits. Each course of antibiotics would lead to transient improvement in cough, but the pleuritic chest pain and breathlessness remained unchanged.

COVID-19

Articles

Algeria's response to COVID-19: an ongoing journey - Klouche-Djedid SN, et al. *Lancet Respiratory Medicine*, 2021, 9(5), p.449.

COVID-19 began its journey in Algeria, the largest African country, on Feb 25, 2020, when the first case was reported by the Ministry of Health, Population and Hospital Reform. The assumption that the virus would spare the country given its warm climate was popular among Algerians, but was soon proven to be erroneous.

Alpha-1 antitrypsin deficiency severity and the risk of COVID-19: A Portuguese cohort - Faria N, et al. *Respiratory Medicine*, 2021, 181, 106387.

Alpha-1 antitrypsin deficiency (AATD) is highly prevalent in Portugal. It is estimated that 1:5249 individuals have a ZZ genotype, and 1:281 have a SZ genotype 1. Patients with AATD have recently been proposed as a susceptible population for COVID-19 and disease severity 2. Data from an Italian registry of AATD revealed a geographical distribution of AATD similar to that of COVID-19 3. A significant positive correlation was reported between the combined frequencies of the PI*SZ genotype in 67 countries and their reported COVID-19 mortality 4. In January 2021, Portugal presented one of the highest incidences of SARS-CoV-2 infection and mortality in the world 5.

Comparison of infection risks and clinical outcomes in patients with and without SARS-CoV-2 lung infection under renin–angiotensin–aldosterone system blockade: Systematic review and meta-analysis. - Chu C, et al. *British Journal of Clinical Pharmacology* 2021;87(6):2475-2492.
ACEIs reduce the risk of getting infected with the SARS-CoV-2 virus. Blocking the RAAS may decrease all-cause mortality in COVID-19 patients. ACEIs also reduce the risk of non-COVID pneumonia. All-cause mortality due to non-COVID pneumonia is reduced by ACEI and potentially by ARBs.

Confronting COVID-19-associated cough and the post-COVID syndrome: role of viral neurotropism, neuroinflammation, and neuroimmune responses - Song WJ, et al. *Lancet Respiratory Medicine*, 2021, 9(5), pp.533-544.

Cough is one of the most common presenting symptoms of COVID-19, along with fever and loss of taste and smell. Cough can persist for weeks or months after SARS-CoV-2 infection, often accompanied by chronic fatigue, cognitive impairment, dyspnoea, or pain—a collection of long-term effects referred to as the post-COVID syndrome or long COVID. We hypothesise that the pathways of neurotropism, neuroinflammation, and neuroimmunomodulation through the vagal sensory nerves, which are implicated in SARS-CoV-2 infection, lead to a cough hypersensitivity state. The post-COVID syndrome might also result from neuroinflammatory events in the brain. We highlight gaps in understanding of the mechanisms of acute and chronic COVID-19-associated cough and post-COVID syndrome, consider potential ways to reduce the effect of COVID-19 by controlling cough, and suggest future directions for research and clinical practice. Although neuromodulators such as gabapentin or opioids might be considered for acute and chronic COVID-19 cough, we discuss the possible mechanisms of COVID-19-associated cough and the promise of new anti-inflammatories or neuromodulators that might successfully target both the cough of COVID-19 and the post-COVID syndrome.

Could a good night's sleep improve COVID-19 vaccine efficacy? - Benedict C, Cedernaes J. *Lancet Respiratory Medicine*, 2021, 9(5), pp.447-448.

