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Respiratory Bulletin

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General

Articles

Effect of exposure to fine particulate matter during pregnancy and infancy on paediatric allergic rhinitis - Lin YT, et al. *Thorax* 2021;76:568-574.

Background: The effect of prenatal and postnatal exposure to fine particulate matter (PM2.5) on the development of allergic rhinitis (AR) is poorly understood. We further identified the vulnerable period for AR development to determine methods to decrease adverse effects.

Five-year outcome of respiratory muscle weakness at intensive care unit discharge: secondary analysis of a prospective cohort study - Van Aerde N, et al. *Thorax* 2021;76:561-567.

Purpose: To assess the association between respiratory muscle weakness (RMW) at intensive care unit (ICU) discharge and 5-year mortality and morbidity, independent from confounders including peripheral muscle strength.

Journal club - Sundaralingam A. *Thorax* 2021;76:634.

Natural history of lung function over one year in patients with Parkinson's disease - Kaminsky DA, et al. *Respiratory Medicine*, 2021, 182, 106396.

Background: Little is known about decline in lung function in Parkinson's disease (PD). To assess these changes, we assessed the changes in lung function that occurred over 12 months in patients on standard PD therapy as part of the observational cohort of an open-label study of inhaled levodopa (CVT-301) in PD.

Acute respiratory distress syndrome

Articles

Surfactant therapy via thin catheter in preterm infants with or at risk of respiratory distress syndrome. - Abdel-Latif ME, et al. *Cochrane Database of Systematic Reviews* 2021;5:CD011672.

Background: Non-invasive respiratory support is increasingly used for the management of respiratory dysfunction in preterm infants. This approach runs the risk of under-treating those with RDS, for whom surfactant administration is of paramount importance. Several techniques of minimally invasive surfactant therapy have been described. This review focuses on surfactant administration to spontaneously breathing infants via a thin catheter briefly inserted into the trachea.

Asthma

Articles

Adverse childhood experiences and asthma: trajectories in a national cohort - Pape K, et al. *Thorax* 2021;76:547-553.

Objective: Research has linked early adverse childhood experiences (ACEs) with asthma development; however, existing studies have generally relied on parent report of exposure and outcome. We aimed to examine the association of early life ACEs with empirically determined trajectories of childhood asthma risk, using independent register information on both exposures and outcome.

Asthma diagnosis: into the fourth dimension - Wang R, et al. *Thorax* 2021;76:624-631.

Asthma is the most common chronic respiratory disease in the UK; however, the misdiagnosis rate is substantial. The lack of consistency in national guidelines and the paucity of data on the performance of diagnostic algorithms compound the challenges in asthma diagnosis. Asthma is a highly rhythmic disease, characterised by diurnal variability in clinical symptoms and pathogenesis. Asthma also varies day to day, seasonally and from year to year. As much as it is a hallmark for asthma, this variability also poses significant challenges to asthma diagnosis. Almost all established asthma diagnostic tools demonstrate diurnal variation, yet few are performed with standardised timing of measurements. The dichotomous interpretation of diagnostic outcomes using fixed cut-off values may further limit the accuracy of the tests, particularly when diurnal variability straddles cut-off values within a day, and careful interpretation beyond the 'positive' and 'negative' outcome is needed. The day-to-day and more long-term variations are less predictable and it is unclear whether performing asthma diagnostic tests during asymptomatic periods may influence diagnostic sensitivities. With the evolution of asthma diagnostic tools, home monitoring and digital apps, novel strategies are needed to bridge these gaps in knowledge, and circadian variability should be considered during the standardisation process. This review summarises the biological mechanisms of circadian rhythms in asthma and highlights novel data on the significance of time (the fourth dimension) in asthma diagnosis.

Combination fixed-dose beta agonist and steroid inhaler as required for adults or children with mild asthma. - Crossingham I, et al. *Cochrane Database of Systematic Reviews* 2021;5:CD013518.

Background: Asthma affects 350 million people worldwide including 45% to 70% with mild disease. Treatment is mainly with inhalers containing beta$_2$-agonists, typically taken as required to relieve bronchospasm, and inhaled corticosteroids (ICS) as regular preventive therapy. Poor adherence to regular therapy is common and increases the risk of exacerbations, morbidity and mortality. Fixed-dose combination inhalers containing both a steroid and a fast-acting beta$_2$-agonist (FABA) in the same device simplify inhalers regimens and ensure symptomatic relief is accompanied by preventative therapy. Their use is established in moderate asthma, but they may also have potential utility in mild asthma.

Objectives: To evaluate the efficacy and safety of single combined (fast-onset beta$_2$-agonist plus an inhaled corticosteroid) inhaler only used as needed in people with mild asthma.

Comparative analysis of effectiveness of asthma control test-guided treatment versus usual care in patients with asthma from China - Ye L, et al. *Respiratory Medicine*, 2021, 182, 106382.

Objective: The present study compared the effectiveness of asthma control test (ACT)-guided treatment vs. usual care (UC) in patients with asthma from China.

Evidence-based European guidelines for the diagnosis of asthma in children aged 5–16 years - Gaillard EA, Moeller A. *Lancet Respiratory Medicine*, 2021, 9(6), pp.558-560.

Asthma is the most common non-communicable disease in children, but there is no single test available to confirm the diagnosis. In most cases, the diagnosis in children is made in non-specialist settings on the basis of clinical history and physical examination alone. 1 Lingering respiratory symptoms, such as prolonged cough, resulting from viral respiratory tract infections, are common in children 2 and often wrongly attributed to asthma. 3 However, non-specialists frequently refrain from diagnosing asthma in children to avoid giving them a potentially life-long diagnostic label that could affect future job choices. 4 As a result, substantial over-diagnosis and under-diagnosis of asthma has been confirmed by several international studies. 56 Both are problematic. Over-diagnosis results in the inappropriate prescription of asthma medications associated with potential side-effects and increased health-care costs. Conversely, under-diagnosis often results in poor quality of life.

Has the time come to end use of the blue inhaler? - Bush A, et al. *Lancet Respiratory Medicine*, 2021, 9(6), e.51.

Asthma attacks can lead to death, and new approaches to prevent asthma deaths, particularly in children and adolescents, are clearly needed, as highlighted by Abrams and colleagues. 1 Underuse of inhaled corticosteroids (ICS) and overuse of short-acting β 2 -agonists (SABA) are risk factors for death in people with asthma. Contributing to these risk factors is poor adherence to ICS, and the fact that many health-care professionals simply ignore the dangers of SABAs. As no evidence is available to suggest that these situations are improving, we ask if the time has come to end use of the blue inhaler.

Identifying preventable risk factors for hospitalised asthma in young Aboriginal children: a whole-population cohort study - Brew B, et al. *Thorax* 2021;76:539-546.

Background: Australia has one of the highest rates of asthma worldwide. Indigenous children have a particularly high burden of risk determinants for asthma, yet little is known about the asthma risk profile in this population.

Pharmacological and surgical interventions for the treatment of gastro-oesophageal reflux in adults and children with asthma. - Kopsaftis Z. *Cochrane Database of Systematic Reviews* 2021;5:CD001496.
Background: Asthma and gastro-oesophageal reflux disease (GORD) are common medical conditions that frequently co-exist. GORD has been postulated as a trigger for asthma; however, evidence remains conflicting. Proposed mechanisms by which GORD causes asthma include direct airway irritation from

micro-aspiration and vagally mediated oesophagobronchial reflux. Furthermore, asthma might precipitate GORD. Thus a temporal association between the two does not establish that GORD triggers asthma.

What's New in Asthma from UpToDate

Tezepelumab for severe asthma (June 2021)

Tezepelumab, an investigational monoclonal antibody to thymic stromal lymphopoietin, has shown promise in reducing asthma exacerbations in patients with moderate-to-severe asthma. In a multicenter, randomized trial (NAVIGATOR) that included 1059 adolescents and adults with severe uncontrolled asthma and a broad range of blood eosinophil counts, tezepelumab or placebo was administered subcutaneously every 4 weeks for 52 weeks; participants continued previously prescribed inhaled glucocorticoids and other nonbiologic controller medications without change 1. The tezepelumab group had approximately 50 percent fewer asthma exacerbations, irrespective of baseline blood eosinophil counts. Asthma control, asthma-related quality of life, and lung function were also improved with tezepelumab. Other biologic agents for severe asthma are limited to patients with high blood eosinophil counts or high immunoglobulin E levels; tezepelumab holds promise for a broader spectrum of patients with severe asthma.

Cancers of the respiratory tract

Articles

Efficacy and safety of pembrolizumab in patients with advanced mesothelioma in the open-label, single-arm, phase 2 KEYNOTE-158 study - Yap TA, et al. *Lancet Respiratory Medicine*, 2021, 9(6), pp.613-621.

