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CLINICAL YEAR IN REVIEW BIBLIOGRAPHY

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*This session was generously supported by an educational grant from
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INTERSTITIAL LUNG DISEASE

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ILD TREATMENT

Distler O, Highland KB, Gahlemann M, Azuma A, Fischer A, Mayes MD, Raghu G, Sauter W, Girard M, Alves M, Clerisme-Beaty E, Stowasser S, Tetzlaff K, Kuwana M, Maher TM; SENSIS Trial Investigators. **Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease.** *N Engl J Med.* 2019 Jun 27;380(26):2518-2528.

Summary

The SENSIS trial was a phase 3 clinical trial that randomized 576 adults with systemic sclerosis-associated ILD and fibrosis affecting at least 10% of the lungs on chest CT scan to receive nintedanib 150 mg twice daily or placebo. Participants had FVC of at least 40% predicted and DLCO 30 to 89% predicted. Almost half of the participants were receiving mycophenolate at baseline. The study found a significantly lower annual rate of FVC decline among participants treated with nintedanib: FVC declined by 52 mL in the nintedanib group and 93 mL in the placebo group (between-group difference of 41 mL at one year). There was no significant or clinically meaningful difference in the modified Rodnan skin score, health-related quality of life, or respiratory symptoms between the two groups. Diarrhea was the most common adverse event, and was reported by 76% of participants taking nintedanib. Elevations in ALT/AST at least three times the upper limit of normal occurred in 5% of those on nintedanib. An adverse event that led to treatment discontinuation occurred in 16% of participants on nintedanib vs. 9% on placebo.

Comments

1. This was a large, well-designed clinical trial showing that nintedanib is effective in slowing FVC decline in patients with systemic sclerosis-associated ILD.
2. The annual rate of FVC decline was lower for patients on mycophenolate at baseline, and the effect of nintedanib was more modest in this subgroup.
3. Strengths include broad inclusion criteria, making the study widely generalizable to most patients with systemic sclerosis-associated ILD.
4. Study was not powered to assess the effect of nintedanib on mortality.
5. The study does not answer the question of when to initiate nintedanib in patients with systemic sclerosis-associated ILD and how long to treat.

Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, Richeldi L, Kolb M, Tetzlaff K, Stowasser S,

Coeck C, Clerisme-Beaty E, Rosenstock B, Quaresma M, Haeufel T, Goeldner RG, Schlenker-Herceg R, Brown KK; INBUILD Trial Investigators. **Nintedanib in Progressive Fibrosing Interstitial Lung Diseases.** *N Engl J Med.* 2019 Oct 31;381(18):1718-1727.

Summary

The INBUILD study was a phase 3 clinical trial that enrolled 663 patients with progressive fibrosing ILD other than IPF. Criteria for progression included a relative decline in FVC of at least 10% predicted, a relative decline in FVC of 5-10% predicted plus worsening respiratory symptoms or increased fibrosis on chest CT, or worsening respiratory symptoms and increased fibrosis on chest CT. Participants had FVC greater than 45% predicted and DLCO of 30 to 80% predicted. Those on background immunosuppression, including prednisone at a dose of more than 20 mg daily, were excluded. Participants were randomized to placebo or nintedanib 150 mg twice daily. Among the enrolled participants, 62% had a UIP-like pattern on chest CT; chronic hypersensitivity pneumonitis and autoimmune ILD were the most common diagnoses. The study found a significantly lower annual rate of FVC decline among participants treated with nintedanib: 81 mL per year in the nintedanib group and 188 mL per year in the placebo group (between group difference 107 mL). Diarrhea was the most common side effect and occurred in 67% of participants on nintedanib. 20% of participants on nintedanib vs. 10% of those on placebo experienced an adverse event leading to treatment discontinuation.

Comments

1. This was a large, well-designed clinical trial showing that nintedanib is effective in slowing FVC decline in patients with a broad range of progressive fibrosing ILDs.
2. Mortality and acute exacerbations were lower slightly lower in the nintedanib group but the study was not powered to detect a difference in these outcomes.
3. Overall decline in FVC among those with a UIP pattern treated with placebo was similar to the decline in FVC seen in the placebo arm of INPULSIS, which enrolled IPF patients, suggesting shared mechanisms regardless of clinical diagnosis.
4. Strengths include the broad range of ILDs included.
5. The study excluded patients on immunosuppression at baseline, and the effect of nintedanib in this group of patients is unknown, as well as the timing of initiation of nintedanib relative to immunosuppression.

ILD DIAGNOSIS

Troy LK, Grainge C, Corte TJ, Williamson JP, Vallely MP, Cooper WA, Mahar A, Myers JL, Lai S, Mulyadi E, Torzillo PJ, Phillips MJ, Jo HE, Webster SE, Lin QT, Rhodes JE, Salamonsen M, Wrobel JP, Harris B, Don G, Wu PJC, Ng BJ, Oldmeadow C, Raghu G, Lau EMT; Cryobiopsy versus Open Lung biopsy in the Diagnosis of Interstitial lung disease alliance (COLDICE) Investigators.

Diagnostic accuracy of transbronchial lung cryobiopsy for interstitial lung disease diagnosis (COLDICE): a prospective, comparative study. *Lancet Respir Med.* 2020 Feb;8(2):171-181.

Summary

The COLDICE study compared the diagnostic accuracy of transbronchial lung cryobiopsy to surgical lung biopsy for the diagnosis of ILD. 65 patients were enrolled after a multidisciplinary discussion (MDD), if they were deemed to require a lung biopsy for diagnosis of ILD. Key exclusion criteria were oxygen saturation less than 90% on room air, DLCO less than 40% predicted, TLC less than 50% predicted, excessive bleeding risk, body mass index greater than 40, pulmonary hypertension or advanced comorbid conditions. Transbronchial lung cryobiopsy and surgical lung biopsy were done in the same patient, sequentially from two separate ipsilateral lobes (same lobes for both procedures). The study showed good agreement between cryobiopsy and surgical lung biopsy. For histopathological assessment, raw agreement was 71% and kappa 0.70. For MDD final diagnoses (incorporating clinical details, CT findings and cryobiopsy or surgical lung biopsy histopathology), raw agreement was 77% and kappa 0.62. High confidence or definite final MDD diagnoses were reached in 60% of cryobiopsy cases and 74% of surgical lung biopsy cases. Mild to moderate airway bleeding occurred in 22% of cryobiopsy cases and 1 pneumothorax was evident prior to surgical biopsy. There were 2 acute exacerbations of ILD within 2 weeks of surgery.

Comments

1. This was a well designed, prospective, multicenter study that aimed to compare the diagnostic yield of transbronchial lung cryobiopsy and surgical lung biopsy.
2. There was good agreement in histopathological assessment and final MDD diagnosis between the two procedures, but high or definite confidence diagnosis was reached more often with surgical biopsy.
3. The study emphasizes the importance of multidisciplinary discussion both before referring for biopsy and in reaching a final diagnosis.
4. Due to the sequential study design, the safety profiles of transbronchial lung cryobiopsy and surgical lung biopsy could not be compared
5. The study population was highly selected and deemed to be at acceptable risk to undergo surgical lung biopsy.

Walsh SLF, Lederer DJ, Ryerson CJ, Kolb M, Maher TM, Nusser R, Poletti V, Richeldi L, Vancheri C, Wilsher ML, Antoniou KM, Behr J, Bendstrup E, Brown KK, Corte TJ,

Cottin V, Crestani B, Flaherty KR, Glaspole IN, Grutters J, Inoue Y, Kondoh Y, Kreuter M, Johansson KA, Ley B, Martinez FJ, Molina-Molina M, Morais A, Nunes H, Raghu G, Selman M, Spagnolo P, Taniguchi H, Tomassetti S, Valeyre D, Wijsenbeek M, Wuyts WA, Wells AU.

Diagnostic Likelihood Thresholds That Define a Working Diagnosis of Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care Med.* 2019 Nov 1;200(9):1146-1153.

Summary

This study evaluated how diagnostic likelihood thresholds for a diagnosis of idiopathic pulmonary fibrosis (IPF) affect management decisions, and more specifically, the decisions to pursue a surgical lung biopsy and start antifibrotic therapy. The authors surveyed 404 international respiratory physicians, both non-academic and university-affiliated. Physicians were asked to evaluate clinical and imaging findings from 60 patient cases, provide a differential diagnosis, a diagnostic likelihood level, and a decision on surgical lung biopsy and treatment. The authors found that once the diagnostic likelihood threshold for IPF reached high confidence (70% or greater), only 30% of physician requested a surgical lung biopsy, and most (63%) would prescribe antifibrotic therapy without requesting a surgical lung biopsy. They also found no mortality difference between patients given a provisional high-confidence diagnosis of IPF and a definite diagnosis of IPF, after adjusting for disease severity and age. Agreement on the decision to pursue a surgical lung biopsy was poor, but was improved by access to weekly multidisciplinary team meeting.

Comments

1. This paper provides validity for the ontological framework for a diagnosis of fibrotic ILD proposed by Ryerson in 2017, incorporating levels of uncertainty into a decision making, and showing no mortality difference between those with a provisional high confidence diagnosis and a definite diagnosis of IPF.
2. The study was a Delphi-style exercise reflecting the practice of a broad range of international respiratory physicians that were both university and non-university affiliated.
3. It highlights the complexity, and poor agreement, involved in making the decision to pursue a surgical lung biopsy when evaluating patients suspected of having IPF.
4. It does not address the availability and role of cryobiopsy.
5. The cohort of patients was relatively small.

ILD PROGNOSTICATION

Scott MKD, Quinn K, Li Q, Carroll R, Warsinske H, Vallania F, Chen S, Carns MA, Aren K, Sun J, Koloms K, Lee J, Baral J, Kropski J, Zhao H, Herzog E, Martinez FJ, Moore BB, Hinchcliff M, Denny J, Kaminski N, Herazo-Maya JD, Shah NH, Khatri P. **Increased monocyte count as a cellular biomarker for poor outcomes in fibrotic diseases: a retrospective, multicentre cohort study.** *Lancet Respir Med.* 2019 Jun;7(6):497-508.

Summary

This study aimed to investigate whether an immune cell type from peripheral blood mononuclear cell samples could identify IPF patients at higher risk for poor outcomes. The authors used a discovery cohort of 120 IPF patients from University of Pittsburgh and University of Chicago, and two validation cohorts (Yale, 20 patients, and COMET trial, 45 patients). They also analyzed electronic health records of patients from Stanford, Vanderbilt and Optum Clinformatics DataMart to further validate their findings. They found that the higher percentage of monocytes was associated with shorter transplant-free survival. Other immune cells were not associated with poorer survival. These findings were confirmed in the validation cohorts. In 7459 patients with IPF who had medical records available, a monocyte count of 0.95 K/uL or greater was associated with increased risk of death.

Comments

1. Large study found that increased peripheral blood monocyte count may serve as a biomarker of poor outcomes.
2. Strengths include multiple validation cohorts, with both ICD9 diagnoses and confirmed diagnosis.
3. It remains unclear how much monocyte count can add to existing prognostic information, including age and FVC.
4. The study highlights the ongoing search for an easily measurable and quantifiable prognostic biomarker in IPF.

OTHER ARTICLES OF INTEREST

Adegunsoye A, Oldham JM, Bonham C, Hrusch C, Nolan P, Klejch W, Bellam S, Mehta U, Thakrar K, Pugashetti JV, Husain AN, Montner SM, Straus CM, Vij R, Sperling AI, Noth I, Strek ME, Chung JH. **Prognosticating Outcomes in Interstitial Lung Disease by Mediastinal Lymph Node Assessment. An Observational Cohort Study with Independent Validation.** *Am J Respir Crit Care Med.* 2019 Mar 15;199(6):747-759.

Ley B, Torgerson DG, Oldham JM, Adegunsoye A, Liu S, Li J, et al. **Rare Protein-Altering Telomere-related Gene Variants in Patients with Chronic Hypersensitivity Pneumonitis.** *Am J Respir Crit Care Med.* 2019;200(9):1154-63.

Maher TM, Corte TJ, Fischer A, Kreuter M, Lederer DJ, Molina-Molina M, et al. **Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial.** *The Lancet Respiratory medicine.* 2020;8(2):147-57.

Nathan SD, Behr J, Collard HR, Cottin V, Hoeper MM, Martinez FJ, et al. **Riociguat for idiopathic interstitial pneumonia-associated pulmonary hypertension (RISE-IIP): a randomised, placebo-controlled phase 2b study.** *The Lancet Respiratory medicine.* 2019;7(9):780-90.

Newton CA, Zhang D, Oldham JM, Kozlitina J, Ma SF, Martinez FJ, et al. **Telomere Length and Use of Immunosuppressive Medications in Idiopathic Pulmonary Fibrosis.** *American journal of respiratory and critical care medicine.* 2019;200(3):336-47.

O'Dwyer DN, Ashley SL, Gurczynski SJ, Xia M, Wilke C, Falkowski NR, et al. **Lung Microbiota Contribute to Pulmonary Inflammation and Disease Progression in Pulmonary Fibrosis.** *American journal of respiratory and critical care medicine.* 2019;199(9):1127-38.

Raghu G, Flaherty KR, Lederer DJ, Lynch DA, Colby TV, Myers JL, et al. **Use of a molecular classifier to identify usual interstitial pneumonia in conventional transbronchial lung biopsy samples: a prospective validation study.** *The Lancet Respiratory medicine.* 2019;7(6):487-96.

NPPV AND OXYGEN DELIVERY

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RESPIRATORY SUPPORTIVE THERAPY AFTER EXTUBATION

Thille AW, Muller G, Gacouin A, Coudroy R, Decavèle M, Sonnevile R, Beloncle F, Girault C, Dangers L, Lautrette A, Cabasson S, Rouzé A, Vivier E, Le Meur A, Ricard JD, Razazi K, Barberet G, Lebert C, Ehrmann S, Sabatier C, Bourenne J, Pradel G, Bailly P, Terzi N, Dellamonica J, Lacave G, Danin PÉ, Nanadoumgar H, Gibelin A, Zanre L, Deye N, Demoule A, Maamar A, Nay MA, Robert R, Ragot S, Frat JP; HIGH-WEAN Study Group and REVA Research Network. **Effect of Postextubation High-Flow Nasal Oxygen With Noninvasive Ventilation vs High-Flow Nasal Oxygen Alone on Reintubation Among Patients at High Risk of Extubation Failure: A Randomized Clinical Trial.** *JAMA*. 2019; 322(15): 1465-75

Summary

The optimal respiratory supportive therapy after extubation to prevent postextubation respiratory failure and reintubation remains uncertain. In this multicenter randomized clinical trial, 641 patients at high risk of extubation failure were randomized to receive high-flow nasal oxygen (HFNO) with prophylactic noninvasive ventilation (NIV) applied immediately after extubation or HFNO alone, with the hypothesis that HFNO combined with NIV may reduce reintubation rates. Patients were considered at high risk of extubation failure if they were older than 65 years or had any underlying chronic cardiac or lung disease. HFNO was delivered for at least 48 hours with a flow of 50 L/min and fraction of inspired oxygen (FiO₂) adjusted to obtain a pulse oximetry (SpO₂) of at least 92%. In the intervention group, NIV was initiated within the first 4 hours after extubation, and the minimal duration of NIV support was at least 12 hours a day during the 48 hours following extubation. Between NIV sessions, HFNO was delivered as in the control group. The use of the combination of HFNO with NIV immediately after extubation significantly decreased the risk of reintubation compared with the use of HFNO alone. No differences in mortality or length of stay were observed.