More than 2 million people have died from COVID-19, caused by SARS-CoV-2. 1 In an unprecedented effort to develop vaccines to control the COVID-19 pandemic, mRNA, protein subunit, and viral vector-based vaccines have been developed within an extraordinarily swift timeframe. However, the efficacy of these vaccines (ie, their ability to reduce the incidence of severe disease and death from COVID-19) can vary considerably. For example, among 43 448 adults, the efficacy of the mRNA-based COVID-19 vaccine produced by Pfizer and BioNTech ranged between 29·5% and 68·4% against symptomatic COVID-19 after the first dose, and between 90·3 and 97·6% after the second dose. 2 By comparison, in an interim analysis of ongoing clinical trials (involving 23 484 participants), the corresponding efficacy of two standard doses of the ChAdOx1 nCoV-19 adenovirus vector vaccine produced by AstraZeneca ranged between 41·0% and 75·2%.

COVID-19 severity and obesity: are MAIT cells a factor? - McCarthy C, et al. *Lancet Respiratory Medicine*, 2021, 9(5), pp.445-447.

People with obesity have an increased risk of severe COVID-19: a meta-analysis by Popkin and colleagues 1 found that the odds ratio of people with obesity being hospitalised with COVID-19 was 2·13 when compared with those without obesity, and mortality was 48% higher in patients with obesity than in those without. This increased risk of severe disease is linked to higher rates of metabolic and cardiovascular complications. 2 Another major contributing factor is the presence of substantial immune dysregulation and chronic systemic inflammation. Obesity is associated with increased levels of numerous inflammatory mediators, including interleukin (IL)-1, IL-6, IL-17, and tumour necrosis factor α. 3 These cytokines are also implicated in the pathogenesis of COVID-19. 4 In addition to inflammation, obesity is associated with

important defects in immune cells tasked with host protection, including natural killer cells and mucosal associated invariant T (MAIT) cells.

COVID-19 vaccination in athletes: ready, set, go… - Hull JH, et al. *Lancet Respiratory Medicine*, 2021, 9(5), pp.455-456.

In the fight against the COVID-19 global pandemic, the focus in 2021 has fortunately turned to vaccination strategies. The successful development of several vaccines, and their proven efficacy and short-term safety in large scale multinational trials against severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), offers promise in controlling the pandemic. Many countries are now operationalising their vaccination programmes, and prioritising health-care workers and the most vulnerable individuals within the population—eg, the elderly and those with chronic health conditions.

Decreased quality of life and spirometric alterations even after mild-moderate COVID-19 - Navarro AO, et al. *Respiratory Medicine*, 2021, 181, 106391.

Background: The follow-up of recovered COVID-19 patients is still limited. We aimed to evaluate the changes in quality-of-life (QOL) and spirometric alterations in the convalescent phase of 115 patients with at least 30 days post-COVID-19.

Development of a new aerosol barrier mask for mitigation of spread of SARS-CoV-2 and other infectious pathogens - Karam KA, et al. *Respiratory Medicine*, 2021, 181, 106381.

The COVID-19 pandemic has caused huge impact on public health and significantly changed our lifestyle. This is due to the fast airborne oro-nasal transmission of SARS-CoV-2 from the infected individuals. The generation of liquid aerosolized particles occurs when the COVID-19 patients speak, sing, cough, sneeze, or simply breathe. We have developed a novel aerosol barrier mask (ABM) to mitigate the spread of SARS-CoV-2 and other infectious pathogens. This Aerosol Barrier Mask is designed for preventing SARS-CoV-2 transmission while transporting patients within hospital facilities. This mask can constrain aerosol and droplet particles and trap them in a biofilter, while the patient is normally breathing and administrated with medical oxygen. The system can be characterized as an oxygen delivery and mitigation mask which has no unfiltered exhaled air dispersion. The mask helps to prevent the spread of SARS-CoV-2, and potentially other infectious respiratory pathogens and protects everyone in general, especially healthcare professionals.

Early outcomes after lung transplantation for severe COVID-19: a series of the first consecutive cases from four countries - Bharat A, et al. *Lancet Respiratory Medicine*, 2021, 9(5), pp.487-497.