Background: Malignant pleural mesothelioma (MPM) has few treatment options. Pembrolizumab showed preliminary clinical benefit in programmed death ligand 1 (PD-L1)-positive MPM. We evaluated the efficacy and safety of pembrolizumab monotherapy in patients with previously treated MPM irrespective of PD-L1 status in the KEYNOTE-158 study.

Neoadjuvant durvalumab with or without stereotactic body radiotherapy in patients with early-stage non-small-cell lung cancer: a single-centre, randomised phase 2 trial

Altorki NK, et al. *Lancet Oncology*, 2021, 22(6), pp.824-835.

Background: Previous phase 2 trials of neoadjuvant anti-PD-1 or anti-PD-L1 monotherapy in patients with early-stage non-small-cell lung cancer have reported major pathological response rates in the range of 15–45%. Evidence suggests that stereotactic body radiotherapy might be a potent immunomodulator in advanced non-small-cell lung cancer (NSCLC). In this trial, we aimed to evaluate the use of stereotactic body radiotherapy in patients with early-stage NSCLC as an immunomodulator to enhance the anti-tumour immune response associated with the anti-PD-L1 antibody durvalumab.

New and old treatments for malignant mesothelioma: not just immunotherapy - Nowak AK. *Lancet Respiratory Medicine*, 2021, 9(6), pp.547-549.

Systemic therapy for malignant mesothelioma has relied on platinum and pemetrexed chemotherapy since 2003. 1 2 Despite numerous clinical trials over almost two decades, no other cytotoxic chemotherapies have shown a survival benefit in this disease in the first-line or second-line treatment settings. The first positive randomised trial to utilise a maintenance agent in mesothelioma was the MAPS trial. 3 This trial showed that adding the monoclonal antibody bevacizumab to chemotherapy gave a further modest survival benefit, although it was not possible to separate out the contribution of maintenance bevacizumab from that of concurrent bevacizumab with chemotherapy.

Performance monitoring of EBUS for the staging and diagnosis of lung cancer: auditing the Greater Manchester EBUS service against new national standards - Punjabi A, et al. *BMJ Open Respiratory Research* 2021;8:e000777.

Introduction: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a pivotal test in lung cancer staging and diagnosis, mandating robust audit and performance monitoring of EBUS services. We present the first regional cancer alliance EBUS performance audit against the new National EBUS specification.

Pleural recurrence after transthoracic needle lung biopsy in stage I lung cancer: a systematic review and individual patient-level meta-analysis - Hong H, et al. *Thorax* 2021;76:582-590.

Introduction: Conflicting results exist regarding whether preoperative transthoracic biopsy increases the risk of pleural recurrence in early lung cancer. We conducted a systematic, patient-level meta-analysis to evaluate the risk of pleural recurrence in stage I lung cancer after percutaneous transthoracic lung biopsy.

Rucaparib in patients with BAP1-deficient or BRCA1 -deficient mesothelioma (MiST1): an open-label, single-arm, phase 2a clinical trial - Fennell DA, et al. *Lancet Respiratory Medicine*, 2021, 9(6), pp.593-600.

Background: Malignant mesothelioma remains an incurable cancer, with no effective treatments in the setting of relapsed disease. Homologous recombination deficiency predicts sensitivity to poly (ADP-ribose) polymerase (PARP) inhibitors. In mesothelioma, BRCA1 -associated protein 1 carboxy-terminal hydrolase (BAP1), which regulates DNA repair, is frequently mutated. We aimed to test the hypothesis that BAP1-deficient or BRCA1 -deficient mesotheliomas would be sensitive to PARP inhibition by rucaparib.

Single or combined immune checkpoint inhibitors compared to first-line platinum-based chemotherapy with or without bevacizumab for people with advanced non-small cell lung cancer. - Ferrara R, et al. *Cochrane Database of Systematic Reviews* 2021;4:CD013257.

Background: Immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 axis have changed the first-line treatment of people with advanced non-small cell lung cancer (NSCLC). Single-agent pembrolizumab (a PD-1 inhibitor) is currently the standard of care as monotherapy in patients with PD-L1 expression ≥ 50%,

either alone or in combination with chemotherapy when PD-L1 expression is less than 50%. Atezolizumab (PD-L1 inhibitor) has also been approved in combination with chemotherapy and bevacizumab (an anti-angiogenic antibody) in first-line NSCLC regardless of PD-L1 expression. The combination of first-line PD-1/PD-L1 inhibitors with anti-CTLA-4 antibodies has also been shown to improve survival compared to platinum-based chemotherapy in advanced NSCLC, particularly in people with high tumour mutational burden (TMB). The association of ipilimumab (an anti CTLA4) and nivolumab (PD-1 inhibitor) has been approved by the US Food and Drug Administration (FDA) in all patients with PD-L1 expression ≥1%. Although these antibodies are currently used in clinical practice, some questions remain unanswered, such as the best-treatment strategy, the role of different biomarkers for treatment selection and the effectiveness of immunotherapy according to specific clinical characteristics.

Switch-maintenance gemcitabine after first-line chemotherapy in patients with malignant mesothelioma (NVALT19): an investigator-initiated, randomised, open-label, phase 2 trial - De Gooijer CJ, et al. *Lancet Respiratory Medicine*, 2021, 9(6), pp.582-592.

Background: Almost all patients with malignant mesothelioma eventually have disease progression after first-line therapy. Previous studies have investigated maintenance therapy, but none has shown a great effect. We aimed to assess the efficacy and safety of switch-maintenance gemcitabine in patients with malignant mesothelioma without disease progression after first-line chemotherapy.

Twice-daily chemoradiotherapy in limited-stage small-cell lung cancer Levy A, Péchoux CL, Faivre-Finn C. *Lancet Oncology*, 2021, 22(6), e.220.

Acute radiation-induced oesophagitis has been associated with adverse events such as weight loss, substantial effect on quality of life, and reduced survival. 1 Concurrent chemotherapy given with hyperfractionated radiation therapy has been associated with an increased incidence of acute oesophageal toxicity. 2 Several dosimetric parameters and high doses have been associated with an increased risk of acute oesophagitis. 1 However, radiotherapy technical developments (eg, use of intensity-modulated radiotherapy and omission of elective nodal irradiation) allow a reduced dose to the organs at risk, including the oesophagus. Using such techniques, the CONVERT phase 3 trial 3 , which compared twice-daily radiotherapy (45 Gy in 30 fractions over 3 weeks) to once daily concurrent chemoradiotherapy (66 Gy in 33 fractions over 6·5 weeks), reported no difference in grade 3 or more oesophagitis between the 2 groups (19% in both groups). These results compared favourably with another clinical trial 2 (32% grade ≥3 oesophagitis in the 45 Gy in 30 fractions in the twice-daily group).

Twice-daily chemoradiotherapy in limited-stage small-cell lung cancer - Xie L, Fan X, Qian B. *Lancet Oncology*, 2021, 22(6), e.221.

We congratulate Bjørn Henning Grønberg and colleagues 1 for completing the phase 2 clinical trial that compared high-dose, twice-daily thoracic radiotherapy of 45 Gy in 30 fractions with 60 Gy in 40 fractions among patients with limited stage small-cell lung cancer. However, the results raise three important issues and need to be interpreted with caution.

Twice-daily chemoradiotherapy in limited-stage small-cell lung cancer – Authors' reply - Grønberg BH, et al. *Lancet Oncology*, 2021, 22(6), e.222.

We thank Li Xie and colleagues, and Antonin Levy and colleagues, for their interest in our study of thoracic radiotherapy in limited stage small-cell lung cancer. The American Society of Clinical Oncology recommends that granulocyte colony stimulating factors (G-CSF) should be avoided in patients receiving concomitant chemoradiotherapy, particularly involving the mediastinum, 1 which is often the case in limited-stage small-cell lung cancer. We are not aware of studies showing that G-CSF improves outcomes in limited-stage small-cell lung cancer. In the CONVERT trial, 2 the 180 (37%) of 487 participants receiving G-CSF had similar outcomes to other participants who did not receive G-CSF.

Will radiotherapy be a future part of neoadjuvant therapy in operable non-small-cell lung cancer? - Sepesi B, Cascone T. *Lancet Oncology*, 2021, 22(6), pp.744-746.

The testing of new neoadjuvant therapeutic strategies for operable non-small-cell lung cancer (NSCLC) has rapidly progressed as it has benefitted from the practice-changing results that have emerged from trials of immune checkpoint inhibitors in the metastatic setting. To date, more than 20 clinical trials have tested immune checkpoint inhibitors either as monotherapy, in combination with anti-CTLA-4, or in combination with chemotherapy. Several of these studies have used major pathological response as one of the main outcomes.