Comments

1. NIV combined with HFNO, compared with HFNO alone, significantly decreased the rate of reintubation within the first 7 days after extubation (11.8% vs 18.2%; difference, -6.4% [95% confidence interval {CI}, -12.0 to -0.9]; P=.02).

2. Rate of intubation in the NIV group was also lower at 48 hours, at 72 hours, and at intensive care unit (ICU) discharge.
3. The proportion of patients with postextubation respiratory failure at day 7 was significantly lower with NIV plus HFNO compared with HFNO alone (21% vs 29%; difference, -8.7% [95% CI, -15.2% to -1.8%]; P=.01).
4. Differences in outcomes may be more pronounced in hypercapnic patients. However, there was no interaction between PaCO₂ and outcomes (P=.25), and after adjusting by PaCO₂ at enrollment, the odds ratio for reintubation still favored the NIV with HFNO group (odds ratio, 0.60 [95% CI, 0.38 to 0.93]).
5. There were no significant differences in ICU and hospital mortality or length of stay between groups.

PREOXYGENATION BEFORE INTUBATION

Frat JP, Ricard JD, Quenot JP, Pichon N, Demoule A, Forel JM, Mira JP, Coudroy R, Berquier G, Voisin B, Colin G, Pons B, Danin PE, Devaquet J, Prat G, Clere-Jehl R, Petitpas F, Vivier E, Razazi K, Nay MA, Souday V, Dellamonica J, Argaud L, Ehrmann S, Gibelin A, Girault C, Andreu P, Vignon P, Dangers L, Ragot S, Thille AW; FLORALI-2 study group; REVA network. **Non-invasive ventilation versus high-flow nasal cannula oxygen therapy with apnoeic oxygenation for preoxygenation before intubation of patients with acute hypoxaemic respiratory failure: a randomised, multicentre, open-label trial.** *The Lancet Respiratory medicine*. 2019;7(4):303-12

Summary

Severe hypoxemia is one of the more frequent complications of endotracheal intubation, especially when it is performed in patients with acute hypoxemic respiratory failure (AHRF). The aim of this multicenter, open-label, randomized trial was to analyze whether noninvasive ventilation (NIV) or high-flow nasal oxygen (HFNO) used for preoxygenation in patients with AHRF, defined as a PaO₂/FiO₂ ratio <301 mmHg, may decrease the rate of severe hypoxemia during tracheal intubation. A total of 322 patients in 28 French ICUs were randomized to receive 5 minutes of NIV or HFNO prior to intubation. In the NIV group, pressure support was titrated to obtain an expired tidal volume of 6–8 mL/kg of predicted body weight, with a positive end-expiratory pressure of 5 cm H₂O and an FiO₂ of 1.0. Obviously, it was discontinued

during laryngoscopy. HFNO was applied with a flow rate of 60 L/min and an FiO₂ of 1.0, and it was continued during laryngoscopy until the intubation procedure was finished. No bag-mask ventilation was used in either group. No differences in the incidence of severe hypoxemia (SpO₂ <80%) or other secondary outcomes were observed. However, the results of the subgroup analysis showed that NIV decreased the incidence of severe hypoxemia in patients with moderate to severe hypoxemia, which corresponds to 77% of the patients included.

Comments

1. Severe hypoxemia (SpO₂ <80%) is relatively common and occurred in 25.5% of the patients with ongoing intubation for AHRF.
2. No differences in the rates of severe hypoxemia after preoxygenation were observed between the NIV and HFNO groups (23% vs 27%; absolute difference, -4.2% [95% confidence interval {CI}, -13.7 to 5.5]; P=.39).
3. Subgroup analysis revealed that in patients with moderate to severe hypoxemia, severe hypoxemia was less common in patients preoxygenated with NIV than those preoxygenated with HFNO (24% vs 35%; absolute difference estimate, -11.3% [95% CI, -22.3 to 0.3]; P=.0553), and the sensitivity analyses showed that the risk of severe hypoxemia in this subgroup of patients was lower with NIV than with HFNO after adjustment for PaO₂ at randomization (adjusted odds ratio, 0.56 [95% CI, 0.32 to 0.99]; P=.0459).
4. Similarly, in patients with moderate to severe hypoxemia, the lowest pulse oximetry during intubation was higher in the group of NIV patients (86% vs 81%; absolute difference estimate, 5.0% [95% CI, 1.2 to 8.7]; P=.02).
5. No differences in other early or late complications nor intensive care unit mortality was observed.

HIGH FLOW OXYGEN THERAPY IN ACUTE HYPOXEMIC RESPIRATORY FAILURE

Rochweg B, Granton D, Wang DX, Helviz Y, Einav S, Frat JP, Mekontso-Dessap A, Schreiber A, Azoulay E, Mercat A, Demoule A, Lemiale V, Pesenti A, Riviello ED, Mauri T, Mancebo J, Brochard L, Burns K. **High flow nasal cannula compared with conventional oxygen therapy for acute hypoxemic respiratory failure: a systematic review and meta-analysis.** *Intensive Care Med.* 2019;45(5):563-572.

Summary

High-flow nasal oxygen (HFNO) has emerged as a useful therapy for patients with acute hypoxemic respiratory failure (AHRF). However, the evidence regarding its use is still limited. This study is a systematic review and meta-analysis on the use of HFNO in patients with AHRF. It included 9 randomized controlled trials with 1607 patients with AHRF. Compared with the use of conventional oxygen, HFNO decreased the need for intubation and mechanical ventilation in 4.4%. Indeed, 23 (95% confidence interval [CI], 13 to 333) patients were needed to treat to reduce one intubation. Comparable results

were observed with the need for escalation support. In contrast, HFNO had no effect on mortality. Although they considered various subgroup analyses, they could not be performed due to the high risk of imprecision in the results obtained. Moreover, the trial sequential analysis demonstrated that the required information size was not achieved for any of the outcomes.

Comments

1. Compared with the use of conventional oxygen, HFNO may reduce the need for intubation and mechanical ventilation (risk ratio [RR], 0.85 [95% CI, 0.74 to 0.99], 4.4% absolute risk reduction [95% CI, 0.3% to 7.6%], low certainty) with an NNT of 23 (95% CI, 13 to 333) as well as the need for escalation support (RR, 0.71 [95% CI, 0.51 to 0.98], 9.3% absolute risk reduction [95% CI, 0.6% to 15.7%], low certainty) (Fig. 4) with an NNT for this outcome of 11 (95% CI, 6 to 167).
2. HFNO use had no benefit in terms of mortality.
3. No effect on patient-reported dyspnea, comfort, or other outcomes, such as intensive care unit or hospital length of stay, was observed.
4. Complications associated with HFNO use are mild and minimal, and they do not usually require treatment discontinuation.
5. As subgroup analysis could not be performed due to the small number of patients, it remains uncertain which critically ill patients could benefit the most from HFNO therapy or in which patients there is no benefit..

PREOXYGENATION BEFORE INTUBATION

Guitton C, Ehrmann S, Volteau C, Colin G, Maamar A, Jean-Michel V, Mahe PJ, Landais M, Brule N, Bretonnière C, Zambon O, Vourc'h M. **Nasal high-flow preoxygenation for endotracheal intubation in the critically ill patient: a randomized clinical trial.** *Intensive Care Med.* 2019 Apr;45(4):447-458.

Summary

Preoxygenation before intubation may enhance the safety of the procedure. However, the optimal supportive therapy to improve the efficacy of preoxygenation before intubation is still unknown. In this multicenter randomized controlled trial (RCT) performed in 7 French ICUs, 192 non-severely hypoxemic patients (PaO₂/FiO₂ ≥200) were randomized to a 4-minute period of preoxygenation using high-flow nasal oxygen (HFNO) (60 L/min; FiO₂ of 1) vs standard bag-valve mask (SBM) (15 L/min; FiO₂ of 1) during rapid sequence intubation in the intensive care unit (ICU). During laryngoscopy, HFNO was maintained in place, ensuring apneic oxygenation throughout the intubation. In contrast, SBM needed to be removed to ensure correct visualization. The main reason for intubation was decrease in level of consciousness (HFNO 68% and SBM 75%). No differences in the primary outcome, defined as the median lowest SpO₂ during the intubation procedure, were observed. However, the use of HFNO was associated with a threefold reduction of intubation-related complications (risk ratio, 0.31 [95%

CI, 0.13 to 0.76]; $P=.007$). This is an important result, as complications occurred in more than 10% of the patients included. No differences in days of mechanical ventilation, development of ventilator-associated pneumonia, length of ICU stay, or mortality were observed.

Comments

1. This is the first large multicenter RCT that examines the use of HFNO as a preoxygenation supportive therapy in non-severely hypoxemic critically ill patients.
2. Complications during intubation are frequent even in non-severely hypoxemic patients (more than >10% of the patients included).
3. Although the study included patients with a $\text{PaO}_2/\text{FiO}_2 \geq 200$ prior to intubation, the lowest observed SpO_2 during intubation ranged from 69% to 100% in HFNC and from 43% to 100% in SBM.
4. Although this study should be considered as a negative study in terms of the primary outcome (no difference in the median lowest SpO_2 between groups), it shows that the use of HFNO, compared with preoxygenation with SBM, is associated with a lower rate of moderate and severe intubation-related complications.
5. However, whether the best comparator for the use of HFNO is spontaneous breathing through an SBM may be debatable.

RESPIRATORY SUPPORTIVE THERAPY AFTER EXTUBATION

Vaschetto R, Longhini F, Persona P, Ori C, Stefani G, Liu S, Yi Y, Lu W, Yu T, Luo X, Tang R, Li M, Li J, Cammarota G, Bruni A, Garofalo E, Jin Z, Yan J, Zheng R, Yin J, Guido S, Della Corte F, Fontana T, Gregoretti C, Cortegiani A, Giarratano A, Montagnini C, Cavuto S, Qiu H, Navalesi P. **Early extubation followed by immediate noninvasive ventilation vs. standard extubation in hypoxemic patients: a randomized clinical trial.** *Intensive Care Med.*, 2019;45(1):62-71.

Summary

Noninvasive ventilation (NIV) has been used to facilitate the process of liberation from invasive mechanical ventilation (IMV) in different subgroups of patients, such as hypercapnic patients with chronic obstructive pulmonary disease, patients with cardiogenic pulmonary edema, or obese patients. However, no data regarding its use in patients who are recovering from acute hypoxemic respiratory failure are available. This randomized controlled trial compared two different strategies of weaning from IMV in patients who were ventilated with pressure support ventilation with a level of total applied airway pressure (positive end-expiratory pressure [PEEP]+inspiratory support) ≥ 25 cmH₂O, with PEEP level between 8 and 13 cmH₂O. A total of 130 patients were included and randomized to be directly extubated with no spontaneous breathing trial (SBT) and immediate application of NIV or to the standard treatment

(progressive decrease of PEEP and pressure support and SBT with prophylactic NIV during 6–12 hours in those patients who were at risk for postextubation respiratory failure). Direct extubation with NIV was associated with a decrease of days on IMV but had no effect on intensive care unit (ICU) length of stay (LOS). Moreover, it also reduced the rates of ventilator-associated respiratory infection, the need for sedation, and hospital LOS. There was no effect on mortality between groups.

Comments

1. The study has a limited generalizability, as they included a highly selected cohort of patients based on very strict inclusion and exclusions criteria (only 130 [10.3%] of the 1259 potentially eligible patients could be finally included).
2. A post hoc analysis considering the type of patient (medical vs surgical) showed that only surgical patients presented shorter duration of IMV and ICU LOS.
3. At the time of the study was performed (2013–2016), the evidence about the use of high-flow oxygen after extubation was still missing and, therefore, it was not used.
4. Despite these limitations, this novel approach may be useful in a subset of patients, and its utility should be further investigated in future studies..

OTHER ARTICLES OF INTEREST

Grieco DL, Menga LS, Raggi V, Bongiovanni F, Anzellotti GM, Tanzarella ES, Bocci MG, Mercurio G, Dell'Anna AM, Eleuteri D, Bello G, Maviglia R, Conti G, Maggiore SM, Antonelli M. **Physiological Comparison of High-Flow Nasal Cannula and Helmet Noninvasive Ventilation in Acute Hypoxemic Respiratory Failure.** *Am J Respir Crit Care Med.* 2020 Feb 1;201(3):303-312

Roca O, Caralt B, Messika J, Samper M, Sztrymf B, Hernández G, García-de-Acilu M, Frat JP, Masclans JR, Ricard JD. **An Index Combining Respiratory Rate and Oxygenation to Predict Outcome of Nasal High-Flow Therapy.** *Am J Respir Crit Care Med.* 2018 2019;199(11):1368-1376.

Longhini F, Pisani L, Lungu R, Comellini V, Bruni A, Garofalo E, Laura Vega M, Cammarota G, Nava S, Navalesi P. **High-Flow Oxygen Therapy After Noninvasive Ventilation Interruption in Patients Recovering From Hypercapnic Acute Respiratory Failure: A Physiological Crossover Trial.** *Crit Care Med.* 2019 Jun;47(6):e506-e511.

Masa JF, Mokhlesi B, Benítez I, Gomez de Terreros FJ, Sánchez-Quiroga MÁ, Romero A, Caballero-Eraso C, Terán-Santos J, Alonso-Álvarez ML, Troncoso MF, González M, López-Martín S, Marin JM, Martí S, Díaz-Cambriles T, Chiner E, Egea C, Barca J, Vázquez-Polo FJ, Negrín MA, Martel-Escobar M, Barbe F, Corral J; Spanish Sleep Network. **Long-term clinical effectiveness of continuous positive airway pressure therapy**

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CYSTIC FIBROSIS

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Seattle, WA**CFTR MODULATOR THERAPY FOR F508DEL HOMOZYGOUS PATIENTS**

Heijerma HG, McKone EF, Downey DG, Van Braeckel E, Rowe SM, Tullis E, Mall MA, Welter JJ, Ramsey BW, McKee CM, Marigowda G. **Efficacy and safety of the elxacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial.** *The Lancet.* 2019, 394(10212), pp.1940-1948.