Background: Lung transplantation is a life-saving treatment for patients with end-stage lung disease; however, it is infrequently considered for patients with acute respiratory distress syndrome (ARDS) attributable to infectious causes. We aimed to describe the course of disease and early post-transplantation outcomes in critically ill patients with COVID-19 who failed to show lung recovery despite

optimal medical management and were deemed to be at imminent risk of dying due to pulmonary complications.

European guideline on managing adults in hospital with COVID-19 - Venkatesan P. *Lancet Respiratory Medicine*, 2021, 9(5), e.50.

The widespread rollout of COVID-19 vaccines plus national lockdowns seem to have been playing their part in slowing down the pandemic in 2021, particularly for older age groups; in England for example, deaths have decreased in people older than 65 years, and hospital admission rates fell from 6·12 per 100 000 in the week of March 1–7 to 4·63 per 100 000 in the following week. However, there is no room for complacency, as SARS-CoV-2 is still very much in circulation with accompanying risks of serious illness, hospital admissions, and death. Delays and hesitancy might cause difficulties with vaccinations; in addition, SARS-CoV-2 strain variations are of concern. One study has estimated the mortality hazard ratio of the new B.1.1.7 variant as 1·64 (95% CI 1·32–2·04) in UK community patients, representing an increase in deaths from 2·5 to 4·1 per 1000 detected cases. Equally concerning are reports as of March 18, 2021, that the number of cases of this variant and admissions to hospital or intensive care units (ICU) have increased in Europe for the third consecutive week; more than 1·2 million new cases were reported in the previous week, 15 European countries reported increasing hospital or ICU admissions due to COVID-19, and the number of people dying in Europe at this time was apparently higher than the same time last year. With one systematic review and meta-analysis estimating the COVID-19 in-hospital mortality rate as 28·1% (95% CI 23·4–33·0; I 2 =96%), it is clear that effective treatments and optimal management of patients admitted to hospital with COVID-19 are still crucial.

IL-6 blockade for COVID-19: a global scientific call to arms - Murthy S, Lee TC. *Lancet Respiratory Medicine*, 2021, 9(5), pp.438-440.

We are more than 1 year into the COVID-19 pandemic and the need for better treatments for patients admitted to hospital with COVID-19 remains great. Despite clear improvements in care, mortality for severely ill patients remains unacceptably high. Thus far, the only agents that have consistently been shown to reduce mortality in hypoxaemic patients are systemic corticosteroids (mainly dexamethasone). 1 Yet, since early in the pandemic, modulating the immune response beyond steroids has been the source of a great deal of scientific attention, with the role of repurposed IL-6-blocking agents reported in a number of observational studies and randomised controlled trials.

Impact of corticosteroids in hospitalised COVID-19 patients - Ho KS, et al. *BMJ Open Respiratory Research* 2021;8:e000766.

Background: Corticosteroids are a potential therapeutic agent for patients with COVID-19 pneumonia. The RECOVERY (Randomised Trials in COVID-19 Therapy) trial provided data on the mortality benefits of corticosteroids. The study aimed to determine the association between corticosteroid use on mortality and infection rates and to define subgroups who may benefit from corticosteroids in a real-world setting.

Integrative respiratory follow-up of severe COVID-19 reveals common functional and lung imaging sequelae - Froidure A, et al. *Respiratory Medicine*, 2021, 181, 106383.

Background: COVID-19 pandemic resulted in an unprecedented number of hospitalizations in general wards and intensive care units (ICU). Severe and critical COVID-19 patients suffer from extensive pneumonia; therefore, long-term respiratory sequelae may be expected.

Into the abyss - Bigham B. *Lancet Respiratory Medicine*, 2021, 9(5), pp.452-453.

Not infrequently, as I sit in the intensive care unit (ICU) pondering a dilemma, my mind wanders to thoughts of my family and friends. It has been happening less this year, in the COVID-19 world that has thrust itself upon me, as thoughts compete for nanoseconds in my racing mind.