Guideline

Atezolizumab (Tecentriq▼) and other immune-stimulatory anti-cancer drugs: risk of severe cutaneous adverse reactions (SCARs). Medicines & Healthcare products Regulatory Agency; 2021.
Drug Safety Update. Cases of severe cutaneous adverse reactions, including Stevens-Johnsons syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in patients treated with immune-stimulatory anti-cancer drugs, including atezolizumab. Advise patients to be vigilant for the signs of severe skin reactions and to seek urgent medical advice if they occur.

Atezolizumab monotherapy for untreated advanced non-small-cell lung cancer. National Institute for Health and Care Excellence (NICE); 2021.
1 Recommendations. 1.1 Atezolizumab is recommended, within its marketing authorisation, as an option for untreated metastatic non-small-cell lung cancer (NSCLC) in adults if: their tumours have PD-L1 expression on at least 50% of tumour cells or 10% of tumour-infiltrating immune cells; their tumours do not have epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutations and the company provides atezolizumab according to the commercial arrangement...

What's New in Lung Cancer from UpToDate

Aprepitant for cough palliation in lung cancer (June 2021)

Cough can be a bothersome and difficult to treat symptom in patients with lung cancer. Aprepitant, which is used for chemotherapy-related nausea and vomiting, may ameliorate cough by inhibiting activation of neurokinin (NK)-1 receptors by substance P. In a randomized crossover trial of 20 patients with lung cancer and bothersome cough, three days of aprepitant reduced cough while awake (22 percent) and asleep (60 percent) compared with placebo 28. This study supports the participation of NK-1 receptors as a mechanism in chronic cough. Additional research is needed with a larger study population, longer duration, and optimized dosing.

COPD

Articles

A 28-day clinical trial of aerosolized hyaluronan in alpha-1 antiprotease deficiency COPD using desmosine as a surrogate marker for drug efficacy Cantor JO, et al. *Respiratory Medicine*, 2021, 182, 106402.

Introduction: A previous 2-week clinical trial of aerosolized hyaluronan (HA) in COPD showed a rapid reduction in lung elastic fiber breakdown, as measured by sputum levels of the unique elastin crosslinks, desmosine and isodesmosine (DID). To further assess the therapeutic efficacy of HA and the utility of DID as surrogate markers for the development of pulmonary emphysema, we have conducted a 28-day randomized, double-blind, placebo-controlled, phase 2 trial of HA involving 27 subjects with alpha-1 antiprotease deficiency COPD.

The effect of nitrogen dioxide and atmospheric pressure on hospitalization risk for chronic obstructive pulmonary disease in Guangzhou, China She W, et al. *Respiratory Medicine*, 2021, 182, 106424.

Background: The relationship between air pollution and meteorological factors on diseases has become a research hotspot recently. Nevertheless, few studies have touched the inferences of nitrogen dioxide (NO 2) and atmospheric pressure (AP) on hospitalization risk for chronic obstructive pulmonary disease (COPD).

Efficacy of unsupervised exercise in adults with obstructive lung disease: a systematic review and meta-analysis Taylor D, et al. *Thorax* 2021;76:591-600.

Introduction: 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.

Extrathoracic muscle wasting in exacerbations of COPD: no longer outside the region of interest - Greening NJ, Polkey MI, McAuley HJC. *Thorax* 2021;76:530-531.

While airflow limitation is used to diagnose chronic obstructive pulmonary disease (COPD), it is well established that forced expiratory volume in one second alone relates poorly to mortality1 or health-

related quality of life.2 Skeletal muscle dysfunction has been shown to be a better predictor than lung function for both prognosis3 and risk of hospitalisation.4 Moreover, skeletal muscle weakness is increasingly recognised as an important component of both frailty and sarcopaenia. Acute exacerbations of COPD (AECOPD) are a feature of many patients with COPD, with intermittent worsening of symptoms contrasting to many other chronic conditions. The impact of exacerbations is well established, with prevention and treatment an important goal for therapy with COPD.

Fibroblast growth factor 23 is an independent marker of COPD and is associated with impairment of pulmonary function and diffusing capacity - Kraen M, et al. *Respiratory Medicine*, 2021, 182, 106404.

Fibroblast growth factor 23 (FGF23) is a phosphaturic hormone that in recent years has been reported to have significant effects on numerous tissues. Chronic obstructive pulmonary disease (COPD) is associated with hypophosphatemia but the evidence for elevated plasma levels of FGF23 in COPD subjects is ambiguous. Recently, FGF23 has even been shown to be involved in the inflammatory pathways activated in COPD, so FGF23 could be a novel biomarker for COPD and impairment of pulmonary function. The purpose was thus to explore the association of FGF23 with COPD and measures of pulmonary function. This was a cross sectional study of 450 subjects who underwent spirometry, body plethysmography, determination of diffusing capacity (DL,CO) and biomarker analysis of FGF23, interleukin (IL)-1 receptor antagonist, IL-6 and IL-8. Forty-four participants were excluded due to missing data or renal impairment (eGFR <45 mL/min/m2). Spirometry identified 123 subjects with COPD. FGF23 levels were elevated in COPD subjects compared to non COPD subjects, and this remained significant after adjustment for age, sex and smoking habits (OR = 1.6, p = 0.02). Linear regression showed significant relationships between FGF23 and FEV1 (β = −0.15, p = 0.003), RV/TLC (β = 0.09, p = 0.05) and DL, CO (β = −0.24, p < 0.001). In conclusion we found that plasma levels of FGF23 are elevated in COPD subjects even when adjusting for traditional risk factors. Furthermore, FGF23 is associated with impairment in lung function as measured by FEV1 and DL,CO. Further studies are needed to establish whether FGF23 could serve as a novel biomarker of COPD and emphysema development.

High parathyroid hormone predicts exacerbations in COPD patients with hypovitaminosis D - Amado CA, et al. *Respiratory Medicine*, 2021, 182, 106416.

Background: Hypovitaminosis D has been linked to deterioration in clinical parameters and lung function in COPD. As a response to low levels of vitamin D serum Parathyroid Hormone (iPTH) is increased in some, but not all, patients. The aim of this study was to determine whether COPD patients with elevated PTH levels are at higher risk of COPD exacerbations and hospitalizations.

Predicting long-term mortality with two different criteria of exercise-induced desaturation in COPD - Kim C, et al. *Respiratory Medicine*, 2021, 182, 106393.

Background: There are few reports on exercise-induced desaturation (EID) as a predictor of mortality in chronic obstructive pulmonary disease (COPD). However, the definitions of EID vary in published reports. The main purpose was to evaluate the association between EID and long-term mortality by applying two criteria of EID.

Respiratory exacerbations are associated with muscle loss in current and former smokers - Mason SE, et al. *Thorax* 2021;76:554-560.

Objectives: Muscle wasting is a recognised extra-pulmonary complication in chronic obstructive pulmonary disease and has been associated with increased risk of death. Acute respiratory exacerbations are associated with reduction of muscle function, but there is a paucity of data on their long-term effect. This study explores the relationship between acute respiratory exacerbations and long-term muscle loss using serial measurements of CT derived pectoralis muscle area (PMA).

TRICOP – A Real-world effectiveness study with a single-inhaler extrafine triple therapy over 52 weeks in Austrian patients with COPD - Marth K, Renner A, Pohl W. *Respiratory Medicine*, 2021, 182, 106398.

Objective: Evidence of the efficacy of single-inhaler triple therapy in COPD patients inferred from RCTs has not been assessed in a real-world setting in Austria. In this non-interventional study (NIS) tolerability and effectiveness of extrafine beclometasone-dipropionate, formoterol-fumarate and glycopyrronium (Trimbow® 87/5/9 µg) was evaluated in COPD patients.

Reports

National Asthma and COPD Audit Programme: COPD clinical audit 2019/20. Healthcare Quality Improvement Partnership (HQIP); 2021.
The COPD audit is continuous and captures the process and clinical outcomes of treatment in patients admitted to hospital in England, Scotland and Wales with COPD exacerbations. Data describing the cohort of patients discharged between 1 October 2019 and 29 February 2020 – the period just prior to the COVID-19 pandemic. Key process measures are included in the report.

Cystic fibrosis

Articles

Drug therapies for reducing gastric acidity in people with cystic fibrosis. - Ng SM, Moore HS. *Cochrane Database of Systematic Reviews* 2021;4:CD003424.
Background: Malabsorption of fat and protein contributes to poor nutritional status in people with cystic fibrosis. Impaired pancreatic function may also result in increased gastric acidity, leading in turn to heartburn, peptic ulcers and the impairment of oral pancreatic enzyme replacement therapy. The administration of gastric acid-reducing agents has been used as an adjunct to pancreatic enzyme therapy to improve absorption of fat and gastro-intestinal symptoms in people with cystic fibrosis. It is important to establish the evidence regarding potential benefits of drugs that reduce gastric acidity in people with cystic fibrosis. This is an update of a previously published review.

Objectives: To assess the effect of drug therapies for reducing gastric acidity for: nutritional status; symptoms associated with increased gastric acidity; fat absorption; lung function; quality of life and survival; and to determine if any adverse effects are associated with their use.