Summary

Cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapies are targeted therapeutics that address the defective CFTR protein that causes cystic fibrosis (CF). F508del is the most frequently identified mutation of CFTR and approximately 50% of individuals with CF are homozygous for the F508del mutation in the United States. This study was a phase 3, double-blind, randomized, active-controlled trial of elxacaftor in combination with clinically-available tezacaftor/ivacaftor versus tezacaftor/ivacaftor alone. The study took place at 44 sites in 4 countries from August – December 2018. CF patients homozygous for F508del were eligible at age 12 years or older and forced expiratory volume in one second (FEV1) 40-90% of predicted. The primary outcome was absolute change from baseline FEV1 at week 4. A key secondary outcome was change in CF Questionnaire-Revised (CFQ-R) respiratory domain score, a measure of CF-specific health-related quality of life, at 4 weeks. Treatment with elxacaftor/tezacaftor/ivacaftor led to an absolute increase of 10% in the FEV1 ($p < 0.001$) when compared to the clinically available CFTR modulator (tezacaftor/ivacaftor), along with a clinically meaningful improvement in CFQ-R (17 points, $p < 0.001$; minimum clinically important difference is 4 points). Elxacaftor/tezacaftor/ivacaftor was well-tolerated and there were no discontinuations of the drug due to side effects.

Comments

1. Prior CFTR modulators (i.e. lumacaftor/ivacaftor, tezacaftor/ivacaftor) meaningfully reduced exacerbation frequency but led to a small increase in FEV1 for individuals with two copies of the F508del mutation.
2. Elxacaftor/tezacaftor/ivacaftor provided a substantial increase in FEV1 and health-related quality of life, in addition

- to the effects of the already available CFTR modulator for the CF population homozygous for F508del.
3. Elxacaftor/tezacaftor/ivacaftor was tested among individuals over the age of 12 years in this study, but investigation into the use of the drug earlier in the course of the disease is warranted.
 4. Elxacaftor/tezacaftor/ivacaftor was well tolerated in this 4-week study, but the safety profile is better assessed in the longer-duration study among patients heterozygous for F508del.

CFTR MODULATOR THERAPY FOR F508DEL HETEROZYGOUS PATIENTS

Middleton PG, Mall MA, Dřevínek P, Lands LC, McKone EF, Polineni D, Ramsey BW, Taylor-Cousar JL, Tullis E, Vermeulen F, Marigowda G. **Elxacaftor–tezacaftor–ivacaftor for cystic fibrosis with a single Phe508del allele.** *New England Journal of Medicine.* 2019 Nov 7;381(19):1809-19.

Summary

In the United States, 85-90% of individuals with CF have at least one copy of the F508del mutation of the CFTR gene. This study was a phase 3, double-blind, randomized, placebo-controlled trial of elxacaftor/tezacaftor/ivacaftor, a triple-combination CFTR modulator. The study took place at 115 sites in 13 countries from June 2018 – April 2019. CF patients heterozygous for F508del in combination with a minimal function CFTR mutation were eligible at age 12 years or older and FEV1 40-90% of predicted. The primary outcome was absolute change from baseline FEV1 at week 4. Randomization was stratified by FEV1 ($< 70\%$ vs $\geq 70\%$ predicted) at screening, age (< 18 vs ≥ 18 years), and sex. Treatment with elxacaftor/tezacaftor/ivacaftor led to an absolute increase of 13.8% in the FEV1 ($p < 0.001$) at 4 weeks. Secondary endpoints were significantly improved at 24 weeks, including an absolute increase in FEV1 of 14.3% ($p < 0.001$), decrease in pulmonary exacerbations by 63% ($p < 0.001$), increase in health-related quality of life (20 points on CFQ-R respiratory domain, $p < 0.001$), and an increase in body mass index (BMI) by 1.04 kg/m² ($p < 0.001$). Two patients discontinued the study drug due to side effects – 1 rash, and 1 developed portal hypertension (pre-existing cirrhosis).

Comments

1. Elexacaftor/tezacaftor/ivacaftor is the first CFTR modulator approved for individuals with a single copy of the F508del mutation in CFTR.
2. Elexacaftor/tezacaftor/ivacaftor drastically improved lung function and reduced pulmonary exacerbations, such that the study was effectively non-blinded to participants and their providers.
3. Every secondary endpoint tested was significantly improved.
4. Mean sweat chloride values in the treatment group were <60 mmol/L while values in the placebo group were >100 mmol/L, reflecting a significant physiologic change among patients treated with triple therapy; sweat chloride levels between 30-60 mmol/L are considered indeterminate during the diagnostic work-up for CF.
5. Adverse events were generally mild or moderate and led to discontinuation of study drug in 1% of the patients in the treatment group.

CFTR MODULATOR THERAPY USE IN UTERO AND POSTNATALLY IN A FERRET MODEL

Sun X, Yi Y, Yan Z, Rosen BH, Liang B, Winter MC, Evans TIA, Rotti PG, Yang Y, Gray JS, Park SY. *In utero and postnatal VX-770 administration rescues multiorgan disease in a ferret model of cystic fibrosis. Science translational medicine*, 2019. 11(485).

Summary

Multiorgan disease caused by CFTR mutations begins before birth, with prime examples including meconium ileus of the newborn and congenital bilateral absence of the vas deferens. Safety of CFTR modulators during pregnancy is under investigation for expectant mothers with CF, but unanswered questions remain about the potential effects of CFTR modulators on a fetus with CF. Ivacaftor has been evaluated in children as young as 2 years old and is currently FDA approved in the US for children 1 year of age or older with responsive CFTR mutations. In this study of CF ferrets, the authors compare ferrets with an ivacaftor-responsive mutation of CFTR (G551D) with ivacaftor-nonresponsive CF controls in order to study in vitro and in vivo endpoints. The exposure of interest is in utero treatment with ivacaftor and varying durations of postnatal continuation of therapy. In utero treatment with ivacaftor led to a reduction in incidence of meconium ileus at birth and rescue from developmental abnormalities. Continued treatment with ivacaftor postnatally led to improved pancreatic exocrine function, glucose tolerance, weight gain, and survival. After withdrawal of ivacaftor postnatally, ferrets lost weight, developed gut obstruction and lung infections, and died from these complications.

Comments

1. These results provide compelling evidence that CFTR modulators have the potential to prevent the fundamental

- manifestations of CF if administered prior to birth and suggest continuation after birth is necessary to perpetuate this effect.
2. This study provides proof of concept for in utero and early postnatal pharmacologic correction of CF that could be generalizable to patients with other CFTR mutations responsive to highly effective CFTR modulator therapy (e.g. F508del treatment with elexacaftor/tezacaftor/ivacaftor).
3. The study demonstrates that a higher level of CFTR function may be required to overcome specific CF conditions (e.g. meconium ileus, male infertility) based on experiments comparing heterozygous G551D/KO ferrets to homozygous G551D/G551D ferrets.
4. Removal of ivacaftor at any age (even into adulthood) led to reestablished disease of the pancreas, gut, and lungs, which was most remarkable when ivacaftor was stopped during the first 2 weeks after birth.

RISKS ASSOCIATED WITH CYSTIC FIBROSIS CARRIER STATUS

Miller AC, Comellas AP, Hornick DB, Stoltz DA, Cavanaugh JE, Gerke AK, Welsh MJ, Zabner J, Polgreen PM. *Cystic fibrosis carriers are at increased risk for a wide range of cystic fibrosis-related conditions. Proceedings of the National Academy of Sciences*, 2020; 117(3), pp.1621-1627.

Summary

Mutations in the CFTR gene that produce lower levels of CFTR function are associated with worsened CF phenotypes. CF carriers, people with only one mutation in CFTR, are routinely counseled that they are not at an increased risk of disease. This study aimed to determine whether CF carriers had increased risk for CF-related conditions, with cohorts and outcomes identified via ICD-9/ICD-10 codes in a large commercial claims research database. The authors identified patient cohorts (e.g. CF carrier cohort, CF cohort) and generated age- and sex-matched cohorts at a 5:1 ratio for comparison. They estimated the odds of subjects being diagnosed with a CF-related condition relative to subjects in their matched cohort using conditional logistic regression. CF carriers had an increased risk for nearly all 59 tested CF-related conditions, across multiple organ systems, when compared to matched controls. The relative log odds ratios across the 59 conditions were correlated between CF carriers and subjects with CF with a Pearson correlation coefficient of 0.7 – meaning that as the relative odds of a given condition increased among subjects with CF compared to their matched controls, so did the corresponding relative odds for carriers.

Comments

1. Multiple sensitivity analyses showed robust results demonstrating increased relative risk for CF carriers compared to matched controls, but the authors stress that the absolute

risk for a majority of the CF-related conditions in CF carriers remains low.

2. The authors estimated the effects of misclassification, the contribution of false discovery in the setting of multiple comparisons, and the impact of ascertainment bias for CF genetic testing in the setting of clinical suspicion for CF.
3. Sensitivity analyses included a cohort of non-CF mothers to babies with CF (by definition, mothers are CF carriers) and identified an increased risk of CF-related conditions in mothers prior to the diagnosis of CF in the baby when compared to matched controls.
4. CF carriers are at increased risk for most conditions that commonly occur in people with CF, which may have implications for screening, prevention, and/or treatment of those conditions.
5. Given the cost of CFTR modulators, there will be controversy surrounding treating CF carriers who have CF-related conditions.

OTHER ARTICLES OF INTEREST

CFTR Modulators

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Advanced Lung Disease, Lung Transplant, and Prognostication

Ramos KJ, Smith PJ, McKone EF, Pilewski JM, Lucy A, Hempstead SE, Tallarico E, Faro A, Rosenbluth DB, Gray AL, Dunitz JM. **Lung transplant referral for individuals with cystic fibrosis: Cystic Fibrosis Foundation consensus guidelines.** *Journal of Cystic Fibrosis*, 2019. 18(3), pp.321-333.

Hebestreit H, Hulzebos EH, Schneiderman JE, Karila C, Boas SR, Kriemler S, Dwyer T, Sahlberg M, Urquhart DS, Lands LC, Ratjen F. **Cardiopulmonary exercise testing provides additional prognostic information in cystic fibrosis.** *American journal of respiratory and critical care medicine*, 2019. 199(8), pp.987-995.

Lehr CJ, Skeans M, Dasenbrook E, Fink A, Fernandez G, Faro A, Valapour M. **Effect of including important clinical**

variables on accuracy of the lung allocation score for cystic fibrosis and chronic obstructive pulmonary disease. *American journal of respiratory and critical care medicine*, 2019. 200(8), pp.1013-1021.

Kapnadak SG, Dimango E, Hadjiliadis D, Hempstead SE, Tallarico E, Pilewski JM, Faro A, Albright J, Benden C, Blair S, Dellon EP. **Cystic Fibrosis Foundation consensus guidelines for the care of individuals with advanced cystic fibrosis lung disease.** *Journal of Cystic Fibrosis*. 2020.

Pediatric Diagnostics And Therapeutics

Ratjen F, Davis SD, Stanojevic S, Kronmal RA, Stukovsky KDH, Jorgensen N, Rosenfeld M, Kerby G, Kopecky C, Anthony M, Mogayzel P. **Inhaled hypertonic saline in preschool children with cystic fibrosis (SHIP): a multicentre, randomised, double-blind, placebo-controlled trial.** *The Lancet Respiratory Medicine*, 2019. 7(9), pp.802-809.

Stahl M, Wielpütz MO, Ricklefs I, Dopfer C, Barth S, Schlegtendal A, Graeber SY, Sommerburg O, Diekmann G, Hüsing J, Koerner-Rettberg C. **Preventive inhalation of hypertonic saline in infants with cystic fibrosis (PRESIS). A randomized, double-blind, controlled study.** *American journal of respiratory and critical care medicine*, 2019. 199(10), pp.1238-1248.

Margaroli C, Garratt LW, Horati H, Dittrich AS, Rosenow T, Montgomery ST, Frey DL, Brown MR, Schultz C, Gugliani L, Kicic A. **Elastase exocytosis by airway neutrophils is associated with early lung damage in children with cystic fibrosis.** *American Journal of Respiratory and Critical Care Medicine*, 2019. 199(7), pp.873-881.

Jorth P, Ehsan Z, Rezayat A, Caldwell E, Pope C, Brewington JJ, Goss CH, Benscoter D, Clancy JP, Singh PK. **Direct lung sampling indicates that established pathogens dominate early infections in children with cystic fibrosis.** *Cell reports*, 2019. 27(4), pp.1190-1204.

Endocrine Disorders

Kilberg MJ, Sheikh S, Stefanovski D, Kubrak C, De Leon DD, Hadjiliadis D, Rubenstein RC, Rickels MR, Kelly A. **Dysregulated insulin in pancreatic insufficient cystic fibrosis with post-prandial hypoglycemia.** *Journal of Cystic Fibrosis*, 2020. 19(2), pp.310-315.

ASTHMA

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NEW THERAPEUTIC APPROACHES TO MILD ASTHMA

Beasley R, Holliday M, Reddel, HK, Braithwaite I, Ebmeier BM, Hancox RJ, Harrison T, Houghton C, Oldfield K, Papi A, Pavord ID, Williams M, Weatherall M. **Controlled trial of budesonide-formoterol as needed for mild asthma.** *N Engl J Med* 2019; 380:220-30.

Summary

The treatment paradigm for the management of mild asthma has changed in the last two years with a recognition of as-needed beta agonist therapy alone results in increased asthma exacerbation rates. The Novel Symbicort Turbuhaler Asthma Reliever Therapy Trial (Novel START) was performed to investigate whether budesonide-formoterol therapy could be used on an as-needed basis among adults with mild asthma who had been treated with as-needed short acting β_2 agonist therapy. In this 52-week, randomized, open-label parallel group, controlled trial of mild asthmatics previously treated with as needed β_2 agonist therapy, the use of as-needed budesonide-formoterol was associated with a decreased annual asthma exacerbation rate compared to subjects treated with as-needed albuterol, but provided a similar reduction in the annual asthma exacerbation rate to subjects in the budesonide maintenance therapy arm. Notably, the use of as-needed budesonide-formoterol therapy was associated with a decreased risk of severe asthma exacerbations compared to subjects taking albuterol as needed and as compared to subjects on budesonide maintenance therapy. Although the as-needed budesonide-formoterol treatment was associated with a similar reduction in the annual exacerbation rate compared to budesonide maintenance therapy, budesonide maintenance provided superior asthma symptom control throughout the follow-up period.