Lung ultrasonography for long-term follow-up of COVID-19 survivors compared to chest CT scan - Giovannetti G, et al. *Respiratory Medicine*, 2021, 181, 106384.

Background: While lung ultrasonography (LUS) has utility for the evaluation of the acute phase of COVID-19 related lung disease, its role in long-term follow-up of this condition has not been well described. The objective of this study is to compare LUS and chest computed tomography (CT) results in COVID-19 survivors with the intent of defining the utility of LUS for long-term follow-up of COVID-19 respiratory disease.

Major differences in ICU admissions during the first and second COVID-19 wave in Germany - Karagiannidis C, et al. *Lancet Respiratory Medicine*, 2021, 9(5), ee.47-48.

The mortality of mechanically ventilated patients with COVID-19 in German intensive care units (ICUs) during the first wave of the pandemic was reported to be 53%. 1 Several treatment options for patients with COVID-19 have been established since then. Corticosteroid treatment has been established for severely ill patients 234 and in light of the ongoing RECOVERY trial (NCT04381936), IL-6 blockade might have an advantage in patients with organ failure, including the prevention of progression to mechanical ventilation in those receiving non-invasive respiratory support. It is, thus, suggested that this, as part of a bundle of different measures, may have impacted on the ICU admission rate and outcome. We, therefore, have analysed the data from the federal German hospital payment institute (Institut für das Entgeltsystem im Krankenhaus InEK) at the time of discharge of patients with COVID-19 from all hospitals in Germany in 2020, including data from both the first and second waves of the pandemic.

Pandemic fans the flames of smoking and health inequity - The Lancet Respiratory Medicine. *Lancet Respiratory Medicine*, 2021, 9(5), p.435.

During the COVID-19 pandemic, evidence suggests that fewer people are stopping smoking and more ex-smokers are relapsing. This finding is especially concerning because smokers are at a higher risk of severe disease and death if they become infected with SARS-CoV-2.

Peginterferon lambda for the treatment of outpatients with COVID-19: a phase 2, placebo-controlled randomised trial - Feld JJ, et al. *Lancet Respiratory Medicine*, 2021, 9(5), pp.498-510.

Background: To date, only monoclonal antibodies have been shown to be effective for outpatients with COVID-19. Interferon lambda-1 is a type III interferon involved in innate antiviral responses with activity against respiratory pathogens. We aimed to investigate the safety and efficacy of peginterferon lambda in the treatment of outpatients with mild-to-moderate COVID-19.

Predictive factors for success of awake proning in hypoxemic respiratory failure secondary to COVID-19: A retrospective cohort study - Cherian SV, et al. *Respiratory Medicine*, 2021, 181, 106379.

Background: Awake prone positioning has been recommended as an adjunctive measure in spontaneously breathing patients with hypoxemic respiratory failure during the COVID-19 pandemic. It remains uncertain as to how long this should be implemented, what variables to follow and who would be the ideal candidates for this adjunctive therapy.

Renin-angiotensin system blocker and outcomes of COVID-19: a systematic review and meta-analysis - Lee HW, et al. *Thorax* 2021;76:479-486.

Background: The association of ACE inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) with disease severity of patients with COVID-19 is still unclear. We conducted a systematic review and meta-analysis to investigate if ACEI/ARB use is associated with the risk of mortality and severe disease in patients with COVID-19.

Safety and immunogenicity of one versus two doses of the COVID-19 vaccine BNT162b2 for patients with cancer: interim analysis of a prospective observational study. - Monin L, et al. *The Lancet Oncology* 2021;:https://doi.org/10.1016/S1470-2045(21)00213-8.
In patients with cancer, one dose of the BNT162b2 vaccine yields poor efficacy. Immunogenicity increased significantly in patients with solid cancer within 2 weeks of a vaccine boost at day 21 after the first dose. These data support prioritisation of patients with cancer for an early (day 21) second dose of the BNT162b2 vaccine.