Single versus combination intravenous anti-pseudomonal antibiotic therapy for people with cystic fibrosis. Holland P, Jahnke N. *Cochrane Database of Systematic Reviews* 2021;6:CD002007.

Background: The choice of antibiotic, and the use of single or combined therapy are controversial areas in the treatment of respiratory infection due to Pseudomonas aeruginosa in cystic fibrosis (CF). Advantages of combination therapy include wider range of modes of action, possible synergy and reduction of resistant organisms; advantages of monotherapy include lower cost, ease of administration and reduction of drug-related toxicity.

Objectives: To assess the effectiveness of single compared to combination intravenous anti-pseudomonal antibiotic therapy for treating people with CF.

Practice Changing Update from UpToDate

Pediatrics (June 2021) Elexacaftor-tezacaftor-ivacaftor for children ≥6 years with cystic fibrosis

●For patients ≥6 years old with cystic fibrosis who are homozygous for the F508del variant, we recommend triple therapy (elexacaftor-tezacaftor-ivacaftor) rather than dual therapy (tezacaftor-ivacaftor or lumacaftor-ivacaftor) (Grade 1B). For patients ≥6 years old who have one F508del mutation (heterozygotes) or other eligible mutation based on in vitro data, we suggest triple therapy rather than dual therapy or monotherapy (ivacaftor) (Grade 2C).

Elexacaftor-tezacaftor-ivacaftor is an important therapy for most patients with cystic fibrosis (CF), but its use has been limited to adolescents and adults. The drug combination was evaluated in a 24-week open-label study in 66 children 6 to 11 years old who were homozygous for F508del or heterozygous for F508del with a second minimal function mutation 4. The safety profile and pharmacokinetics were similar to that in older individuals, and patients experienced improvement in pulmonary function (change in FEV1, 10.2 percentage points; 95% CI 7.9-12.6); respiratory symptoms; sweat chloride; and body weight. On the basis of this study, the US Food and Drug Administration approved this drug for children ≥6 years with CF and eligible genotypes (algorithm 1), and we now recommend treatment in eligible patients starting at the age of six years.

Infections (including COVID-19)

General

Development of new antibacterial agents: a sense of urgency needed - Burki TK. *Lancet Respiratory Medicine*, 2021, 9(6), e.54.

On April 15, 2021, WHO released its annual report on the antibacterial clinical and preclinical pipeline. “The report reveals a near static pipeline with only a few antibiotics being approved by regulatory agencies in recent years”, stated WHO. It added that none of the antibiotics currently in clinical development “sufficiently address the problem of drug resistance in the world's most dangerous bacteria”. The report covered the year to September, 2020. It identified phase 1–3 trials of 43 new antibiotics, targeting drug-resistant bacteria on the WHO Priority Pathogen List, Mycobacterium tuberculosis, or Clostridium difficile. Of the 26 antibiotics active against the priority pathogens, seven satisfy at least one of the criteria for

innovation: absence of cross-resistance to existing antibiotics, new chemical class, target, or mechanism of action.

COVID-19

Articles

Air quality, Environment and Respiratory Outcomes in Bronchopulmonary Dysplasia, the AERO-BPD cohort study: design and adaptation during the SARS-CoV-2 pandemic - Ruran HB, et al. *BMJ Open Respiratory Research* 2021;8:e000915.

Introduction: Almost half of all school-age children with bronchopulmonary dysplasia (BPD) have asthma-like symptoms and more suffer from lung function deficits. While air pollution and indoor respiratory irritants are known to affect high-risk populations of children, few studies have objectively evaluated environmental contributions to long-term respiratory morbidity in this population. This study aimed to examine the role of indoor environmental exposures on respiratory morbidity in children with BPD.

Alone, lonely, and missed - Kahn J. *Lancet Respiratory Medicine*, 2021, 9(6), pp.565-566.

The COVID-19 epidemic changed my practice, transforming patient flow from what were mostly face-to-face encounters into telephone and video interactive experiences. I was concerned when these new modes of patient care were first rolled out and we substituted technology-based interactions for in-person visits. I was worried that patients without access to computers or without high-speed internet connections, or cell phones, or lacking the knowledge and experience to use their computer and phones for health-care visits would be marginalised and left out of the health-care enterprise. Although the technology facilitated encounters were initially presented as an option intended to improve care, it soon became an enterprise-wide necessity in response to the spreading epidemic. Patients were initially sceptical, and physicians were not gung-ho either, and yet, once the epidemic broadened and threatened our patients and ourselves, we had to respond and mitigate risky activities and still provide the needed health care. The technology was necessary. Nevertheless, I was concerned. Would the new connections support our interactions and provide a platform for effective health care? Would our empathetic bonds deteriorate and worsen clinical outcomes?

British Transplantation Society guidance during COVID-19. - Specialist Pharmacy Service (SPS); 2021.
Background: The British Transplant Society (BTS) and the Centre of Evidence in Transplantation have collaborated to provide an open access repository of current and emerging evidence for solid organ donors, recipients and potential recipients in the context of COVID-19.

Changes in the incidence of invasive disease due to Streptococcus pneumoniae, Haemophilus influenzae, and Neisseria meningitidis during the COVID-19 pandemic in 26 countries and territories in the Invasive Respiratory Infection Surveillance Initiative: a prospective analysis of surveillance data.
Brueggemann AB, et al. *The Lancet Digital Health* 2021
Background: Streptococcus pneumoniae, Haemophilus influenzae, and Neisseria meningitidis, which are typically transmitted via respiratory droplets, are leading causes of invasive diseases, including bacteraemic pneumonia and meningitis, and of secondary infections subsequent to post-viral respiratory disease. The aim of this study was to investigate the incidence of invasive disease due to these pathogens during the early months of the COVID-19 pandemic.

COVID-19 and ethnicity: has history repeated itself? - Learoyd AE, Douiri A, Hart N. *Thorax* 2021;76:537-538.

In the year since its discovery, the novel virus SARS-CoV-2 has spread across the world and ignited, in a short pace of time, an entire area of research into its origins, symptoms and outcomes of the resultant disease (COVID-19), possible treatments and contributing risk factors. The speed at which this field has grown has enabled us to more proactively treat individuals with COVID-19 and has brought us to the precipice of mass vaccination against this virus. But, despite being a new field of study led by 21st century scientists, research into COVID-19 has fallen into the same pitfall present in older, more established areas of research—namely, the unconscious biases associated with ethnicity.

COVID-19 pathophysiology: looking beyond acute disease - The Lancet Respiratory Medicine. *Lancet Respiratory Medicine*, 2021, 9(6), p.545.

Careful descriptions of the clinical features of acute disease in patients infected with the novel coronavirus SARS-CoV-2 had begun to emerge before WHO declared the outbreak of COVID-19 a public health emergency of international concern on Jan 30, 2020. As the global pandemic took hold, the need for data to inform patient management drove research efforts to describe the clinical spectrum of COVID-19, the determinants of disease severity, the mechanisms underlying the multiorgan manifestations of SARS-CoV-2 infection, and the response to a range of interventions. Little more than a year on, a picture of a new disease entity is coming into focus—with a distinct range of clinical and pathophysiological features—as described by Marcin Osuchowski and colleagues in the first of a Series of four papers in The Lancet Respiratory Medicine.

The COVID-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity - Osuchowski MF, et al. *Lancet Respiratory Medicine*, 2021, 9(6), pp.622-642.

The zoonotic SARS-CoV-2 virus that causes COVID-19 continues to spread worldwide, with devastating consequences. While the medical community has gained insight into the epidemiology of COVID-19, important questions remain about the clinical complexities and underlying mechanisms of disease phenotypes. Severe COVID-19 most commonly involves respiratory manifestations, although other systems are also affected, and acute disease is often followed by protracted complications. Such complex manifestations suggest that SARS-CoV-2 dysregulates the host response, triggering wide-ranging immuno-

inflammatory, thrombotic, and parenchymal derangements. We review the intricacies of COVID-19 pathophysiology, its various phenotypes, and the anti-SARS-CoV-2 host response at the humoral and cellular levels. Some similarities exist between COVID-19 and respiratory failure of other origins, but evidence for many distinctive mechanistic features indicates that COVID-19 constitutes a new disease entity, with emerging data suggesting involvement of an endotheliopathy-centred pathophysiology. Further research, combining basic and clinical studies, is needed to advance understanding of pathophysiological mechanisms and to characterise immuno-inflammatory derangements across the range of phenotypes to enable optimum care for patients with COVID-19.

COVID-19 survivor experiencing long-term symptoms - Kirby T. *Lancet Respiratory Medicine*, 2021, 9(6), pp.570-572.

Anne Cahill of Dublin, Ireland, would describe herself as a relatively fit and healthy woman in her early 50s, married to husband Tony and with four adult children. She could not have known that the new coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was going to hit her like a hurricane, nearly taking her life and changing her outlook on life and health forever.