Comments

1. The use of as-needed budesonide-formoterol therapy was associated with a decreased risk of severe asthma exacerbations compared to subjects taking albuterol as needed and as compared to subjects on budesonide maintenance therapy
2. There was no significant difference in lung function in any of the three treatment arms.
3. This study offers an approach for the treatment of patients with mild asthma particularly those who experience exacerbations, but have few asthma symptoms.
4. As needed budesonide-formoterol therapy is now recommended as Step 1 and 2 therapy and is to be used in an as needed basis with concurrent asthma maintenance therapy in

Steps 3-5 as outlined in the 2019 Global Initiative for Asthma (GINA) report for patients with mild disease. However, the most recent National Asthma Education and Prevention Program Guidelines for the Diagnosis and Management of Asthma (EPR-4) only recommends it as needed for Steps 3-5 in addition to an appropriate asthma maintenance regimen.

ASTHMA THERAPY IN MINORITY POPULATIONS

Wechsler ME, Szeffler SJ, Ortega VE, Pongracic JA, Chinchilli V, Lima JJ, Krishnan JA, Kunselman SJ, Mauger D, Bleecker ER, Bacharier LB, Beigelman A, Benson M, Blake KV, Cabana MD, Cardet J-C, Castro M, Chmiel JF, Covar R, Denlinger L, DiMango E, Fitzpatrick AM, Gentile D, Grossman N, Holguin F, Jackson DJ, Kumar H, Kraft M, LaForce CF, Lang J, Lazarus SC, Lemanske RF, Long D, Lugogo N, Martinez F, Meyers DA, Moore WC, Moy J, Naureckas E, Olin JT, Peters SP, Phipatanakul W, Que L, Raissy H, Robison RG, Ross K, Sheehan W, Smith LJ, Solway J, Sorkness CA, Sullivan-Vedder L, Wenzel S, White S, Israel E. **Step-up therapy in black children and adults with poorly controlled asthma.** *N Engl J Med* 2019;381:1227-39.

Summary

Epidemiologic studies demonstrate a disproportionate burden of asthma morbidity in children and adults identified as black compared to white subjects. Previous studies have demonstrated that black patients have differential responses to asthma medication, yet few randomized controlled trials have been performed to determine the preferred step-up regimen in children, adolescents, and adults who identify as black. The Best African American Response to Asthma Drugs (BARD) trials were performed to determine whether increasing inhaled steroids or the addition of a long acting beta agonist improves outcomes in black children and adults with inadequately controlled asthma on low dose inhaled corticosteroid. This study demonstrated that in children, who were reported to have at least one black grandparent, 46% had improved asthma outcomes when the dose of inhaled corticosteroid was increased, similar to a regimen that included the addition of a long acting beta agonist. In contrast to the results for black children, black adolescents and adults had responses similar to white adults in that the addition of a long acting beta agonist was more likely to lead to a superior response in a larger group of patients than an increase in the dose of the inhaled corticosteroid. In a pharmacogenetic

analysis investigating the impact of genetic ancestry on treatment response in this same patient population, genetic ancestry informative markers were not associated with differences in treatment response in black children, adolescents, and adults. These findings suggest that data cannot be extrapolated from clinical trials involving mixed populations to specific subgroups, including those of different ages and races.

Comments

1. The preferred asthma step-up treatment regimens in children, adolescents, and adults who identify as black were previously unknown.
2. The Best African American Response to Asthma Drugs (BARD) trial was performed to determine whether increasing inhaled steroids or the addition of a long acting beta agonist improves outcomes in black children and adults with inadequately controlled asthma on low dose inhaled corticosteroid.
3. Children, who were reported to have at least one black grandparent, had similar improvement in asthma outcomes when the dose of inhaled corticosteroid was increased or a long acting beta agonist was added to the regimen.
4. Black adolescents and adults had a superior response to the addition of a long acting beta agonist than an increase in the dose of the inhaled corticosteroid.
5. In a pharmacogenetic analysis investigating the impact of genetic ancestry on treatment response in this same patient population, genetic ancestry informative markers were not associated with differences in treatment response in black children, adolescents, and adults.

ASTHMA PREVENTION

Litonjua AA, Carey VJ, Laranjo N, Stubbs BJ, Mirzakhani, O'Connor GT, Sandel M, Beigelman A, Bacharier LB, Zeiger RS, Schatz M, Hollis BW, Weiss ST. **Six-year follow-up of a trial of antenatal vitamin D for asthma reduction.** *N Engl J Med* 2020; 382:525-33.

Summary

Vitamin D deficiency has long been postulated to contribute to the rise in asthma and allergies in developing countries. Wheezing and asthma begin in very early life, suggesting that there are likely developmental origins of the disease. Thus, the Vitamin D Antenatal Asthma Reduction Trial (VDAART) was a randomized trial to investigate whether prenatal vitamin D supplementation could prevent asthma and wheeze in childhood. A meta-analysis of the VDAART results with another trial suggested that antenatal supplementation of Vitamin D resulted in significant protective effect on asthma and recurrent wheeze at 3 years of age. However, because asthma is difficult to definitively diagnose in early life, it remained unclear whether the early effects would be sustained through school age children. The current study examines the impact of antenatal vitamin D supplementation on asthma and recurrent wheeze at 6 years of age. The results demonstrate that the early effect of maternal vitamin D supplementation on the incidence

of asthma or recurrent wheeze was not sustained through age 6. Furthermore, prenatal vitamin D supplementation did not reduce the risk of the subsequent development of eczema, allergic rhinitis, or lower respiratory tract infections by 6 years of age. These results suggest that supplementation with vitamin D in the prenatal period alone did not prevent the development of asthma or recurrent wheeze in children through the age of 6 years of age.

Comments

1. Previous observational studies have demonstrated that higher maternal vitamin D level is associated with lower risk of asthma-related outcomes among children.
2. Although prenatal vitamin D supplementation in pregnant women was able to increase Vitamin D level, it did not prevent asthma or recurrent wheeze at the age of 6 years.
3. Prenatal vitamin D supplementation also did not reduce the risk of atopic conditions including eczema and allergic rhinitis at the age of 6 years. Because the trial did not supplement the children, the question remains whether combined prenatal and postnatal supplementation would have an effect on asthma and allergy incidence.
4. Although these results suggest that vitamin D supplementation during pregnancy alone did not reduce the subsequent risk of asthma and recurrent wheeze, there may be a subgroup of people who would still benefit from this approach.
5. Additional investigation into the timing and duration of vitamin D supplementation both in the prenatal and neonatal period are warranted to fully understand the impact of vitamin D supplementation on childhood asthma risk.

OTHER ARTICLES OF INTEREST

Holguin F, Cardet JC, Chung KF, Diver S, Ferreira DS, Fitzpatrick A, Gaga M, Kellermeier L, Khurana S, Knight S, McDonald VM, Morgan RL, Ortega VE, Rigau D, Subbarao P, Tonia T, Adcock IM, Bleecker ER, Brightling C, Boulet LP, Cabana M, Castro M, Chanez P, Custovic A, Djukanovic, Frey U, Frankemolle B, Gibson P, Hamerlijnck D, Jarjour N, Konno S, Shen H, Vitary C, Bush A.

Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J* 2020; 55(1): 1900588.

Han JJ, Forno E, Celedón. **Sex steroid hormones and asthma in a nationwide study of U.S. adults.** *Am J Respir Crit Care Med* 2019;201(2):158-66.

Yaghoubi M, Adibi A, Safari A, FitzGerald JM, Sadatsafavi M. The projected economic and health burden of uncontrolled asthma in the United States. *Am J Respir Crit Care Med* 2019; 200(9):1102-1112.

Taylor SL, Leong LEX, Mobegi FM, Choo JM, Wesselingh S, Yang IA, Upham JW, Reynolds PN, Hodge S, James AL, Jenkins C, Peters MJ, Baraket M, Marks GB, Gibson PG, Rogers GB, Simpson JL. **Long-Term Azithromycin Reduces Haemophilus influenzae and Increases Antibiotic Resistance in Severe Asthma.** *Am J Respir Crit Care Med* 2019; 200 (3):309-317.

Brigham EP, Woo H, McCormack M, Rice J, Koehler K, Vulcain T, Wu T, Koch A, Sharma S, Kolaheer F, Bose S, Hanson C, Romero K, Diette G, Hansel NN. **Omega-3 and Omega-6 intake modifies asthma severity and response to indoor air pollution in children.** *Am J Respir Crit Care Med* 2019; 199 (12):1478-1486.

Virchow JC, Kuna P, Paggiaro P, Papi A, Singh D, Corre S, Zuccaro F, Vele A, Kots M, Georges G, Petruzelli S, Canonica GW. **Single inhaler extrafine triple therapy in uncontrolled asthma (TRIMARAN and TRIGGER): two double-blind, parallel-group, randomized, controlled phase 3 trials.** *Lancet* 2019; 394:1737-49.

SLEEP MEDICINE

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**GENETICS OF CIRCADIAN RHYTHMS;
CIRCADIAN RHYTHMS, BIG DATA**

Jones SE, Lane JM, Wood AR, van Hees VT, Tyrrell J, Beaumont RN, Jeffries AR, Dashti HS, Hillsdon M, Ruth KS, Tuke MA, Yaghootkar H, Sharp SA, Jie Y, Thompson WD, Harrison JW, Dawes A, Byrne EM, Tiemeier H, Allebrandt KV, Bowden J, Ray DW, Freathy RM, Murray A, Mazzotti DR, Gehrman PR, Lawlor DA, Frayling TM, Rutter MK, Hinds DA, Saxena R, Weedon MN. **Genome-wide Association Analyses of Chronotype in 697,828 Individuals Provides Insights Into Circadian Rhythms.** *Nat Commun.* 2019 Jan 29;10(1):343.

Summary

Prior studies have determined some of the genes and polymorphisms related to circadian timing. However, these prior studies were moderate size and generally relied on subjective recall/assessment of morning lark vs. night owl phenotypes. In this study, the authors used data from 697,828 individuals (some part of a UK biobank, and others from the company 23andME) and performed the largest GWAS study of chronotype and expanded the number of chronotype-associated loci from 24 to 351. What is more, the authors also had recordings of activity in 85,760 participants, thus they could quantify the impact of these variants are associated with objective measures of sleep timing. For example, they noted that previously reported subjective impact of some polymorphisms were very different than the objective measurements. These same authors have used similar approaches to assess sleep quality, duration, and insomnia symptoms.

Comments

1. "Big Data" are increasingly used in Sleep Medicine research.
2. Activity trackers are able to provide longitudinal data at relatively low cost, and which aid in understanding biology.
3. Subjective and objective measurements of sleep may differ, although both may have value.
4. While this article focuses on sleep timing, this same approach was used to assess other aspects of sleep.
5. The combination of big data and wearables has the potential to substantially increase understanding of sleep medicine.

**CIRCADIAN RHYTHM, TIME RESTRICTED FEEDING,
OBESITY**

Wilkinson MJ, Manoogian ENC, Zadourian A, Lo H, Fakhouri S, Shoghi A, Wang X, Fleischer JG, Navlakha S, Panda S, Taub PR. **Ten-Hour Time-Restricted Eating Reduces Weight, Blood Pressure, and Atherogenic Lipids in Patients With Metabolic Syndrome.** *Cell Metab.* 2020 Jan 7;31(1):92-104.e5. doi: 10.1016/j.cmet.2019.11.004. Epub 2019 Dec 5.

Summary

Time restricted feeding is the concept of taking in food only during the active phase of the day. In animal models, a high fat diet is associated with weight gain and other deleterious effects. However, if food is available only at night (the active period for the animal, as opposed to throughout the whole 24 period) then weight gain is mitigated despite the same overall caloric intake. This human study in a relatively small number of subjects with metabolic syndrome showed that such time restricted feeding was associated with weight loss and other improvements in health, such as reductions in blood pressure. The intervention was to limit food intake to a 10 hour window each day (compared with more than 14 hours at baseline).

Comments

1. Time restricted feeding has been shown in animal models to protect against obesity and obesity related complications.
2. There have only been a few, relatively small studies of time restricted eating in humans
3. Alignment of eating and attention to the circadian rhythm might have implications for both individuals and population health.
4. The mechanism of improvement in weight is not clear – it might be circadian timing of food intake, but might relate to overall caloric intake (which was slightly reduced), sleep duration (which improved as well), or other effects.
5. Some of the mechanisms/effects might be similar to intermittent fasting, which usually extends fasting beyond the circadian window.

SLEEP DEPRIVATION, COGNITION

Holth JK, Fritschi SK, Wang C, Pedersen NP, Cirrito JR, Mahan TE, Finn MB, Manis M, Geerling JC, Fuller PM, Lucey BP, Holtzman DM. **The Sleep-Wake Cycle Regulates Brain Interstitial Fluid Tau in Mice and CSF Tau in Humans.** *Science*. 2019 Feb 22;363(6429):880-884.

Summary

The sleep-wake cycle regulates cerebrospinal fluid levels of b-amyloid (Ab) that accumulates in Alzheimer's disease. Furthermore, chronic sleep deprivation (SD) increases Ab plaques. However, tau, not Ab, accumulation appears to drive AD neurodegeneration. These authors tested the hypothesis that Tau spreading was influenced by sleep wake cycle changes and sleep deprivation in mice and in humans, with serial samples of CSF in both groups. In both mice and humans, sleep deprivation was associated with increases in Tau, and this increase persisted into the next day as well.

Comments

1. B-Amyloid and Tau protein are important in Alzheimer's Dementia
2. Chronic sleep deprivation is linked to AD, but mechanisms are unknown.
3. These data show accumulations in Tau in mice and humans with a single night of behavioral sleep deprivation.
4. More chronic short sleep in mice shows similar Tau accumulation, which does not improve with recovery sleep.
5. Thus, optimization of the sleep wake cycle might be an important treatment target to prevent AD.

OBSTRUCTIVE SLEEP APNEA, COGNITION

Ram A. Sharma, Andrew W. Varga et al. **Obstructive Sleep Apnea Severity Affects Amyloid Burden in Cognitively Normal Elderly: A Longitudinal Study.** *Am J Respir Crit Care Med* Vol 197, Iss 7, pp 933–943, Apr 1, 2018

Summary

About 200 cognitively normal older adults underwent cognitive testing, brain imaging, CSF sampling, and a sleep study at baseline and then follow up at two years. The presence and severity of OSA at baseline was a predictor of beta amyloid change in the CSF over 2 years, and was independent of age, gender, BMI and even ApoE status. Similarly, the presence of OSA was associated with more concerning imaging findings. The authors speculate that sleep fragmentation and/or intermittent hypoxia from OSA are likely candidate mechanisms, and call for a clinical trial of OSA treatment to slow progression to or of AD.

Comments

1. Basic science studies suggest a role for sleep fragmentation in the pathogenesis of AD (see Article 4 above).
2. Obstructive sleep apnea is a very common cause of sleep fragmentation.
3. The association between OSA severity and brain abnormality suggests that OSA might contribute to dementia progression, although the mechanism is not known.
4. These data suggest that treatment of OSA might slow development of AD.