Sarilumab in patients admitted to hospital with severe or critical COVID-19: a randomised, double-blind, placebo-controlled, phase 3 trial - Lescure FX, et al. *Lancet Respiratory Medicine*, 2021, 9(5), pp.522-532.

Background: Elevated proinflammatory cytokines are associated with greater COVID-19 severity. We aimed to assess safety and efficacy of sarilumab, an interleukin-6 receptor inhibitor, in patients with severe (requiring supplemental oxygen by nasal cannula or face mask) or critical (requiring greater supplemental oxygen, mechanical ventilation, or extracorporeal support) COVID-19.

Symptomatic, biochemical and radiographic recovery in patients with COVID-19 - Mallia P, et al. *BMJ Open Respiratory Research* 2021;8:e000908.

Background: The symptoms, radiography, biochemistry and healthcare utilisation of patients with COVID-19 following discharge from hospital have not been well described.

Tocilizumab plus standard care versus standard care in patients in India with moderate to severe COVID-19-associated cytokine release syndrome (COVINTOC): an open-label, multicentre, randomised, controlled, phase 3 trial - Soin AS, et al. *Lancet Respiratory Medicine*, 2021, 9(5), pp.511-521.

Background: Global randomised controlled trials of the anti-IL-6 receptor antibody tocilizumab in patients admitted to hospital with COVID-19 have shown conflicting results but potential decreases in time to discharge and burden on intensive care. Tocilizumab reduced progression to mechanical ventilation and death in a trial population enriched for racial and ethnic minorities. We aimed to investigate whether tocilizumab treatment could prevent COVID-19 progression in the first multicentre randomised controlled trial of tocilizumab done entirely in a lower-middle-income country.

Young person with long COVID after mild disease - Kirby T. *Lancet Respiratory Medicine*, 2021, 9(5), pp.453-455.

Shannon (name has been changed) is a nurse in her 20s who works at a busy hospital in Dublin, Ireland. When the COVID-19 pandemic struck in March, 2020, Ireland was one of the countries that went into a relatively early lockdown. But still, the patients began to mount. At work, Shannon was told her ward would be made a COVID ward and she was scared. “It was so much to take in. We basically learned as we went along. All the policy changes, the changes to personal protective equipment (PPE). And all this combined with the constant worry we ourselves could be infected and take the virus home to our families”, she explains.

Guidelines

Clinician FAQs and guidance on covid-19 vaccine for patients receiving systemic anti-cancer therapy (SACT), version 4.0. - UK Chemotherapy Board; 2021.
This document has been revised to include updated information on the Pfizer/BioNTech COVID-19 vaccine, Oxford University/AstraZeneca vaccine and Moderna vaccine, reflecting updated guidance from JCVI and the MHRA. May 2021.

Practice Changing Update from UpToDate

Vaccines to prevent SARS-CoV-2 infection (November 2020, Modified May 2021)

●For individuals who are eligible for vaccination according to local allocation priorities, we recommend COVID-19 vaccination (Grade 1B). Vaccine selection depends on local availability.

Various vaccines to prevent SARS-CoV-2 infection have become available in different countries. In the United States, the COVID-19 mRNA vaccines BNT162b2 (Pfizer-BioNTech COVID-19 vaccine) and mRNA 1273 (Moderna COVID-19 vaccine) and the COVID-19 adenovirus vector vaccine Ad26.COV2.S (Janssen COVID-19 vaccine) have received emergency use authorization for use in individuals 18 years and older; BNT162b2 is also authorized for use in children and adolescents 12 through 17 years 4-6. The mRNA vaccines are each given as two intramuscular doses separated by a few weeks; the adenovirus vector vaccine is a single intramuscular dose. In large placebo-controlled trials, these vaccines were highly effective in preventing laboratory-confirmed COVID-19, especially severe/critical disease 7-9. Local and systemic adverse effects (pain, fever, fatigue, headache) are common but usually nonsevere. Ad26.COV2.S is associated with an extremely small risk of thrombosis with thrombocytopenia, but its benefits outweigh this rare risk 10.