Desperation in the time of COVID-19 - Adhikari B. *Lancet Respiratory Medicine*, 2021, 9(6), pp.567-569.

It is a pleasant April day in Mulpani, Kathmandu. The staff on duty at Mulpani Primary Health Center (PHC) sit together in the main lobby, remarking on the sudden downsurge in patients frequenting the facility. The halls, once teeming with patients, now echo with the sighs of health-care workers. The reasons for the quietude are obvious—the diagnosis of some of the earliest cases of COVID-19 in Nepal at this facility and the establishment of a quarantine and isolation centre.

Disputes over the production and dissemination of misinformation in the time of COVID-19 - Cazzola M, et al. *Respiratory Medicine*, 2021, 182, 106380.

Ultimate coronavirus disease 2019 (COVID-19) mitigation and crisis resolution is dependent on trustworthy data and actionable information. At present time, there is still no cure for COVID-19, although some treatments are being used in severe illness. Regrettably, as the SARS-CoV-2 virus spreads, the lack of cure has been accompanied by an increasing amount of medical misinformation. In particular, there is a lot of misinformation about how to treat patients who have tested positive for SARS-CoV-2 and who are asymptomatic or have mild symptoms and for whom management at home is deemed appropriate. In this editorial, we highlight the risks deriving from this misinformation, which often arises from the publication of studies that are not conceptually and methodologically accurate.

Evolution of lung function and chest CT 6 months after COVID-19 pneumonia: Real-life data from a Belgian University Hospital - Stylemans D, et al. *Respiratory Medicine*, 2021, 182, 106421.

Introduction: Most post COVID-19 follow-up studies are limited to a follow-up of 3 months. Whether a favorable evolution in lung function and/or radiological abnormalities is to be expected beyond 3 months is uncertain.

From female warriors in the rainforest to infectious disease specialists: COVID-19 in the Amazon - Safe I. *Lancet Respiratory Medicine*, 2021, 9(6), pp.566-567.

Amazonas, the biggest state in Brazil, owes its name to female warriors who according to an ancient legend rode horses in the dark lost forest. The first case of COVID-19 in Manaus, the Amazonas' capital city of 2·5 million inhabitants, was reported on March 13, 2020. Within weeks, chaos set in earlier and was unlike other cities in Brazil. The city soon received media attention from all over the world when an aerial view of a local cemetery with trenches being dug by an excavator became popular. The image was more shocking than those of Milan or Quito. Politicians in charge said it was a lie, that the number of deaths were being swaddled by left-wing interests, but I, living near the cemetery, noticed the movement even before it was reported. Facing empty streets daily on my way to patients' houses, I used to come across funeral cars. It was like a video game with me going towards life and others going towards death.

High COVID-19 death rates in prisons in England and Wales, and the need for early vaccination - Braithwaite I, et al. *Lancet Respiratory Medicine*, 2021, 9(6), pp.569-570.

Institutional settings such as prisons are high-risk environments for infectious disease outbreaks and need to be given high priority in the rollout of COVID-19 vaccines. Prisons are typically overcrowded, access to sanitation is inconsistent, and people in prisons have contact with a large staff pool. Early modelling suggested a worst-case scenario of more than 77 000 COVID-19 cases and 2000 deaths in prisons across England and Wales, if explosive prison outbreaks were not prevented. From March, 2020, UK prisons implemented extensive physical distancing and infection control measures. For example, many people in prison have been required to remain in their cells for 23 h per day for the past year, family visits have not been permitted, and many education, work, and rehabilitation opportunities have been stopped. Other changes have included reduced transfers of people between prisons and cohorting or quarantining those who are vulnerable, symptomatic, or returning from hospital.

Immunotherapy in COVID-19: why, who, and when? - Sinha P, Calfee CS. *Lancet Respiratory Medicine*, 2021, 9(6), pp.549-551.

Nearly 1·5 years into the global COVID-19 pandemic, immense progress has been made against SARS-CoV-2 in health care, most prominently in vaccine development. However, why some people infected with SARS-CoV-2 rapidly develop fulminant respiratory failure, while others have mild, self-limited, or even asymptomatic disease, is not fully understood. In the absence of highly effective antiviral therapy, treatment has focused on modulating the host immune response to SARS-CoV-2. Unsurprisingly, given human genetic variation and the burgeoning genetic variance of the virus itself, evidence for the efficacy of

many interventions is unclear. Mortality rates approaching 50% among mechanically ventilated patients in the recent RECOVERY trial of tocilizumab, 1 in both study arms, are a sobering reminder of the limitations of such treatments.

Impact of COVID-19 on cancer care in India: a cohort study. - Ranganathan P, et al. *The Lancet Oncology* 2021

Background: The COVID-19 pandemic has disrupted health-care systems, leading to concerns about its subsequent impact on non-COVID disease conditions. The COVID-19 pandemic has had considerable impact on the delivery of oncology services in India.

Impaired diffusing capacity for carbon monoxide is common in critically ill Covid-19 patients at four months post-discharge - Ekbom E, et al. *Respiratory Medicine*, 2021, 182, 106394.

There is limited knowledge about the long-term effects on pulmonary function of COVID-19 in patients that required intensive care treatment. Spirometry and diffusing capacity for carbon monoxide (DLCO) were measured in 60 subjects at 3-6 months post discharge. Impaired lung function was found in 52% of the subjects, with reduced DLCO as the main finding. The risk increased with age above 60 years, need for mechanical ventilation and longer ICU stay as well as lower levels of C-reactive protein at admission. This suggests the need of follow-up with pulmonary function testing in intensive-care treated patients.

Interleukin-6: obstacles to targeting a complex cytokine in critical illness - McElvaney OJ, et al. *Lancet Respiratory Medicine*, 2021, 9(6), pp.643-654.

Circulating concentrations of the pleiotropic cytokine interleukin-6 (IL-6) are known to be increased in pro-inflammatory critical care syndromes, such as sepsis and acute respiratory distress syndrome. Elevations in serum IL-6 concentrations in patients with severe COVID-19 have led to renewed interest in the cytokine as a therapeutic target. However, although the pro-inflammatory properties of IL-6 are widely known, the cytokine also has a series of important physiological and anti-inflammatory functions. An adequate understanding of the complex processes by which IL-6 signalling occurs is crucial for the correct interpretation of IL-6 concentrations in the blood or lung, the use of IL-6 as a critical care biomarker, or the design of effective anti-IL-6 strategies. Here, we outline the role of IL-6 in health and disease, explain the different types of IL-6 signalling and their contribution to the net biological effect of the cytokine, describe the approaches to IL-6 inhibition that are currently available, and discuss implications for the future use of treatments such as tocilizumab in the critical care setting.

Interleukin-6 receptor blockade in patients with COVID-19: placing clinical trials into context - Angriman F, et al. *Lancet Respiratory Medicine*, 2021, 9(6), pp.655-664.

The pleiotropic cytokine interleukin-6 (IL-6) has been implicated in the pathogenesis of COVID-19, but uncertainty remains about the potential benefits and harms of targeting IL-6 signalling in patients with the disease. The efficacy and safety of tocilizumab and sarilumab, which block the binding of IL-6 to its receptor, have been tested in adults with COVID-19-related acute respiratory illness in randomised trials,

with important differences in trial design, characteristics of included patients, use of co-interventions, and outcome measurement scales. In this Series paper, we review the clinical and methodological heterogeneity of studies of IL-6 receptor antagonists, and consider how this heterogeneity might have influenced reported treatment effects. Timing from clinical presentation to treatment, severity of illness, and concomitant use of corticosteroids are among the factors that might have contributed to apparently inconsistent results. With an understanding of the sources of variability in these trials, available evidence could be applied to guide clinical decision making and to inform the enrichment of future studies.

Non-invasive respiratory support strategies in COVID-19 - Gorman E, et al. *Lancet Respiratory Medicine*, 2021, 9(6), pp.553-556.

In hospitalised patients with COVID-19, an increase in oxygen requirements prompts the clinician to decide how and when to escalate treatment. A key treatment goal is to avoid, where possible, the need for invasive mechanical ventilation. However, up to 20% of hospitalised patients in the UK require admission to critical care units, and around 40% of those requiring invasive mechanical ventilation for COVID-19 pneumonitis do not survive. 1 To date, the only treatments that have been shown to reduce the need for invasive mechanical ventilation are dexamethasone and interleukin-6 blockade.

Safety, Immunogenicity, and Efficacy of a COVID-19 Vaccine (NVX-CoV2373) Co-administered With Seasonal Influenza Vaccines. - Toback S, et al. *medRxiv* 2021

Background: The safety and immunogenicity profile of COVID-19 vaccines when administered concomitantly with seasonal influenza vaccines has not yet been reported.