EXCESSIVE SLEEPINESS; NARCOLEPSY; ALERTING AGENTS

Schweitzer PK, Rosenberg R, Zammit GK, Gotfried M, Chen D, Carter LP, Wang H, Lu Y, Black J, Malhotra A, Strohl KP; TONES 3 Study Investigators. **Solriamfetol for Excessive Sleepiness in Obstructive Sleep Apnea (TONES 3). A Randomized Controlled Trial.** *Am J Respir Crit Care Med*. 2019 Jun 1;199(11):1421-1431. doi: 10.1164/rccm.201806-1100OC.PMID: 30521757

Summary

Excessive sleepiness associated with obstructive sleep apnea persists in some patients despite use of or attempts to use a primary obstructive sleep apnea therapy. Sleepiness affects quality of life, employment, and may have consequences such as motor vehicle accidents. This 12-week, phase III clinical trial showed that solriamfetol, a dopamine and norepinephrine reuptake inhibitor, resulted in objective improvements in sleep latency and subjective sleepiness on the Epworth Sleepiness Scale. There were some generally minor side-effects such as headache, nausea, but of more concern, some increase in heart rate and blood pressure. Of note, some subjects were on OSA therapies, others were untreated.

Comments

1. Despite optimal treatment excessive with PAP therapy, daytime sleepiness remains an important symptom for patients with obstructive sleep apnea.
2. There are now more medication options for treatment of the symptoms of OSA, including solriamfetol which is FDA approved for residual sleepiness in OSA and narcolepsy.
3. Pitolisant, an H3 receptor antagonist, is approved for sleepiness in narcolepsy, but was also recently studied in untreated OSA.
4. The role of stimulating or alerting agents, vs. optimal sleep hygiene, increased sleep duration, optimal PAP adherence, is not known
5. Long term safety data, particularly in untreated OSA patients, are not yet available.

ENDOTYPES, PHENOTYPES, PERSONALIZED MANAGEMENT OF OSA

Mazzotti DR, Keenan BT, Lim DC, Gottlieb DJ, Kim J, Pack AI. Symptom Subtypes of Obstructive Sleep Apnea Predict Incidence of Cardiovascular Outcomes. *Am J Respir Crit Care Med*. 2019 Aug 15;200(4):493-506. doi: 10.1164/rccm.201808-1509OC.PMID: 30764637

Summary

Prior works have shown that different patients with OSA experience different symptoms, e.g. minimally symptomatic, disturbed sleep, vs excessively sleepy. Furthermore, it is increasingly recognized that the apnea-hypopnea index (AHI) is an imperfect marker of sequelae from OSA. In fact, depending on the outcome of interest there may be other metrics on a polysomnogram that could be used. Here, the authors use the Sleep Heart Health Study to re-demonstrate symptoms clusters, and show that the clinical subtype characterized primarily by excessive sleepiness has increased prevalence of adverse cardiovascular outcomes and is at a higher risk of incident cardiovascular events. The patients in the most symptomatic cluster were slightly heavier and slightly higher AHI than those in other clusters, but these baseline differences were relatively minor. These findings will help determine which patients with OSA need to be treated and why.

Comments

1. OSA is associated with many symptoms, however, not all symptoms are present in each individual with OSA.
2. Patients can be clustered according to symptom severity/type, i.e. minimally symptomatic, disturbed sleep, sleepy, etc. and these “phenotypes” have been reproduced in multiple cohorts.
3. For the first time, these cohorts are given relevance in terms of outcomes.
4. Knowledge of this phenotype may help determine which patients need treatment and what benefits might be expected – that is, personalized medicine for OSA.
5. These findings might explain why trials of CPAP to prevent cardiovascular disease in those without excessive sleepiness have largely been negative.

OTHER ARTICLES OF INTEREST

SLEEP AND COVID

Blume C., Schmidt MH and Cajochen C. Effects of the COVID-19 lockdown on human sleep and rest-activity rhythms. *Curr Biol*. 2020 Jun 10. Epub ahead of print.

Attias D, Pepin JL, Pathak A. Impact of COVID-19 lockdown on adherence to continuous positive airway pressure (CPAP) by obstructive sleep apnoea patients. *Eur Respir J*. 2020 May 19. Epub ahead of print.

Widome R, Berger AT, Iber C, Wahlstrom K, Laska MN, Kilian G, Redline S, Erickson DJ. Association of Delaying

School Start Time With Sleep Duration, Timing, and Quality Among Adolescents. *JAMA Pediatr*. 2020 Apr 27;174(7):1-9

WEARABLES AND BIG DATA

Shahab Haghayegh, Sepideh Khoshnevis, Michael H. Smolensky, Kenneth R. Diller & Richard J. Castriotta. Performance assessment of new-generation Fitbit technology in deriving sleep parameters and stages. *Chronobiology International* 2020, VOL. 37, NO. 1, 47–59

Cistulli PA, Armitstead J, Pepin JL, Woehrle H, Nunez CM, Benjafeld A, Malhotra A. Short-term CPAP adherence in obstructive sleep apnea: a big data analysis using real world data. *Sleep Med*. 2019 Jul;59:114-116.

Pandey A, Mereddy S, Combs D, Shetty S, Patel SI, Mashaq S, Seixas A, Littlewood K, Jean-Luis G, Parthasarathy S. Socioeconomic Inequities in Adherence to Positive Airway Pressure Therapy in Population-Level Analysis. *J Clin Med*. 2020 Feb 6;9(2):442.

DRUGS FOR SLEEPINESS AND SLEEP APNEA

Dauvilliers Y, Verbraecken J, Partinen M, Hedner J, Saaresranta T, Georgiev O, Tiholov R, Lecomte I, Tamisier R, Lévy P, Scart-Gres C, Lecomte JM, Schwartz JC, Pépin JL; HAROSA II Study Group collaborators. Pitolisant for Daytime Sleepiness in Patients with Obstructive Sleep Apnea Who Refuse Continuous Positive Airway Pressure Treatment. A Randomized Trial. *Am J Respir Crit Care Med*. 2020 May 1;201(9):1135-1145.

Taranto-Montemurro L, Messineo L, Sands SA, Azarbarzin A, Marques M, Edwards BA, Eckert DJ, White DP, Wellman A. The Combination of Atomoxetine and Oxybutynin Greatly Reduces Obstructive Sleep Apnea Severity. A Randomized, Placebo-controlled, Double-Blind Crossover Trial. *Am J Respir Crit Care Med*. 2019 May 15;199(10):1267-1276.

OBSTRUCTIVE SLEEP APNEA PREVALENCE

Benjafeld AV, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, Nunez CM, Patel SR, Penzel T, Pépin JL, Peppard PE, Sinha S, Tufik S, Valentine K, Malhotra A. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med*. 2019 Aug;7(8):687-698.

OBSTRUCTIVE SLEEP APNEA PERI-OPERATIVE MANAGEMENT

Chan MTV, Wang CY, Seet E, Tam S, Lai HY, Chew EFF, Wu WKK, Cheng BCP, Lam CKM, Short TG, Hui DSC, Chung F; Postoperative Vascular Complications in Unrecognized Obstructive Sleep Apnea (POSA) Study Investigators. Association of Unrecognized Obstructive Sleep Apnea With Postoperative Cardiovascular Events in Patients Undergoing Major Noncardiac Surgery. *JAMA*. 2019 May 14;321(18):1788-1798.

OBSTRUCTIVE SLEEP APNEA ENDOTYPES AND PHENOTYPES

Edwards BA, Redline S, Sands SA, Owens RL. **More Than the Sum of the Respiratory Events: Personalized Medicine Approaches for Obstructive Sleep Apnea.** *Am J Respir Crit Care Med.* 2019 Sep 15;200(6):691-703

Zinchuk AV, Redeker NS, Chu JH, Liang J, Stepnowsky C, Brandt CA, Bravata DM, Wellman A, Sands SA, Yaggi HK. **Physiological Traits and Adherence to Obstructive Sleep Apnea Treatment in Patients with Stroke.** *Am J Respir Crit Care Med.* 2020 Jun 15;201(12):1568-1572.

Budhiraja R, Javaheri S, Parthasarathy S, Berry RB, Quan SF. **Incidence of hypertension in obstructive sleep apnea using hypopneas defined by a 3 percent oxygen desaturation or arousal but not by only 4 percent oxygen desaturation.** *J Clin Sleep Med.* 2020 Jul 9. Epub ahead of print

OCCUPATIONAL LUNG DISEASE

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POST-DEPLOYMENT RESPIRATORY DISEASES IN MILITARY PERSONNEL

Garshick E, Abraham JH, Baird CP, et al. **Respiratory Health after Military Service in Southwest Asia and Afghanistan. An Official American Thoracic Society Workshop Report.** *Ann Am Thorac Soc.* 2019;16(8):e1-e16.

Summary

Since 2001, more than 2.7 million U.S. military personnel have been deployed in support of operations in Southwest Asia and Afghanistan. Land-based personnel experienced elevated exposures to particulate matter and other inhalational exposures from multiple sources, including desert dust, and burn pit combustion. This workshop reviewed epidemiologic studies that demonstrated more frequent encounters for respiratory symptoms post-deployment compared with non-deployers, and for airway disease, predominantly asthma, as well as case series describing post-deployment dyspnea, asthma, and a range of other respiratory tract findings. On the basis of particulate matter effects in other populations, it also is possible that deployers experienced reductions in pulmonary function as a result of such exposure. The workshop also gave particular attention to constrictive bronchiolitis, which has been reported in lung biopsies of selected deployers. Workshop participants had heterogeneous views regarding the definition and frequency of constrictive bronchiolitis and other small airway pathologic findings in deployed populations. The workshop concluded that the relationship of airway disease, including constrictive bronchiolitis, to exposures experienced during deployment remains to be better defined.

Comments

1. The most common specific diagnosis in previously deployed military personnel is asthma, as noted from data from four centers that regularly evaluate this population.
2. In the STAMPEDE II study, pre-deployment and post-deployment spirometry tests were compared in 873 soldiers. A pre-deployment history of asthma and post-deployment wheezing were associated with airflow obstruction after deployment.
3. A post-deployment isolated reduction in diffusing capacity was noted in 18% to 50% of symptomatic soldiers.

4. Constrictive bronchiolitis, characterized by subepithelial scarring resulting in narrowing of the bronchioles, may be seen on lung biopsy, despite the presence of differing views among workshop participants regarding the interpretation of the histologic changes in study participants.
5. Other findings on lung biopsy specimens of post-deployment symptomatic soldiers include emphysema, granulomatous pneumonitis, hypersensitivity pneumonitis, respiratory bronchiolitis associated interstitial lung disease, and sarcoidosis.

THE OCCUPATIONAL BURDEN OF NONMALIGNANT RESPIRATORY DISEASES

Blanc PD, Annesi-Maesano I, Balmes JR, et al. **The Occupational Burden of Nonmalignant Respiratory Diseases. An Official American Thoracic Society and European Respiratory Society Statement.** *Am J Respir Crit Care Med.* 2019;199(11):1312-1334.

Summary

Workplace inhalational hazards remain common worldwide, even though they are ameliorable. The goal of this document was to report an in-depth literature review and data synthesis of the occupational contribution to the burden of the major nonmalignant respiratory diseases. The occupational population attributable fraction (PAF) was estimated for those conditions for which there were sufficient population-based studies to allow pooled estimates. For the other conditions, the occupational burden of disease was estimated on the basis of attribution in case series, incidence rate ratios, or attributable fraction within an exposed group. Workplace exposures contribute substantially to the burden of multiple chronic respiratory diseases, including asthma (PAF, 16%); chronic obstructive pulmonary disease (PAF, 14%); chronic bronchitis (PAF, 13%); idiopathic pulmonary fibrosis (PAF, 26%); hypersensitivity pneumonitis (occupational burden, 19%); other granulomatous diseases, including sarcoidosis (occupational burden, 30%); pulmonary alveolar proteinosis (occupational burden, 29%); tuberculosis (occupational burden, 2.3% in silica-exposed workers and 1% in healthcare workers); community-acquired pneumonia in working-age adults (PAF, 10%), and 100% burden for the classic occupational pneumoconiosis. Workplace exposures contribute to the burden of disease across a range of nonmalignant lung conditions in adults.

Comments

1. Sarcoidosis, the disease with the highest occupational burden (30%), can be seen among beryllium and other metal exposed workers, as well as firefighters, workers in the lumber industry, rock or glass wool workers, and World Trade Center disaster emergency responders.
2. Pulmonary alveolar proteinosis has a reported occupational burden of 29% with a range of exposures reported, including vapors or gases such as cleaning fluids and hairspray, inorganic dust such as silica (PAF for silica 5%), organic dust such as wood, and metal dusts or fumes such as aluminum.
3. Idiopathic pulmonary fibrosis, the disease with the third highest occupational burden (26%) was associated with exposure to the VGDF (PAF of 26%), metal dust or fume (PAF 8%), wood dust (PAF 4%), silica dust (PAF 3%), and agricultural dust (PAF 4% not statistically significant).
4. This analysis demonstrates a substantial occupational burden for multiple respiratory conditions not typically considered potentially work-related.
5. Limitations of this analysis include censoring study eligibility for the purposes of data synthesis after December 2017, and study heterogeneity.

IMPACT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) ON SUBSEQUENT ECONOMIC ACTIVITY

Schofield SJ, Woods A, Szram J, Newman Taylor AJ, Cullinan P. Chronic Obstructive Pulmonary Disease and Breathlessness in Older Workers Predict Economic Inactivity. A Prospective Cohort Study. *Am J Respir Crit Care Med.* 2019;200(10):1228-1233.

Summary

There is an aspiration to retain increasing numbers of older workers in employment, and strategies to achieve this need to make provision for the increasing prevalence of COPD with age. This article reported the findings of the first longitudinal study of the impact of COPD on subsequent economic activity. Investigators recruited full-time employed men and women in their 50s and followed them for a period of 18 months; they examined, after adjustment for potential confounders, the associations between breathlessness and airway obstruction at baseline and loss of employment in the intervening period. Among participants responding to the follow-up questionnaire (1,656 of 1,773 [93%]), the majority (78.5%) continued in full-time employment, but 10.6% were in part-time employment and 10.9% were no longer in paid employment. The adjusted risk of loss of employment was increased for those with moderate or severe COPD (risk ratio, 2.89; 95% C.I., 1.80-4.65) or breathlessness (risk ratio, 3.07; 95% C.I., 2.16-4.37) at baseline. There was no evident modification by sex or by manual/nonmanual work. Airway obstruction and breathlessness are independently associated with premature loss from the workforce in older workers. Interventions to help those with COPD who wish to remain in work need to be tested.