Interstitial lung diseases (pulmonary fibrosis)

Articles

Feasibility of cardiopulmonary exercise testing in interstitial lung disease: the PETFIB study - Tomlinson O, et al. *BMJ Open Respiratory Research* 2021;8:e000793.

Introduction: Cardiopulmonary exercise testing (CPET) provides a series of biomarkers, such as peak oxygen uptake, which could assess the development of disease status in interstitial lung disease (ILD). However, despite use in research and clinical settings, the feasibility of CPET in this patient group has yet to be established.

Pirfenidone in patients with non-IPF progressive fibrotic interstitial lung diseases: expert guidance is urgently needed - Wells AU. *Lancet Respiratory Medicine*, 2021, 9(5), pp.437-438.

It has been proposed that patients with fibrotic lung diseases other than idiopathic pulmonary fibrosis (IPF) that progress despite conventional management (ie, the progressive fibrotic phenotype) are likely to have pathogenetic mechanisms in common with IPF, potentially responding to antifibrotic therapies. 1 This was the conceptual basis of the successful INBUILD trial 2 of nintedanib for progressive fibrotic interstitial lung diseases (ILDs) other than IPF, and there has been considerable interest in whether pirfenidone is equally efficacious in these difficult-to-treat diseases. The first pirfenidone trial, in patients with fibrotic non-specific interstitial pneumonia or unclassifiable ILD, was deemed a negative study, on the basis of a non-validated primary endpoint (ie, home spirometric measurements, analysed parametrically and confounded by outlying observations in patients remaining in the study for short periods). 3 However, many experts view this study as providing convincing evidence of pirfenidone efficacy versus placebo in patients with a progressive fibrotic phenotype; a key secondary endpoint, serial forced vital capacity (FVC) measured in lung function laboratories, which equated to the primary endpoint in INBUILD, was unequivocally positive. Thus, the results of the RELIEF trial of pirfenidone, presented by Jürgen Behr and colleagues in the Lancet Respiratory Medicine , 4 in patients with progressive fibrotic ILDs other than IPF, have been eagerly anticipated.

Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial - Behr J, et al. *Lancet Respiratory Medicine*, 2021, 9(5), pp.476-486.

Background: Pirfenidone has been shown to slow disease progression in patients with idiopathic pulmonary fibrosis (IPF). However, there are few treatment options for progressive fibrotic interstitial lung diseases (ILDs)) other than IPF. In view of the pathomechanistic and clinical similarities between IPF and other progressive fibrotic ILDs, we aimed to assess the efficacy and safety of pirfenidone in patients with four non-IPF progressive fibrotic ILDs.

Pretreatment of aged mice with retinoic acid supports alveolar regeneration via upregulation of reciprocal PDGFA signalling - Gokey JJ, et al. *Thorax* 2021;76:456-467.

Objectives: Idiopathic pulmonary fibrosis (IPF) primarily affects the aged population and is characterised by failure of alveolar regeneration, leading to loss of alveolar type 1 (AT1) cells. Aged mouse models of lung repair have demonstrated that regeneration fails with increased age. Mouse and rat lung repair models have shown retinoic acid (RA) treatment can restore alveolar regeneration. Herein, we seek to determine the signalling mechanisms that become activated on RA treatment prior to injury, which support alveolar differentiation.

Pneumonia

Articles

Low vitamin D and risk of bacterial pneumonias: Mendelian randomisation studies in two population-based cohorts - Çolak Y, Nordestgaard BG, Afzal S. *Thorax* 2021;76:468-478.