Saliva as a gold-standard sample for SARS-CoV-2 detection - Tan SH, et al. *Lancet Respiratory Medicine*, 2021, 9(6), pp.562-564.

As COVID-19 continues to strain public health systems and vaccination programmes race against new variants that might be more transmissible or capable of evading immune responses, the urgent need for simple, accessible, and frequent testing remains. Inexpensive, scalable, and sustainable strategies that allow easily repeatable testing over time need to be made widely available. This is possible by testing saliva.

Shift work is associated with positive COVID-19 status in hospitalised patients - Maidstone R, et al. *Thorax* 2021;76:601-606.

Introduction: Shift work is associated with lung disease and infections. We therefore investigated the impact of shift work on significant COVID-19 illness.

A tricompartmental model of lung oxygenation disruption to explain pulmonary and systemic pathology in severe COVID-19 - McGonagle D, Bridgewood C, Meaney JFM. *Lancet Respiratory Medicine*, 2021, 9(6), pp.665-672.

The emergent 21st century betacoronaviruses, including SARS-CoV-2, lead to clinicopathological manifestations with unusual features, such as early-onset chest pain, pulmonary infarction, and pulmonary and systemic thromboembolism that is pathologically linked to extensive capillary, arteriolar, and venular thrombosis. Early ground glass opacities detected by CT, which are reminiscent of lung infarcts associated with pulmonary embolism, point to a novel vascular pathology in COVID-19. Under physiological conditions, normal parenchymal oxygenation is maintained by three sources: the alveolus itself and dual oxygen supply from the pulmonary and bronchial artery circulations. We propose a model in which these three components are disrupted in COVID-19 pneumonia, with severe viral alveolitis and concomitant immunothrombotic obstruction of the pulmonary and bronchiolar circulation. Tricompartmental disruption might have two main consequences: systemic clot embolisation from pulmonary vein territory immunothrombosis, and alveolar–capillary barrier disruption with systemic access of thrombogenic viral material. Our model encompasses the known pathological and clinical features of severe COVID-19, and has implications for understanding patient responses to immunomodulatory therapies, which might exert an anti-inflammatory effect within the vascular compartments.

Vascular mechanisms and manifestations of COVID-19 - Levi M, Coppens M. *Lancet Respiratory Medicine*, 2021, 9(6), pp.551-553.

Severe COVID-19 is dominated by a multifaceted severe respiratory infection. The pathophysiology of acute disease is the focus of a Series of four papers in The Lancet Respiratory Medicine . Dennis McGonagle and colleagues 1 propose that COVID-19 simultaneously affects three compartments of the lungs, thereby leading to disruption of oxygenation: inflammation of the alveolar space, immunothrombosis of the juxtaposed pulmonary vascular compartment, and thrombotic obstruction of the pulmonary and bronchial circulation. Apart from the respiratory features of COVID-19, many extrapulmonary manifestations can occur as well. Some of these disease characteristics might be expected in patients with severe acute lung injury and a systemic inflammatory response; however, COVID-19 includes some complications that seem to be specific to SARS-CoV-2 infection. Marcin Osuchowski and colleagues 2 describe the most common phenotypes of COVID-19 in their comprehensive review of disease pathophysiology.

Reports

Long COVID and speech and language therapy: Understanding the mid- to long-term speech and language therapy needs and the impact on services. - Royal College of Speech and Language Therapists (RCSLT); 2021.

Between 24 February and 10 March 2021, the RCSLT conducted a survey of members, to gather their insights into working with people with Long COVID over the previous year (February 2020 to March 2021) – the results of which are shared in our new report ‘Long COVID and speech and language therapy: Understanding the mid- to long-term speech and language therapy needs and the impact on services’,

published today.

Practice Changing Update from UpToDate

Infectious Diseases; Emergency Medicine (adult and pediatric) (February 2021, Modified June 2021)
Adjunctive baricitinib or tocilizumab for COVID-19

●For hospitalized adults with COVID-19 who have initiated mechanical ventilation in the prior 24 to 48 hours, we suggest adding tocilizumab to usual care (which includes dexamethasone) (Grade 2B). For hospitalized adults with COVID-19 who have initiated high-flow supplemental oxygen or noninvasive ventilation within the prior 24 to 48 hours, we suggest adding baricitinib or tocilizumab to usual care (Grade 2B). For hospitalized adults with COVID-19 who are receiving low-flow supplemental oxygen and have both progressively increasing oxygen requirements despite dexamethasone and significantly elevated inflammatory markers, we suggest adding baricitinib or tocilizumab to usual care (Grade 2C). However, if availability of these agents is limited, we prioritize them for patients on higher levels of oxygen support.

Results from recent randomized trials suggest adjunctive use of the Janus kinase inhibitor baricitinib or the interleukin-6 pathway inhibitor tocilizumab has a survival benefit in hospitalized adults with severe COVID-19.

•In one unpublished randomized trial of patients who were not receiving invasive mechanical ventilation, adding baricitinib to standard of care reduced 28-day mortality; among those on high-flow oxygen or noninvasive ventilation at baseline, mortality was 17.5 versus 29.4 percent with placebo 1.

•In two open-label trials that included patients on oxygen support with a C-reactive protein level ≥75 mg/L or patients who had recently started high-flow oxygen or more intensive respiratory support, adding tocilizumab reduced 28-day mortality (28 to 29 percent versus 33 to 36 percent with usual care alone) 2,3.

In the majority of patients, usual care included dexamethasone. Baricitinib and tocilizumab have not been compared directly or studied together. We suggest either baricitinib or tocilizumab as an adjunct to dexamethasone for select patients with severe or critical COVID-19. (See "COVID-19: Management in hospitalized adults", section on 'IL-6 pathway inhibitors (eg, tocilizumab)'.)

What's New in Critical Care from UpToDate

Anticoagulation intensity in people hospitalized for COVID-19 (March 2021, Modified June 2021)

Thromboembolic complications of severe COVID-19 are common in hospitalized patients, especially in the intensive care unit (ICU), but the optimal approach to venous thromboembolism (VTE) prophylaxis has been unclear. Limited data from the early months of the pandemic suggested that increased dosing intensity might be reasonable. However, recent randomized trials have found that prophylactic dose anticoagulation is equally effective as higher doses of anticoagulation in reducing VTE risk, including in patients in the ICU, with trends towards lower rates of bleeding 8-10. Based on currently available evidence, standard prophylactic dosing is appropriate for patients hospitalized for COVID-19 who do not have a VTE.

What's New in Other Pulmonary Medicine from UpToDate

Invasive fungal infections following COVID-19 (June 2021)

Patients with COVID-19, particularly those treated with immunosuppressants, are at risk for developing secondary fungal and parasitic infections. Case reports of invasive rhino-orbital mucormycosis have been reported in patients recovering from COVID-19, most commonly among those treated with corticosteroids and individuals with poorly controlled diabetes mellitus 33-35. Secondary invasive fungal infection should be suspected in patients with these risk factors who develop sinus congestion, blackish or discolored nasal discharge, facial or ocular pain, or visual symptoms following acute COVID-19 illness.

Interstitial lung diseases (pulmonary fibrosis)

Articles

Changing priorities for pulmonary fibrosis: the patient will see you now! - Fabbri L, Jones S. *Thorax* 2021;76:534-535.

Over the last century, the doctor–patient relationship has gradually evolved from a paternalistic to a more patient-centred approach, with a marked change in the last 20 years. This cultural shift is reflected in health research, where patients and the public have become increasingly engaged and empowered. The UK pioneered these changes, with patient and public involvement becoming, in 2006, a founding principle of the National Institute of Health Research (NIHR). The NIHR aims 'to conduct leading edge research focussing on the needs of patients and the public', with research being undertaken with or by members of the public, rather than on or to them.1 A basic premise is that involving lay people and bringing in different perspectives and experiences can improve research quality, while also empowering patients to influence change on issues they consider important. There are many different frameworks but one of the most useful is described by NIHR INVOLVE, the English national advisory group on public involvement, shown in table 1.

Integrating new therapies for systemic sclerosis-associated lung fibrosis in clinical practice - Khanna D, Denton CP. *Lancet Respiratory Medicine*, 2021, 9(6), pp.560-562.

Systemic sclerosis-associated interstitial lung disease (SSc-ILD) is a common disease feature and among the most common causes of death in patients with systemic sclerosis. 1 SSc-ILD is the consequence of an autoimmune-mediated inflammatory and fibrotic nexus, which leads to lung fibrosis. 1 Our research group classified interstitial lung disease (ILD), in particular SSc-ILD, as subclinical ILD, in which patients have no ILD-specific symptoms, minimal evidence of ILD on high-resolution CT (HRCT), and normal pulmonary physiology; and clinical ILD, in which patients are symptomatic and have decrements in their pulmonary physiology or moderate-to-extensive disease on HRCT. 2 The management of fibrotic ILDs, including SSc-ILD, is largely targeted at patients with clinical ILD. The Scleroderma Lung Studies (I and II) and the SENSCIS trial all included this subgroup classification as an inclusion criterion.