Comments

1. This is the first cohort study to investigate the association between COPD and subsequent economic activity.
2. The prospective design and the findings of an increasing risk of leaving employment with increasing severity of breathlessness and airflow obstruction lend strong support to the association being casual.
3. The risk estimates are independent of cardiovascular and musculoskeletal comorbidities. They apply equally to manual and nonmanual workers, and are not confounded by any of several psychosocial determinants of employment.
4. The limitations of the study include low response rate to the baseline survey, and unmeasured confounders.
5. The findings of the study pose an important question for policy makers: How best to enable those with COPD and with significant breathlessness to remain economically active? In this study population, those leaving employment were on average 10 years younger than the current pensionable age in the country of study.

OCCUPATIONAL CONTRIBUTION TO CHRONIC BRONCHITIS

Lytras T, Kogevinas M, Kromhout H, et al. Occupational exposures and incidence of chronic bronchitis and related symptoms over two decades: the European Community Respiratory Health Survey. *Occup Environ Med.* 2019;76(4):222-229

Summary

Chronic bronchitis (CB) is an important COPD-related phenotype, with distinct clinical features and prognostic implications. Occupational exposures have been previously associated with increased risk of CB but few studies have examined this association prospectively using objective exposure assessment. The investigators examined the effect of occupational exposures on CB incidence in the European Community Respiratory Health Survey. Population samples aged 20-44 were randomly selected in 1991-1993, and followed up twice over 20 years. Participants without chronic cough or phlegm at baseline were analyzed. Coded job histories during follow-up were linked to the ALOHA Job Exposure Matrix, generating occupational exposure estimates to 12 categories of chemical agents. Their association with CB incidence over both follow-ups was examined with Poisson models using generalized estimating equations. 8,794 participants fulfilled the inclusion criteria, contributing 13,185 observations. Only participants exposed to metals had a higher incidence of CB (relative risk (RR) 1.70, 95% CI 1.16 to 2.50) compared with non-exposed to metals. Mineral dust exposure increased the incidence of chronic phlegm (RR 1.72, 95% CI 1.43 to 2.06). Incidence of chronic phlegm was increased in men exposed to gases/fumes and to solvents and in women exposed to pesticides. Occupational exposures are associated with chronic phlegm and CB, and the evidence is strongest for metals and mineral dust exposure.

Comments

1. This study provides strong prospective evidence for an association between occupational exposures, particularly metals and mineral dust exposure, and incidence of chronic bronchitis/chronic phlegm.
2. Occupations involving any exposure to metals in the study included jobs such as motor vehicle mechanics, other machinery engineers and technicians, plumbers, and pipefitters. Although metals are a heterogeneous category of exposure, one metal in particular, i.e., vanadium, present in steel and in fossil fuels, has both occupational epidemiologic and experimental evidence of an association with bronchitis.
3. Occupations involving mineral dust exposure include truck and lorry drivers, and helpers/cleaners in offices, hotels, and other establishments.
4. Study limitations include low incidence rates of chronic bronchitis in the study population, low proportion of occupationally exposed women than men, and possible exposure misclassification since not all individuals in the same occupation in the job exposure matrix would have similar exposures.
5. The strengths of the study include prospective design, long follow-up of 20 years and a large population size.

DETERMINANTS OF SEVERE OCCUPATIONAL ASTHMA

Vandenplas O, Godet J, Hurdubaea L, et al. Severe Occupational Asthma: Insights From a Multicenter European Cohort. *J Allergy Clin Immunol Pract*. 2019;7(7):2309-2318 e2304

Summary

Although sensitizer-induced occupational asthma (OA) accounts for an appreciable fraction of adult asthma, the severity of OA has received little attention. The study aim was to characterize the burden and determinants of severe OA. This retrospective study included 997 subjects with OA ascertained by a positive specific inhalation challenge completed in 20 tertiary centers in 11 European countries during the period 2006 to 2015. Severe asthma was defined by a high level of treatment and any one of the following criteria: (1) daily need for a reliever medication, (2) 2 or more severe exacerbations in the previous year, or (3) airflow obstruction. Overall, 162 (16.2%; 95% CI, 14.0%-18.7%) subjects were classified as having severe OA. Multivariable analysis revealed that severe OA was associated with persistent exposure to the causal agent at work (OR, 2.78; 95% CI, 1.50-5.60); a longer duration of the disease (OR, 1.04; 95% CI, 1.00-1.07); a low level of education (OR, 2.69; 95% CI, 1.73-4.18); childhood asthma (OR, 2.92; 95% CI, 1.13-7.36); and sputum production (OR, 2.86; 95% CI, 1.87-4.38). This study indicates that a substantial proportion of subjects with OA experience severe asthma and identifies potentially modifiable risk factors for severe OA.

Comments

1. This study shows that the determinants of severe OA include not only potentially modifiable factors (i.e., "unchanged/persistent" exposure to the causal agent and duration of

- symptomatic exposure before diagnosis) but also a low sociodemographic status and clinical characteristics (i.e., childhood asthma and daily sputum production).
2. These results further support the need for an early diagnosis and prompt implementation of occupational interventions to reduce the burden of severe OA. In addition, these findings may help clinicians to identify subjects with OA at high risk for a more severe outcome.
3. The strengths of this study are its large sample size, the homogeneous diagnostic criteria used for identifying OA, and the multidimensional assessment of asthma severity.
4. Limitations include some potential determinants of SA were not collected, including nonsteroidal anti-inflammatory drug sensitivity, gastroesophageal reflux disease, psychological disorders, and magnitude of postbronchodilator FEV1 reversibility. More importantly, the level of asthma control could not be fully captured because detailed information about the frequency of daytime/nighttime symptoms and asthma-related limitation of daily activities was not systematically collected.

RESURGENCE OF THE BLACK LUNG EPIDEMIC IN THE U.S.

Hall NB, Blackley DJ, Halldin CN, Laney AS. Continued increase in prevalence of r-type opacities among underground coal miners in the USA. *Occup Environ Med*. 2019;76(7):479-481.

Summary

Respirable crystalline silica exposure has been implicated in the resurgence of coal workers' pneumoconiosis in the USA. This analysis assesses the prevalence of r-type opacities during 2010-2018 compared with earlier decades. Data from the Coal Workers' Health Surveillance Program were used to calculate the prevalence of r-type opacities on radiographs of working underground coal miners. The data were restricted to radiographs taken during 1 January 1980 to 15 September 2018. Prevalence ratios for r-type opacities were calculated using log binomial regression. Radiograph classifications for 106,506 miners were included in analysis. For the USA overall, the prevalence of r-type opacities among miners with radiographs taken during 2010-2018 compared with 1980-1989 has increased (PR 2.4; 95% CI 1.9 to 3.0). For central Appalachia, the proportion of r-type opacities observed increased when comparing 1980-1989 to 2010-2018 (PR 6.0; 95% CI 4.6 to 7.9). The prevalence of r-type opacities on the radiographs of Appalachian underground coal miners continues to increase, implicating exposure to crystalline silica in respirable coal mine dust. The current findings underscore the importance of monitoring and controlling exposure to silica in coal mines.

Comments

1. R-type opacities are associated with silicosis, based on prior pathology reports. The prevalence of r-type opacities among underground coal miners of central Appalachia continues to increase.

2. This finding suggests that respirable crystalline silica exposures in recent decades are an important factor in the resurgence of Black Lung in the region.
3. These findings may increase scrutiny on current dust monitoring practices and place increased focus on efforts to develop continuous personal dust monitors specifically for respirable crystalline silica dust.

OTHER ARTICLES OF INTEREST

PNEUMOCONIOSIS

Assad N, Wigh S, Kocher E, et al. **Post-1971 Era Uranium Workers in New Mexico Have Significant Lung Disease Burden.** *Ann Am Thorac Soc.* 2019;16(4):515-518.

Halldin CN, Hale JM, Weissman DN, et al. **The National Institute for Occupational Safety and Health B Reader Certification Program-An Update Report (1987 to 2018) and Future Directions.** *J Occup Environ Med.* 2019;61(12):1045-1051.

Kurth L, Casey M, Schleiff P, Halldin C, Mazurek J, Blackley D. **Medicare Claims Paid by the Federal Black Lung Benefits Program: US Medicare Beneficiaries, 1999 to 2016.** *J Occup Environ Med.* 2019;61(12):e510-e515.

OCCUPATIONAL ASTHMA

Carder M, Seed MJ, Money A, Agius RM, van Tongeren M. **Occupational and work-related respiratory disease attributed to cleaning products.** *Occup Environ Med.* 2019;76(8):530-536.

Logar-Henderson C, MacLeod JS, Arrandale VH, et al. **Adult Asthma among Workers in Ontario. Results from the Occupational Disease Surveillance System.** *Ann Am Thorac Soc.* 2019;16(5):563-571.

Vandenplas O, Godet J, Hurdubaea L, et al. **Are high- and low-molecular-weight sensitizing agents associated with different clinical phenotypes of occupational asthma?** *Allergy.* 2019;74(2):261-272.

OCCUPATIONAL COPD

Pahwa P, Rana M, Amin K, Chu LM, Karunanayake CP, Dosman JA. **Incidence and Longitudinal Changes in Prevalence of Chronic Bronchitis in Farm and Non-Farm Rural Residents of Saskatchewan.** *J Occup Environ Med.* 2019;61(4):347-356.

Sood A, Shore X, Myers O, Assad N, Pollard C, Cook LS. **Among All Miners, Coal Miners Demonstrate a Disproportionately High Prevalence of Obstructive Spirometric Abnormality and Chronic Bronchitis.** *J Occup Environ Med.* 2019;61(4):328-334.

OCCUPATIONAL FIBROTIC INTERSTITIAL LUNG DISEASES

Algamdi M, Sadatsafavi M, Fisher JH, et al. **Costs of Workplace Productivity Loss in Patients With Fibrotic Interstitial Lung Disease.** *Chest.* 2019;156(5):887-895.

POST-DEPLOYMENT RESPIRATORY DISEASE IN MILITARY PERSONNEL

Kreffth SD, Wolff J, Zell-Baran L, et al. **Respiratory Diseases in Post-9/11 Military Personnel Following Southwest Asia Deployment.** *J Occup Environ Med.* 2020.

LUNG CANCER

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LUNG CANCER EARLY DETECTION

de Koning HJ, van der Aalst CM; de Jong PA; Scholten ET, Nackaerts K, Heuvelmans MA, Lammers J-WJ, Weenink C, Yousaf-Khan U, Horeweg N, van't Westeinde S, Prokop M, Mali WP, Mohamed Hoesein FAA, van Ooijen PMA, Aerts JGJV, den Bakker MA, Thunnissen E, Verschakelen J, Vliegenthart R, Walter JE, ten Haaf K, Groen HJM, Oudkerk M. **Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial.** *New Engl J Med* 2020; 382(6):503-513.

Summary

The Dutch-Belgian lung cancer screening study, called NELSON (Nederlands-Leuven Longkanker Screenings Onderzoek), was a randomized controlled trial of 13,195 men. Participants were randomized to receive baseline CT screening with repeat screening exams at year 1, year 3, and year 5.5, or no screening. A total of 2,594 women were included in the study as a subgroup analysis. Eligibility criteria included age 50-74, current smokers or former smokers who quit within the preceding 10 years, and having smoked more than 15 cigarettes per day for over 25 years or more than 10 cigarettes per day for over 30 years. The trial used a volume-based nodule management protocol. The NELSON study identified a reduction in lung cancer mortality in the screening group in both men (24% reduction) and women (33% reduction). Screen-detected cancers were more commonly Stage IA or IB (58.6%), with a much smaller percentage being Stage IV (9.4%). The proportion of participants with a positive screening test was 2.1%. The estimated overdiagnosis rate for screen-detected cancers was 8.9%.

Comments

1. In the NELSON trial, low-dose CT screening reduced mortality from lung cancer.
2. Volume-based nodule management protocols may reduce the proportion of false positives from lung cancer screening exams.
3. The rate of overdiagnosis for screen-detected cancers in the NELSON trial is low compared to the number of lives saved by lung cancer screening.
4. Lung cancer screening may benefit ever smokers with a younger age and lower pack-year histories than are currently eligible in based on the 2014 United State Preventive Services Task Force lung cancer screening guidelines.

5. Further study is needed to determine whether and why lung cancer screening has a greater relative benefit to woman compared to men, and the optimal interval and duration of lung cancer screening.

Tammemagi MC, ten Haaf K, Toumazis I, Kong CY, Han SS, Jeon J, Commins J, Riley T, Meza R. **Development and Validation of a Multivariable Lung Cancer Risk Prediction Model That Includes Low-Dose Computed Tomography Screening Results.** *JAMA Network Open* 2019; 2(3):e190204.

Summary

Clinical variables are currently used to predict risk for lung cancer. More recent studies have suggested that lung cancer screening results may also predict future lung cancer risk. In this study, the authors conducted a secondary analysis of data from the National Lung Screening Trial (NLST) data with the goal of developing a risk prediction model that incorporated both clinical variables and prior lung cancer screening results. The model was calculated using NLST Lung Screening Study (LSS) data and validated using the NLST American College of Radiology Imaging Network (ACRIN) data. Participants were included if they had 3 screening exams, adequate follow up, and complete predictor information. The final model, which included lung cancer screening results, demonstrated better overall prediction (Brier score 0.012 versus 0.013), discrimination (AUC 0.761 versus 0.687), and calibration (observed versus predicted of 0.84 versus 0.57) compared to a similar risk prediction model using clinical variables only.

Comments

1. A combined model incorporating clinical risk variables and the results from prior lung cancer screening exams can help predict future lung cancer risk.
2. Consecutive negative lung cancer screening exams are associated with a lower lung cancer risk than the risk calculated by using clinical variables alone.
3. The refined risk model (PLCO2012results) is available online for use.
4. Application of the combined risk model using clinical variables and lung cancer screening results may help guide decision making about continuing screening in patients who have undergone 3 consecutive screening rounds.
5. Use of a combined risk model accounting for clinical risk factors and prior lung cancer screening results may ultimately improve the cost effectiveness of lung cancer screening.

DISPARITIES IN LUNG CANCER CARE

Aldrich MC, Mercaldo SF, Sandler KL, Blot WJ, Grogan EL, Blume JD. **Evaluation of USPSTF Lung Cancer Screening Guidelines Among African American Adult Smokers.** *Jama Oncology* 2019; 5(9):1318-1324.

Summary

The Southern Community Cohort Study conducted a prospective observational study of 48,364 current and former smokers aged 40 through 79 years. Participants were followed for cancer incidence. A total of 32,463 participants were African American, and 15,901 were white. Exclusion criteria included never smokers, missing smoking information, self-reported unknown race, or race other than African American or white. African American ever smokers diagnosed with lung cancer had lower cumulative smoke exposure histories compared to white ever smokers (25.8 pack-years versus 48 pack-years). African American ever smokers were diagnosed at a younger age on average than white ever smokers (59 years versus 64 years). Among participants diagnosed with lung cancer, a lower proportion of African American ever smokers would have been eligible for lung cancer screening based on USPSTF guidelines compared to white ever smokers (32.2% versus 56.5%). A greater proportion of African American smokers compared to white smokers with lung cancer did not meet USPSTF requirements for lung cancer screening based on pack-years and age. Modeling demonstrated that revising the USPSTF guidelines by decreasing the pack-year eligibility criteria to 20 would increase the number of African American persons eligible for lung cancer screening.