Background: Vitamin D may regulate the innate immune system, and randomised controlled trials suggest a beneficial effect of vitamin D supplementation against acute respiratory tract infections. By using a Mendelian randomisation approach, we tested the hypothesis that low 25-hydroxyvitamin D is associated with increased risk of bacterial pneumonia in observational and genetic analyses.

Vitamin D and bacterial pneumonias: the question of causality - Allen RJ. *Thorax* 2021;76:426-427.

Vitamin D controls calcium and phosphates in the body, maintains healthy bones and muscles, and has been shown to play an important role in the regulation of the innate immune system. Vitamin D is found in some foods, but the main source for most people comes from sunlight. Over recent years, there has been much debate as to the benefit of vitamin D supplementation and the UK's National Health Service now advises everyone to consider vitamin D supplementation during winter months.

Pulmonary embolism

Articles

Association of Intravenous Tranexamic Acid With Thromboembolic Events and Mortality: A Systematic Review, Meta-analysis, and Meta-regression. - Taeuber I, et al. *JAMA Surgery* 2021;:e210884.
Findings from this systematic review and meta-analysis of 216 studies suggested that intravenous TXA, irrespective of dosing, is not associated with increased risk of any TE. These results help clarify the incidence of adverse events associated with administration of intravenous TXA and suggest that TXA is safe for use with undetermined utility for patients receiving neurological care.

Pulmonary hypertension

Articles

Depression, anxiety and psychological distress in patients with pulmonary hypertension: a mixed-methods study - Takita Y, et al. *BMJ Open Respiratory Research* 2021;8:e000876.

Introduction: Pulmonary hypertension (PH) is a chronic and progressive disease. While prognoses have improved, PH patients still experience side effects and activity restrictions. Accordingly, the key questions asked by this study are 'How many PH patients have depression/anxiety symptoms?' and 'Is there a difference in the symptoms and distress factors between pulmonary arterial hypertension (PAH) and chronic thromboembolic PH (CTEPH) patients, and how are they experiencing distress?'

Does Duke Activity Status Index help predicting functional exercise capacity and long-term prognosis in patients with pulmonary hypertension? - Mustafaoglu R, et al. *Respiratory Medicine*, 2021, 181, 106375.

Background: To investigate the association of Duke Activity Status Index (DASI) with 6-minute walk test (6MWT) and WHO-Functional Class (WHO-FC) in patients with pulmonary hypertension (PH), as well as exploring whether DASI can discriminate between the patients with better and worse long-term prognosis according to 400 m cut-off score in 6MWT.

Respiratory interventions (aspiration, chest drain, drug therapy, mechanical ventilation, oxygen therapy)

Articles

Bronchial thermoplasty: 10 years and counting - Langton D. *Lancet Respiratory Medicine*, 2021, 9(5), pp.436-437.

10-year follow-up studies are a rare commodity in respiratory medicine. By their very nature, long-term studies inform us more about negative outcomes, such as adverse events and loss of effect, and hence are not as attractive to researchers as are the short-term, positive outcomes observable with a novel therapy. Furthermore, cost, participant and staff mobility, and difficulty in maintaining patient engagement all conspire to impede long-term participant follow-up and degrade the quality of research. Rekha Chaudhuri and colleagues 1 should be congratulated for their study in The Lancet Respiratory Medicine, and for their dedication in making the findings of this work available to the clinical world. To our knowledge, this is the

first time such a study has been undertaken in relation to bronchial thermoplasty, which is a rarity among asthma treatments.

Paediatric long term continuous positive airway pressure and noninvasive ventilation in France: A cross-sectional study - Fauroux F, et al. *Respiratory Medicine*, 2021, 181, 106388.

Objective: To describe the characteristics of children treated with long term continuous positive airway pressure (CPAP) or noninvasive ventilation (NIV) in France.

Particulate generation with different oxygen delivery devices - Helgeson SA, et al. *Respiratory Medicine*, 2021, 181, 106386.