Prognostic significance of peripheral blood monocyte and neutrophil counts in rheumatoid arthritis-associated interstitial lung disease - Saku A, et al. *Respiratory Medicine*, 2021, 182, 106420.

Objectives: Interstitial lung disease (ILD) is a common pulmonary manifestation of rheumatoid arthritis (RA) associated with clinical heterogeneity and high mortality. This study aimed to determine whether non-invasive biomarkers, especially monocyte count in peripheral blood, would be useful for predicting outcomes in patients with RA-associated ILD (RA-ILD).

Psychological impact of genetic and clinical screening for pulmonary fibrosis on asymptomatic first-degree relatives of affected individuals - Carmichael N, et al. *Thorax* 2021;76:621-623.

Screening for pulmonary fibrosis may help to identify early stages of the disease. We assessed the psychological impact of screening undiagnosed first-degree relatives of patients with pulmonary fibrosis by administering two validated measures after participants received their results: the Decisional Regret Scale and the Feelings About genomiC Testing Results Questionnaire. More than 90% of relatives reported either no or mild decisional regret. Increased measures of decisional regret and negative feelings were present in those found to have a low diffusion capacity of carbon monoxide or interstitial lung abnormalities. Results of telomere length and genetic testing did not significantly impact regret.

Pulmonary fibrosis screening: quantifying the psychological impact - Newton CA. *Thorax* 2021;76:532-533.

Screening programmes have transformed outcomes in a number of conditions such as diabetes, cardiovascular disease and cancer. For example, lung cancer screening has effectively reduced cancer-associated mortality1 by identifying premetastatic lesions amenable to curative or highly effective therapies. Therefore, it is natural to wonder if screening for a similarly morbid disease such as pulmonary fibrosis (PF) could yield comparable results. A decade ago, screening for PF would likely have had little impact on the natural history of these disorders. However, three recent discoveries have made PF screening potentially more consequential: (1) the identification of interstitial lung abnormalities (ILA) which are thought to be PF precursor lesions2 3; (2) the realisation that asymptomatic relatives of patients with PF represent a sizeable at-risk population that are enriched for ILAs4–6; and (3) the development of antifibrotic therapies that are effective even for individuals with preserved lung function.7 8 Thus, the stage is now set to determine if PF screening is a viable avenue for improving clinical outcomes.

Top 10 research priorities for people living with pulmonary fibrosis, their caregivers, healthcare professionals and researchers - Tikellis G, et al. *Thorax* 2021;76:575-581.

Introduction: People with pulmonary fibrosis (PF) experience a high symptom burden, reduced quality of life and a shortened lifespan. Treatment options are limited and little is known about what patients, caregivers and healthcare professionals (HCPs)/researchers consider as the most important research priorities. This study aimed to identify the top 10 research priorities for PF across all stakeholders.

Guideline

CDK4/6 inhibitors (abemaciclib▼, palbociclib▼, ribociclib▼): reports of interstitial lung disease and pneumonitis, including severe cases. - Medicines and Healthcare products Regulatory Agency (MHRA); 2021.
Drug Safety Update. Cases of interstitial lung disease and pneumonitis have been reported in patients receiving CDK4/6 inhibitors indicated for some breast cancers. Ensure that patients taking these medicines are aware of the need to seek advice right away if they develop new or worsening respiratory symptoms.

Lifestyle interventions (diet, exercise, smoking)

Articles

Association of heated tobacco product use with tobacco use cessation in a Japanese workplace: a prospective study - Kanai M, et al. *Thorax* 2021;76:615-617.

We investigated how use of heated tobacco products (HTPs) affects tobacco cessation in a Japanese workplace. We offered cessation programmes for 158 tobacco users from November 2018 to April 2019 and surveyed the quitting rate in August 2019. Successful quitting was defined as stopping use of all kinds of nicotine-containing tobacco products. A Poisson regression analysis adjusted with inverse probability weighting showed that HTP users (either exclusive HTP users or dual users) were less likely than exclusive cigarette users to quit tobacco (risk ratio, 0.77; 95% CIs 0.61 to 0.97, p=0.024). The use of HTPs should not be recommended to assist in smoking cessation. Trial registration UMIN000034719.

Cooling off the heated controversy of a safer cigarette: heat-not-burn no better than traditional combustion cigarettes - Petrache I, De Boer E. *Thorax* 2021;76:536.

In response to overwhelming evidence of harmful effects of cigarette smoking, the tobacco industry launched heat-not-burn cigarettes (HNBC), a hybrid between traditional combustion cigarettes (TCCs) and electronic vaping devices. They marketed HNBC as a less harmful alternative to TCC due to absence of specific toxicants released by burning the tobacco. However, similar to TCC smoke, aerosols released by heating the tobacco (up to 350°C) in HNBC contain nicotine and harmful elements generated by incomplete combustion (pyrolysis) and thermogenic degradation of tobacco. The claims that these by-products are present in amounts too small to be harmful suggest that a threshold concentration for the toxic effects of heated tobacco by-products exists. This assertion requires further elucidation, due to a paucity of studies on long-term health effects of HNBC and the increasing use of HNBC, especially among current TCC smokers.1 Therefore, the two reports in this issue of Thorax, by Loffredo et al and Kanai et al,2 ,3 two research groups unaffiliated with tobacco industry, are timely, providing new insights into the harmful impact of chronic HNBC use on endothelial function and questioning its usefulness for tobacco cessation, respectively.

Impact of chronic use of heat-not-burn cigarettes on oxidative stress, endothelial dysfunction and platelet activation: the SUR-VAPES Chronic Study - Loffredo L, et al. *Thorax* 2021;76:618-620.

Tobacco habit still represents the leading preventable cause of morbidity and mortality worldwide. Heat-not-burn cigarettes (HNBCs) are considered as an alternative to traditional combustion cigarettes (TCCs) due to the lack of combustion and the absence of combustion-related specific toxicants. The aim of this observational study was to assess the effect of HNBC on endothelial function, oxidative stress and platelet activation in chronic adult TCC smokers and HNBC users. The results showed that both HNBC and TCC display an adverse phenotype in terms of endothelial function, oxidative stress and platelet activation. Future randomised studies are strongly warranted to confirm these data.

Smoking and risk of COVID-19 hospitalization - Neira DB, et al. *Respiratory Medicine*, 2021, 182, 106414.

Rationale: The association between smoking status and severe Coronavirus Disease 2019 (COVID-19) remains controversial.

Objective: To assess the risk of hospitalization (as a marker of severe COVID-19) in patients by smoking status: former, current and never smokers, who tested positive for the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV2) at an academic medical center in the United States.

Vitamin D deficiency and lung function decline in healthy individuals: A large longitudinal observation study - Ahn KM, et al. *Respiratory Medicine*, 2021, 182, 106395.

Aim: A reliable evidence from a comprehensive large-scale study supporting associations between serum vitamin D (25-hydroxyvitamin D) level (SVDL) and lung function decline (LFD) in healthy individuals has been unavailable. Using a well-established health screening database, we assessed the associations between SVDL and LFDs, measured as the forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1) and FEV1/FVC ratio.

Obstructive sleep apnoea

Articles

Sudden death in individuals with obstructive sleep apnoea: a systematic review and meta-analysis - Heilbrunn ES, et al. *BMJ Open Respiratory Research* 2021;8:e000656.

Objectives: Over 1 billion individuals worldwide experience some form of sleep apnoea, and this number is steadily rising. Obstructive sleep apnoea (OSA) can negatively influence one's quality of life and potentially increase mortality risk. However, the association between OSA and mortality has not been reliably estimated. This meta-analysis estimates the risk of all-cause and cardiovascular mortality in individuals with OSA.

Pneumonia

Articles

Evolution of lung function and chest CT 6 months after COVID-19 pneumonia: Real-life data from a Belgian University Hospital - Stylemans D, et al. *Respiratory Medicine*, 2021, 182, 106421.

Introduction: Most post COVID-19 follow-up studies are limited to a follow-up of 3 months. Whether a favorable evolution in lung function and/or radiological abnormalities is to be expected beyond 3 months is uncertain.

Occult primary Sjögren Syndrome in patients with interstitial pneumonia with autoimmune features - Auteri S, et al. *Respiratory Medicine*, 2021, 182, 106405.

Introduction/Objectives: To define the performance of Minor Salivary Gland Biopsy (MSGB) and Dry Eye Tests (DET) to detect occult Sjögren Syndrome (SS) among Interstitial Pneumonia with Autoimmune Features (IPAF) patients.

Pulmonary hypertension

Articles

REPLACE and the role of riociguat in pulmonary arterial hypertension therapy - Frantz RP. *Lancet Respiratory Medicine*, 2021, 9(6), pp.546-547.