Comments

1. African American smokers had higher rates of lung cancer with lower self-reported pack-years.
2. African American smokers were diagnosed with lung cancer at younger ages than white smokers.
3. In this study, a large proportion of African American smokers diagnosed with lung cancer would not have been eligible for lung cancer screening based on the current USPSTF guidelines.
4. Further study is needed to determine whether there are disparities in the implementation of lung cancer screening among other races and ethnicities.
5. Further study is needed to determine whether modification to the 2014 USPSTF lung cancer screening guidelines would decrease disparities in lung cancer screening by increasing the proportion of eligible African American persons without increasing the rate of potential harms.

LUNG CANCER STAGING

Martinez-Sayas G, Almeida FA, Simoff MJ, Yarmus L, Molina S, Young B, Feller-Kopman D, Sagar A-ES, Gildea T, Debiante LG, Grosu HB, Casal RF, Arain MH, Eapen GA,

Jimenez CA, Noor LZ, Baghaie S, Song J, Li L, Ost DE. **A Prediction Model to Help with Oncologic Mediastinal Evaluation for Radiation: HOMER.** *Am J Resp Crit Care Med* 2020; 201(2):212-223.

Summary

For patients with non-small cell lung cancer (NSCLC), accurate mediastinal lymph node staging is important to determine the appropriate therapy. This study aimed to develop a prediction model to assess the probability of N0, N1, and N2-3 disease. Participants with stage T1 to T3, N0 to N3 and M0 disease at a single hospital were included in the study. Participants underwent endobronchial ultrasound (EBUS) for staging. An ordinal logistic regression model was calculated to predict N0, N1, or N2-3 disease. The model, termed HOMER (Help with Oncologic Mediastinal Evaluation for Radiation), was validated prospectively in the same hospital and in three other hospitals. The model incorporated PET imaging, and used either contrast-enhanced or noncontrast CT imaging to determine the clinical-radiographic N stage and whether the tumor was central or peripheral. The model was evaluated in both surgical and nonsurgical candidates.

Comments

1. The HOMER model is an ordinal model to predict N0 versus N1 versus N2-3 metastatic nodal disease in patients with non-small cell lung cancer.
2. The HOMER model was temporally and externally validated.
3. The HOMER model may have utility in determining which patients that are candidates for surgery or stereotactic ablative radiotherapy should undergo EBUS for pathologic staging of their mediastinum.
4. Further study of larger cohorts may permit examination of additional variables that may influence the predictive performance of the model.
5. Interpretation of model results should also take into account the sensitivity of EBUS in detecting lymph node metastases.

LUNG CANCER THERAPY

Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, Castro G, Srimuninnimt V, Laktionov KK, Bondarenko I, Kubota K, Lubiniecki GM, Zhang J, Kush D, Lopes G, KEYNOTE-042 Investigators. **Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): A randomized, open-label, controlled, phase 3 trial.** *Lancet*, 2019; 393(10183):1819-1830.

Summary

First-line pembrolizumab has previously been shown to improve overall and progression-free survival for patients with untreated metastatic non-small-cell lung cancer

(NSCLC) with a PD-L1 tumor progression score (TPS) of 50% or greater. This randomized, open-label, phase 3 study evaluated pembrolizumab versus platinum-based chemotherapy in 1274 patients with locally advanced or metastatic NSCLC without sensitizing EGFR or ALK mutations and with a PD-L1 TPS of 1% or greater. Primary endpoints were overall survival in patients with a PD-L1 TPS 50% or greater, 20% or greater, and 1% or greater. Median follow up was 12.8 months. Overall survival was longer in the pembrolizumab group for all three TPS groups, as compared to platinum-based chemotherapy. However, in tumors with PD-L1 TPS of 1-49%, there was no significant difference in overall survival. Median survival in the pembrolizumab arm was 20 months, versus 12.2 months in the chemotherapy arm. Severe adverse events occurred in 18% of patients treated with pembrolizumab, and 41% patients treated with chemotherapy. Pneumonitis occurred in 8% of patients treated with pembrolizumab, though only 3% were classified as Grade 3 or worse. Adverse events led to death in 2% of patients treated with pembrolizumab, and 2% of patients treated with chemotherapy.

Comments

1. Pembrolizumab monotherapy may be associated with longer overall survival compared to platinum-based chemotherapy in patients with NSCLC and a PD-L1 TPS of 1% or greater.
2. Tumor PD-L1 expression level may be associated with the degree of response to pembrolizumab.
3. Although overall survival was improved with pembrolizumab monotherapy, there was no significant difference in progression-free survival in patients treated with pembrolizumab compared to standard chemotherapy.
4. Although there were fewer severe treatment-related adverse events in the patients treated with pembrolizumab compared to chemotherapy, pneumonitis did occur in 8% of patients treated with pembrolizumab.
5. Further study is needed to determine whether there is additional benefit to pembrolizumab plus platinum-based chemotherapy compared to pembrolizumab monotherapy.

OTHER ARTICLES OF INTEREST

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Balekian AA, Wisnivesky JP, Gould MK. **Surgical disparities among patients with Stage I lung cancer in the National Lung Screening Trial.** *Chest*, 2019; 155(1):44-52.

Yarmus L, Akulian J, Wahidi M, Chen A, Steltz J, Solomon SL, Yu D, Maldonado F, Cardenas-Garcia J, Molena D, Lee H, Vachani A, Interventional Pulmonary Outcomes Group (IPOG). **A prospective randomized comparative study of three guided bronchoscopic approaches for investigating pulmonary nodules.** *Chest*, 2020; 157(3):694-701.

Ramalingam SS, Vansteenkiste J, Planchard D, Cho BC, Gray JE, Ohe Y, Zhou C, Reungwetwattana T, Cheng Y, Chewaskulyong B, Shah R, Cobo M, Lee KH, Cheema P, Tiseo M, John T, Lin MC, Imamura F, Kurata T, Todd A, Hodge R, Saggese M, Rukazenzov Y, Soria J-C, for the FLAURA Investigators. **Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC.** *New Engl J Med*, 382(1):41-50.

Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, Statsenko G, Hochmair MJ, Ozguroglu M, J JH, Voitko O, Poltoratskiy A, Ponce S, Verderame F, Havel L, Bondarenko I, Kazarnowcz A, Losonczy G, Conev NV, Armstrong J, Byrne N, Shire N, Jiang H, Golman JW, for the CASPIAN investigators. **Durvalumab plus platinum-etoposide versus platinum-etoposide in the first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomized, controlled, open-label, phase 3 trial.** *Lancet*, 2019; 394:1929-1939.

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RARE LUNG DISEASE

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ALPHA-1 ANTITRYPSIN DEFICIENCY

Campos MA, Geraghty P, Holt G, et al. The Biological Effects of Double-Dose Alpha-1 Antitrypsin Augmentation Therapy. A Pilot Clinical Trial. *Am J Respir Crit Care Med.* 2019 Aug 1; 200(3): 318–326.

Summary

Alpha-1 antitrypsin deficiency (AATD) is an autosomal codominant condition characterized by low circulating levels of alpha-1 antitrypsin (AAT) protein. This results in unopposed activity of proteases, including neutrophils elastase, resulting in loss of lung parenchyma and emphysema. Intravenous replacement therapy is the only current specific treatment for AATD, and the recommended dose is 60mg/kg per week, based on data to achieve levels above a putative protective threshold of 11 μ M. Data from clinical trials of AAT augmentation have been underwhelming, while showing benefits in lung tissue density, the effect on exacerbations, symptoms and quality of life has not been demonstrated.

This pilot study was a prospective, open-label trial to evaluate the biological effects of 1 month of double-dose (DD) AAT therapy (120mg/kg per week) in 10 patients previously receiving standard dose (SD) therapy. Following an observation period of 4 weeks, DD AAT was administered for 4 weeks, and then SD as recommended. DD AAT restored serum AAT trough levels to the normal range increasing from 16.7 \pm 2.3 μ M to 27.2 \pm 5.0 μ M. DD therapy was associated with reduced NE activity in the BALF, reduced inflammatory cytokines and decreased elastin degradation products. DD augmentation was safe and well tolerated.

Comments

1. The putative protective threshold of AAT at 1 μ M may require reevaluation as this may be why numerous clinical trials of AAT augmentation therapy have failed to show a clinically meaningful benefit.
2. This pilot study is a proof of concept that double dose AAT augmentation can achieve “normal” AAT levels and further improve antielastase activity in the lung
3. This study was underpowered to demonstrate any clinical outcome data; hence a larger randomized study may be required
4. In this study there was surprisingly some biological carryover of the effect of double dose therapy as demonstrated by

maintained improvement in certain inflammatory cytokines even after return to single dosing regimen.

PULMONARY ALVEOLAR PROTEINOSIS

Tazawa R, Ueda T, Abe M, et al. Inhaled GM-CSF for Pulmonary Alveolar Proteinosis. *N Engl J Med.* 2019;381(10):923–932

Summary

Pulmonary alveolar proteinosis (PAP) is a rare syndrome characterized by abnormal alveolar surfactant accumulation and hypoxic respiratory insufficiency that occurs in a group of heterogeneous diseases. Autoimmune PAP caused by anti-GM-CSF antibodies accounts for approximately 90% of all cases of PAP syndrome. The current standard therapy for autoimmune PAP is whole-lung lavage a moderately invasive procedure performed under general anaesthesia that is not widely available. Initial descriptions of open label studies of aerosolized GM-CSF therapy were promising, and the therapy was well tolerated. This randomized, double blind study of inhaled GM-CSF therapy was conducted in 64 mild to moderate autoimmune PAP patients in Japan. Mild to moderate disease was defined as a PaO₂ of less than 75mmHg but greater than 50mmHg. Trial participants received either recombinant human GM-CSF (sargramostim, produced in yeast) at a dose of 125 μ g nebulized twice daily for 7 days every alternate week or placebo for a total of 24 weeks. A statistically significant reduction in A-aDO₂ was noted in the treatment arm compared to placebo (–4.50 \pm 9.03 mmHg vs 0.17 \pm 10.50 mmHg; p=0.02) and improvements in CT lung densitometry scores, reflecting a reduction in surfactant accumulation, were also reported. However, there were no significant clinical, or patient reported benefits noted in this trial.

Comments

1. Autoimmune PAP accounts for approximately 90% of PAP syndrome and can be diagnosed with high sensitivity and specificity by checking levels of serum anti-GM-CSF antibodies. Inhaled GM-CSF therapy remains an appealing therapeutic possibility.
2. It remains unclear whether the dose of inhaled GM-CSF should be higher or if continuous dosing is better than alternate week dosing. A subgroup of autoimmune PAP

- patients do not respond to inhaled GM-CSF and may do so after whole lung lavage removes the excess sediment.
3. This trial demonstrated an improvement in Aa-DO₂ which is encouraging but failed to show any clinical impact. This may be due to a short treatment period.
 4. This study showed a minimal effect of therapy in smokers, indicating that inhaled GM-CSF may not be viable in current smokers with autoimmune PAP.
 5. This study indicates that DLCO and KL-6 may be useful biomarkers of therapeutic response in AaDO₂

LYMPHANGIOLEIOMYOMATOSIS

Gupta N, Lee HS, Ryu JH, et al. **The NHLBI LAM Registry: Prognostic Physiologic and Radiologic Biomarkers Emerge From a 15-Year Prospective Longitudinal Analysis.** *Chest.* 2019;155(2):288-296.

Gupta N, Lee HS, Young LR, et al. **Analysis of the MILES cohort reveals determinants of disease progression and treatment response in lymphangioleiomyomatosis.** *Eur Respir J.* 2019;53(4):1802066.

Summary

Lymphangioleiomyomatosis (LAM) is a rare, female-predominant, low-grade, metastasizing neoplasm characterized by infiltration of lung parenchyma with “LAM cells” resulting in diffuse cystic changes. Until recently the natural history of LAM has been poorly understood, and with proven beneficial therapy available it is increasingly important to understand disease progression and to identify prognostic indicators. In these two studies the groups have utilised two separate large well characterized cohorts of LAM patients to determine clinically relevant biomarkers. In the first study, data from the NHLBI LAM Registry was analysed, which included information on 217 of 246 patients enrolled between 1998 and 2001. Demographic and clinical indices were analysed and deaths or transplantations were determined from the National Death Index and the United Network for Organ Sharing databases. The average FEV₁ decline was 89mL/year, and post-menopausal participants had slower rate of decline. Interestingly, a positive bronchodilator response correlated with more rapid lung function deterioration. Favourable prognostic characteristics included postmenopausal status, higher baseline FEV₁ and higher DLCO; all independently associated with lower risk of death or need for lung transplantation. The second study analysed data for 89 women who partook in the MILES trial. Similarly, pre-menopausal women demonstrated more rapid FEV₁ decline, but there was no difference between those with or without a bronchodilator response. A serum VEGF-D level of >600pg/mL were more likely to progress and responded better to sirolimus therapy.

Comments

1. The NHLBI cohort of LAM patients, enrolled a large number of women with a broad spectrum of severity prior to therapy with

- mTOR inhibitors, and outcome data for 20 years indicates several prognostic indicators than can now inform current practice.
2. Both studies indicate that menopausal status significantly affects the natural progression of LAM, and there is reduced rate of lung function decline post menopause, further supporting the data that female sex steroids are implicated in pathogenesis of LAM.
 3. It remains unclear whether bronchodilator response is a negative predictive factor
 4. VEGF-D levels can be used as both a prognostic biomarker and as a predictor of therapeutic response
 5. Importantly, the survival rate determined from the NHLBI cohort, estimated 5-year, 10-year, 15-year and 20-year transplant-free survival rates as 94%, 85%, 75%, and 64% respectively, this may be even better with mTOR inhibitor therapy.

PRIMARY CILIARY DYSKINESIA

Davis SD, Rosenfeld M, Lee HS, et al. **Primary Ciliary Dyskinesia: Longitudinal Study of Lung Disease by Ultrastructure Defect and Genotype.** *Am J Respir Crit Care Med.* 2019;199(2):190–198.