Background: The Coronavirus pandemic has a high mortality rate in patients that are mechanically ventilated, which has led to an ever increasing interest in noninvasive forms of oxygenation. The use of these devices has the theoretical risk of increased exposure risk because of possible particulate generation. This study aimed to quantify the particulate generation associated with different oxygen devices.

Guidelines

Ex-situ machine perfusion for extracorporeal preservation of lungs (ex-vivo lung perfusion) for transplant. National Institute for Health and Care Excellence (NICE); 2021.
1 Recommendations. 1.1 Evidence on the safety and efficacy of ex-situ machine perfusion for extracorporeal preservation of lungs for transplant is adequate to support the use of this procedure provided that standard arrangements are in place for clinical governance, consent and audit...

Newborn resuscitation and support of transition of infants at birth - Resuscitation Council (UK); 2021.
Resuscitation Council UK (RCUK) has produced these Newborn Life Support Guidelines, based on the International Liaison Committee on Resuscitation (ILCOR) 2020 Consensus on Science and Treatment Recommendations (CoSTR) for Neonatal Life Support. NLS CoSTR's 2019 and 2020, and the European Resuscitation Council Guidelines for Newborn resuscitation and support of transition of infants at birth. The guidelines cover the management of the term and preterm infant.

What's New in Critical Care from UpToDate

High flow nasal oxygen for hypoxemic respiratory failure (May 2021)

In patients with hypoxemic respiratory failure not due to acute exacerbation of chronic bronchitis or acute cardiogenic pulmonary edema and who are failing low flow oxygen, use of noninvasive modalities, either high flow oxygen delivered by nasal cannulae (HFNC) or noninvasive ventilation (NIV), may prevent the need for endotracheal intubation and mechanical ventilation. However, the best approach is unclear. In a recent meta-analysis of 29 randomized trials of mixed population of patients with acute respiratory failure,

HFNC resulted in lower intubation rates and mortality and improved patient comfort compared with NIV 4. Important limitations, including small sample size and heterogeneity in patient characteristics, type of respiratory failure, measured outcomes, and study design, qualify data interpretation. Nevertheless, HFNC appears to be at least as good as NIV for these patients. We prefer a short trial of HFNC rather than NIV, provided expertise for HFNC is available.

Intravascular catheter infusion set replacement interval (May 2021)

An infusion set consists of the sterile devices designed to conduct fluid to a patient's circulation via intravascular catheter. The optimal duration of infusion set use prior to replacement (to minimize the risk of infection and optimize resource use) is uncertain. In a randomized trial including more than 2200 patients with a central venous access device who were randomly assigned to infusion set replacement every seven days or every four days, catheter-related bloodstream infection rates were comparable (1.8 versus 1.5 percent); there were no treatment-related adverse events 5. Based on these findings, we favor an infusion set replacement interval of seven days (in the absence of a clinical indication for earlier replacement), to facilitate resource conservation and waste reduction.

Spirometry

Area under the expiratory flow-volume curve: predicted values by regression and deep learning methods and recommendations for clinical practice - Ioachimescu OC, et al. *BMJ Open Respiratory Research* 2021;8:e000925.

Background: In spirometry, the area under expiratory flow-volume curve (AEX-FV) was found to perform well in diagnosing and stratifying physiologic impairments, potentially lessening the need for complex lung volume testing. Expanding on prior work, this study assesses the accuracy and the utility of several models of estimating AEX-FV based on forced vital capacity (FVC) and several instantaneous flows. These models could be incorporated in regular spirometry reports, especially when actual AEX-FV measurements are not available.

Tuberculosis

Articles

Recurrent TB: a systematic review and meta-analysis of the incidence rates and the proportions of relapses and reinfections - Vega V, et al. *Thorax* 2021;76:494-502.

Background: A recurrent tuberculosis (TB) episode results from exogenous reinfection or relapse after cure. The use of genotyping allows the distinction between both.