Following completion of the randomised placebo-controlled study of riociguat for the treatment of inoperable or residual chronic thromboembolic pulmonary hypertension, 1 riociguat became the only vasodilator therapy approved by the US Food and Drug Administration to treat this difficult disease, and accordingly plays a substantive role in therapy for those with WHO Group 4 pulmonary hypertension. On the basis of the robust results of the Pulmonary Arterial Hypertension Soluble Guanylate Cyclase-Stimulator Trial 1 (PATENT-1) study, 2 in which 194 (44%) of 443 participants were on background therapy with an endothelin receptor antagonist, riociguat also received approval for the treatment of pulmonary arterial hypertension (PAH). Availability of riociguat for PAH raised questions about its role compared with that of phosphodiesterase-5 inhibitors (PDE5i; sildenafil and tadalafil), which also act on the nitric oxide pathway, are the most widely prescribed therapy for PAH, and have generic, cost-effective versions available. Without head-to-head studies, comparison of these agents is challenging.

Switching to riociguat versus maintenance therapy with phosphodiesterase-5 inhibitors in patients with pulmonary arterial hypertension (REPLACE): a multicentre, open-label, randomised controlled trial - Hoeper MM, et al. *Lancet Respiratory Medicine*, 2021, 9(6), pp.573-584.

Background: Riociguat and phosphodiesterase-5 inhibitors (PDE5i), approved for the treatment of pulmonary arterial hypertension (PAH), act on the same pathway via different mechanisms. Riociguat might be an alternative option for patients with PAH who do not respond sufficiently to treatment with PDE5i, but comparisons of the potential benefits of riociguat and PDE5i in these patients are needed. The aim of this trial was to assess the effects of switching to riociguat from PDE5i therapy versus continued PDE5i therapy in patients with PAH at intermediate risk of 1-year mortality.

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

Articles

Early humoral response among lung transplant recipients vaccinated with BNT162b2 vaccine - Shostak Y, et al. *Lancet Respiratory Medicine*, 2021, 9(6), ee.52-53.

Lung transplant recipients are given immunosuppressive therapy that might impair their ability to generate an adequate immune response to the BNT162b2 vaccine. 1 However, immunocompromised individuals were not included in the BNT162b2 vaccine clinical trials. We aimed to assess the immunogenicity response to the BNT162b2 vaccine in this population.

Lesson of the month: management for aspiration of a silver nitrate pencil tip during tracheostomy care - Deshayes S, et al. *Thorax* 2021;76:632-633.

We present the cases of two laryngectomised patients who were treated for granulomas of the tracheostomy orifice with a silver nitrate pencil. During tracheostomy care, the tip broke off, was aspirated and fell into the bronchial tree. Necrotising ulcerative injuries of the right bronchial tree with clear delineation were found without lesions in the subsegmental division. To prevent the risk of secondary stenosis of the small airways induced by the spread of silver nitrate, we did not irrigate with saline solution as previously reported. Antibiotherapy and endoscopic monitoring were performed. Complete healing in 4–6 weeks was found without stenosis of the bronchial tree or bleeding.

Lung microbiota predict chronic rejection in healthy lung transplant recipients: a prospective cohort study - Combs MP, et al. *Lancet Respiratory Medicine*, 2021, 9(6), pp.601-612.

Background: Alterations in the respiratory microbiome are common in chronic lung diseases, correlate with decreased lung function, and have been associated with disease progression. The clinical significance of changes in the respiratory microbiome after lung transplant, specifically those related to development of chronic lung allograft dysfunction (CLAD), are unknown. The aim of this study was to evaluate the effect of lung microbiome characteristics in healthy lung transplant recipients on subsequent CLAD-free survival.

Placement of finger oximeter on the ear: comparison with oxygen saturation values taken from the finger. - Shakespeare J, et al. *British Journal of Nursing* 2021;30(11):666-670.

Pulse oximetry is widely used to assess oxygen saturation (SpO2) in order to guide patient care and monitor the response to treatment. However, inappropriate oximeter probe placement has been shown to affect the measured oximetry values in healthy and normoxic outpatients. This study evaluated how treatment decisions might be impacted by SpO2 values obtained using a finger probe placed on the pinna of the ear in a cohort of 46 patients receiving non-invasive ventilation compared with values obtained from a probe on the finger and the results of arterial blood gas (ABG) (SaO2) analysis. Bland-Altman analysis was performed to evaluate agreement between the methods. Finger probe saturation was not statistically different from SaO2, with a mean difference of -0.66% (P>0.05). Saturation from the ear was significantly different (-4.29%; P<0.001). Subgroup analysis in hypoxic patients (SaO2<90%) showed a significant

difference between ABG SaO2, and finger and ear SpO2. The study provides evidence that placement of a finger probe on the ear is unsafe clinical practice, potentially leading to patient mismanagement.

Randomised trial of first-line bronchial artery embolisation for non-severe haemoptysis of mild abundance - Fartoukh M, et al. *BMJ Open Respiratory Research* 2021;8:e000949.

Background: Whereas first-line bronchial artery embolisation (BAE) is considered standard of care for the management of severe haemoptysis, it is unknown whether this approach is warranted for non-severe haemoptysis.

Respiratory rehabilitation

Articles

Bronchodilator reversibility testing in post-COVID-19 patients undergoing pulmonary rehabilitation - Maniscalco M, et al. *Respiratory Medicine*, 2021, 182, 106401.

Background: The usefulness of bronchodilators in coronavirus diseases 2019 (COVID-19) survivors is still uncertain, especially for patients with a concomitant obstructive lung disease. We aimed at verifying the level of bronchodilator reversibility in COVID-19 patients undergoing multidisciplinary pulmonary rehabilitation after the acute phase.

Ensuring rehabilitation is a vehicle for change. Orman K. *British Journal of Occupational Therapy* 2021;84(5):261-262.
The coronavirus pandemic has highlighted more than ever the importance of rehabilitation, and the Royal College of Occupational Therapists (RCOT) has been advising government teams and stakeholders on the most effective use of occupational therapy. This spotlight has also held up a lens to many of our accepted norms – that is, the predominance of reactive, acute access to occupational therapy and the narrowing of practice leading to loss of skills and the lack of outcome data. This editorial argues why it is now the right time to challenge current practice and why rehabilitation can be a catalyst for change.

Spirometry

Applicability of GLI 2012 spirometry equation among preschool aged Jordanian - Al-Qerem WA, Jarab AS. *Respiratory Medicine*, 2021, 182, 106397.

Objectives: The Validation of Global Lung Initiative (GLI 2012) equations is required prior to their application in clinical practice in different regions. This study validated the GLI 2012 equations in Middle Eastern preschool aged children, which was not previously conducted.

Prevalence of reduced carbon monoxide transfer factor in smokers with normal spirometry - Cheung T, et al. *Respiratory Medicine*, 2021, 182, 106422.

We report the prevalence of reduced levels of carbon monoxide transfer factor (TLCO) in middle-aged current or ex-smokers with normal spirometry. Spirometry and TLCO measurements were performed and we identified 391 subjects aged 40–60 years, with a significant smoking history and normal spirometry. In this group, 96 subjects (24%) had TLCO measuremements below the lower limit of normal when using the newly established Global Lung Initiative (GLI) reference equations. The measurement of TLCO should be considered as part of the standard assessment of smokers.

Tuberculosis

Articles

Challenges and opportunities to end tuberculosis in the COVID-19 era - Wingfield T, et al. *Lancet Respiratory Medicine*, 2021, 9(6), pp.556-558.

On World Tuberculosis Day, 2020, we warned of the impending impact of COVID-19 on the tuberculosis pandemic. We also made a plea that the world must not forget tuberculosis while it focused on COVID-19. 1 year later, on World Tuberculosis Day, 2021, we reflect on the compelling evidence of the challenges that COVID-19 has created for tuberculosis control and look forward to opportunities for integrated strategies to address the COVID-19 and tuberculosis pandemics. We are not on course to eliminate tuberculosis. The Stop TB Partnership estimates that the past 12 months have pushed back global tuberculosis progress by 12 years. 2 Achieving the WHO's End TB Strategy goals will require an estimated US$15 billion additional funding annually. Less than half of the funding commitments made at the 2018 UN High Level Meeting on tuberculosis have been delivered. Cuts to the UK overseas Official Development Assistance will further contribute to this shortfall.

'If not TB, what could it be?' Chest X-ray findings from the 2016 Kenya Tuberculosis Prevalence Survey - Mungai BN, et al. *Thorax* 2021;76:607-614.

Background: The prevalence of diseases other than TB detected during chest X-ray (CXR) screening is unknown in sub-Saharan Africa. This represents a missed opportunity for identification and treatment of potentially significant disease. Our aim was to describe and quantify non-TB abnormalities identified by TB-focused CXR screening during the 2016 Kenya National TB Prevalence Survey.