Summary

Primary ciliary dyskinesia (PCD) is a rare lung disease which occurs secondary to abnormal ciliary structure or function leading to impaired mucociliary clearance resulting in chronic infection of the upper and lower respiratory tract. Recent advances have identified many disease-causing mutations in over 40 different genes. Because of locus heterogeneity and allelic heterogeneity, PCD is a clinically heterogeneous condition. Mutations can result in proteins related to ciliary apparatus assembly, these include defects in inner dynein arm (IDA), outer dynein arm (ODA) central apparatus abnormalities (CA), microtubular disorganization (MTD) and combinations of these defect e.g. IDA/ODA. Cross sectional studies have indicated that pulmonary function and growth indices were worse in IDA/MTD/CA defects compared to ODA or combined ODA/IDA defects. The objective of this prospective, longitudinal, multicentre study was to determine progression of early lung disease in a well characterised paediatric PCD cohort and identify associations between genotype and ultrastructural defects with clinical phenotypes. 137 study participants followed over 5 years were enrolled at seven sites of the NIH-supported Genetic Disorders of Mucociliary Clearance Consortium which employs rigorous, standardised diagnostic criteria, based on hallmark ultrastructure defects and/or genetic testing. No difference was noted in microbial colonisation between defect groups. Participants with IDA/CA/MTD defects had a FEV₁ and growth measures compared to isolated ODA defects and specifically CCDC39 or CCDC40 mutations appeared to have worse lung function.

Comments

1. This study identifies potential genotypes/ultrastructural phenotypes that appear to be associated with more severe disease and this adds important information regarding pathogenesis and disease progression
2. Understanding the longitudinal course of this PCD is essential to further the understanding of both pathogenesis and progression and allow for development of meaningful specific therapy
3. Participants with IDA/CA/MTD defects had worse lung function at enrolment and at all ages compared with those with isolated ODA defects, however growth status did not progressively decline with time in any defect group.
4. A limitation of this study was the lack of data on upper airway disease which may underestimate the role of specific ultrastructural defect on the pathogenic mechanism of upper airway disease.
5. Potentially, CCDC39 and CCDC40 may play a role in the function of innate immune cells activity or motility, or other non-epithelial cells, impacting lung health, and this may explain difference rather than the difference in ciliary motion due to structural defect.

PULMONARY LANGERHANS CELL HISTIOCYTOSIS

Liu H, Osterburg AR, Flury J, et al. **MAPK mutations and cigarette smoke promote the pathogenesis of pulmonary Langerhans cell histiocytosis.** *JCI Insight.* 2020;5(4):132048.

Summary

Pulmonary Langerhans cell histiocytosis (PLCH) is a rare, smoking related, progressive diffuse cystic lung disease characterised by dendritic cell (DC) accumulation. Approximately 50% of PLCH patients harbour somatic BRAF-V600E mutations in cells of the myeloid/monocyte lineage. The pathogenesis of PLCH is poorly understood but has long been thought to be related to smoking induced injury, however the effects of smoking on DC function and accumulation in the lung is unknown. Increasing evidence suggests that PLCH is a neoplastic and inflammatory disease. The rarity of PLCH and lack of robust animal models has limited the understanding of pathogenesis. This study employed a novel mouse model to investigate the mechanisms underlying smoking related recruitment of DCs to the lung and subsequent destructive tissue remodeling. This mouse model of disease that had inducible, CD11c100 specific BRAF-V600E mutations and was exposed to chronic smoke exposure, replicated many features of PLCH including peribronchial/perivascular lesions, cellular nodules, and airspace destruction. Pulmonary infiltrates were more prominent after smoke exposure and smoke-exposed BRAF-V600E mice developed cyst-like structures and had an increased number of DCs in the lung. DCs from BRAF-V600E smoke exposed mice demonstrated increased activation,

cell viability and anti-apoptotic activity. The chemokine CCL20 recruits DCs to the lung during inflammation, and this study demonstrated diffuse CCL20 staining in the lesions of patients with PLCH, similarly CCL20 levels were increased in the BAL of BRAF-V600E mice compared to wild type and further increased by smoke exposure. CCL7 levels were associated with BRAF-V600E mutations independent of smoke exposure and was elevated in PLCH patient BAL.

Comments

1. This study demonstrated that the CD11c-BRAF-V600E mouse model of PLCH is an authentic mimic of the human disease and is useful to understand pathogenesis and potentially develop clinically meaningful biomarkers and therapy.
2. This study confirms that smoking is not just a demographic feature of PLCH but a co-factor that is required for full expression of disease pathogenesis in the context of BRAF-V600E mutated myeloid cells.
3. Cigarette smoke generates a conditioned microenvironment in the lung that promotes the accumulation and retention of BRAF-V600E DCs due to a combination of enhanced cell viability and recruitment but not by enhanced proliferation of DCs.
4. CCL7 is elevated in both the mouse model and in PLCH patients, suggesting that the recruitment of inflammatory cells to PLCH lesions is a secondary event driven by CCL7 secreted from the mutated DCs, and CCL7 may be a potential biomarker in PLCH.
5. This study identifies several potential therapeutic targets including the RAS/MAPK pathway, the CCL7 axis and the CCL20 axis.

BIRT HOGG DUBE SYNDROME

Sattler EC, Syunyaeva Z, Mansmann U, Steinlein OK. **Genetic Risk Factors for Spontaneous Pneumothorax in Birt-Hogg-Dubé Syndrome** [published online ahead of print, 2020 Jan 17]. *Chest.* 2020;S0012-3692(20)30031-3.

Summary

Birt-Hogg-Dubé syndrome (BHDS) is a genetic syndrome, inherited in an autosomal dominant manner. It is characterized by diffuse cystic lung disease, fibrofolliculomas, and an increased risk of renal tumors. BHDS is caused by mutations in the FLCN gene which results in loss of function mutations resulting in a truncated folliculin protein, compromising its tumor suppressive activity. The common pulmonary manifestation is spontaneous pneumothorax, which is then likely to recur. This large cohort study assessed non-environmental risk factors for pneumothorax. Data from 63 unique families in Europe consisting of 197 patients were included, with DNA available for 102. Spontaneous pneumothorax occurred in 43.6% of patients and was recurrent in 58.1% of those, and patients who had

recurrent pneumothorax presented at younger age. Unfortunately, data regarding confounding factors such as cigarette smoking or cyst burden was not available. 39 different FLCN mutations were identified with the most common being c.1285dup/ c.1285dup+c.1285del, c.1300G>C and c.250-2A>G. These showed significant correlation with risk of pneumothorax, with a 37% risk in c.1285dup, 59% for c.1300G>C and 77% for c.250-2A>G. This study identifies two FLCN mutations with an apparent increased risk of pneumothorax in BHDS.

Comment

1. Patients that had only a single spontaneous pneumothorax were significantly older at the time of initial event than those who experienced recurrent pneumothoraces, indicating that age at first pneumothorax may be a valuable prognostic indicator.
2. Female patients presented with first spontaneous pneumothorax at a younger age and was very uncommon after the age of 50.
3. 58% of patients had recurrent pneumothoraces, and 70% of those had at least 3 events, hence consideration of pleurodesis or pleurectomy should be given to any patient with BHDS following first pneumothorax.
4. Risk of recurrent pneumothorax varies considerably between the most common FLCN mutations.
5. Specific mutations in FLCN may lead to discovery of pathogenic mechanism of cyst formation and subsequent pneumothorax risk.

OTHER ARTICLES OF INTEREST

ALPHA 1 ANTITRYPSIN DEFICIENCY

Stolk J, Tov N, Chapman KR, et al. Efficacy and safety of inhaled α 1-antitrypsin in patients with severe α 1-antitrypsin deficiency and frequent exacerbations of COPD. *Eur Respir J*. 2019;54(5):1900673. Published 2019 Nov 21.

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Zhang X, Pham K, Li D, et al. Targeting the site encoded by SERPINA1*E342K for treating alpha-1 antitrypsin deficiency-associated liver diseases. *FEBS Lett*. 2019;593(14):1849–1862.

PULMONARY ALVEOLAR PROTEINOSIS

Arumugam P, Suzuki T, Shima K, et al. Long-Term Safety and Efficacy of Gene-Pulmonary Macrophage Transplantation Therapy of PAP in *Csf2ra*^{-/-} Mice. *Mol Ther*. 2019;27(9):1597–1611.

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Hetzel M, Lopez-Rodriguez E, Mucci A, et al. Effective hematopoietic stem cell-based gene therapy in a murine model of hereditary pulmonary alveolar proteinosis [published online ahead of print, 2019 Jul 9]. *Haematologica*. 2019;haematol.2018.214866.

LYMPHANGIOLEIOMYOMATOSIS

Kim W, Giannikou K, Dreier JR, et al. A genome-wide association study implicates NR2F2 in lymphangioleiomyomatosis pathogenesis. *Eur Respir J*. 2019;53(6):1900329.

Gopalakrishnan V, Yao J, Steagall WK, et al. Use of CT Imaging to Quantify Progression and Response to Treatment in Lymphangioleiomyomatosis. *Chest*. 2019;155(5):962–971.

Walkup LL, Roach DJ, Hall CS, et al. Cyst Ventilation Heterogeneity and Alveolar Airspace Dilation as Early Disease Markers in Lymphangioleiomyomatosis. *Ann Am Thorac Soc*. 2019;16(8):1008–1016.

Lamattina AM, Poli S, Kidambi P, et al. Serum endostatin levels are associated with diffusion capacity and with tuberous sclerosis-associated lymphangioleiomyomatosis. *Orphanet J Rare Dis*. 2019;14(1):72.

LYMPHATIC ANOMALIES/LYMPHANGIOMATOSIS

Ozeki M, Nozawa A, Yasue S, et al. The impact of sirolimus therapy on lesion size, clinical symptoms, and quality of life of patients with lymphatic anomalies. *Orphanet J Rare Dis*. 2019;14(1):141.

Ricci KW, Hammill AM, Mobberley-Schuman P, et al. Efficacy of systemic sirolimus in the treatment of generalized lymphatic anomaly and Gorham-Stout disease. *Pediatr Blood Cancer*. 2019;66(5):e27614.

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HERMANSKY-PUDLAK SYNDROME

Korogi Y, Gotoh S, Ikeo S, et al. In Vitro Disease Modeling of Hermansky-Pudlak Syndrome Type 2 Using Human Induced Pluripotent Stem Cell-Derived Alveolar Organoids. *Stem Cell Reports*. 2019;12(3):431–440.

Summer R, Krishna R, Schriener D, et al. Matrix metalloproteinase activity in the lung is increased in Hermansky-Pudlak syndrome. *Orphanet J Rare Dis*. 2019;14(1):162.

PRIMARY CILIARY DYSKINESIA

Yin W, Livraghi-Butrico A, Sears PR, et al. Mice with a Deletion of *RspH1* Exhibit a Low Level of Mucociliary Clearance and Develop a Primary Ciliary Dyskinesia Phenotype. *Am J Respir Cell Mol Biol*. 2019;61(3):312–321.

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PULMONARY LANGERHANS CELL HISTIOCYTOSIS

Wajda N, Zhu Z, Jandarov R, Dilling DF, Gupta N. Clinical outcomes and survival following lung transplantation in patients with pulmonary Langerhans cell histiocytosis [published online ahead of print, 2019 Aug 12]. *Respirology*. 2019;10.1111/resp.13671.

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BIRT-HOGG-DUBÉ SYNDROME

Liu K, Xu W, Tian X, et al. Genotypic characteristics of Chinese patients with BHD syndrome and functional analysis of FLCN variants. *Orphanet J Rare Dis*. 2019;14(1):223.

van de Beek I, Glykofridis IE, Wolthuis RMF, et al. No evidence for increased prevalence of colorectal carcinoma in 399 Dutch patients with Birt-Hogg-Dubé syndrome. *Br J Cancer*. 2020;122(4):590–594.

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GENERAL CRITICAL CARE

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TARGETED TEMPERATURE MANAGEMENT FOR CARDIAC ARREST WITH NONSHOCKABLE RHYTHM

Lascarrou JB, Merdji H, Le Gouge A, Colin G, Grillet G, Girardie P, Coupez E, Dequin PF, Cariou A, Boulain T, Brule N, Frat JP, Asfar P, Pichon N, Landais M, Plantefevre G, Quenot JP, Chakarian JC, Sirodot M, Legriel S, Letheulle J, Thevenin D, Desachy A, Delahaye A, Botoc V, Vimeux S, Martino F, Giraudeau B, Reignier J, for the CRICS-TRIGGERSEP Group. Targeted Temperature Management for Cardiac Arrest with Nonshockable Rhythm. *N Engl J Med* 2019; 381;2327-2337.

Summary

Although moderate therapeutic hypothermia is recommended to improve neurologic outcomes in adult survivors after out-of-hospital cardiac arrest, the effectiveness of this treatment for patients who had cardiac arrest with non-shockable rhythms (asystole or pulseless electrical activity) is unclear. The HYPERION trial examined whether moderate hypothermia at 33 C, as compared with targeted normothermia at 37 C, would improve survival with a favorable neurologic outcome in patients with coma who had been successfully resuscitated after cardiac arrest with non-shockable rhythms. In this open-label, randomized controlled trial, neurologic outcomes were assessed on day 90 after randomization with the use of the Cerebral Performance Category (CPC) scale (which ranges from 1 to 5, with higher scores indicating greater disability). A total of 584 patients from 25 French ICUs underwent randomization; 581 were included in analyses. On day 90, 29 of 284 patients (10.2%) in the hypothermia group were alive with a favorable neurologic outcome (i.e., CPC score of 1-2), as compared with 17 of 297 (5.7%) in the normothermia group (difference, 4.5 percentage points; 95% confidence interval 0.1-8.9, $p=0.04$). There was no difference in mortality at 90 days (81.5% in hypothermia group vs. 83.2% in normothermia group) or incidence of prespecified adverse events.

Comments

1. In contrast to prior studies, the HYPERION study suggests that moderate hypothermia improves neurologic outcomes

among survivors of cardiac arrest with nonshockable rhythms with a number needed to treat of 22.

2. The primary outcome of CPC score at 90 days was assessed during a semi-structured phone interview by a single psychologist who was blinded to group assignments; because neurologic prognostication tools such as CPC have been shown to have significant interrater variability, the use of a single psychologist to assess neurologic outcomes may introduce bias.
3. The fragility index of the trial was 1, indicating that if a single patient in the cohort had been classified as having had a worse neurologic outcome than documented in the study, the findings would no longer be significant.
4. Because the targeted temperature in the control group was 37, many patients in that study arm had fevers, which may have contributed to the worse outcomes observed.
5. The HYPERION trial supports the superiority of cooling to 33 C over 37 C, but does not provide information about whether 33 C or 36 C is superior; based on this study, it is reasonable to target temperatures between 33 C and 36 C for at least 24 hours (and possibly longer) after cardiac arrest from nonshockable rhythms.

STRESS ULCER PROPHYLAXIS IN MECHANICALLY VENTILATED PATIENTS

PEPTIC Investigators for the Australian and New Zealand Intensive Care Society Clinical Trials Group, Alberta Health Services Critical Care Strategic Clinical Network, and the Irish Critical Care Trials Group, Young PJ, Bagshaw SM, Forbes AB, Nichol AD, Wright SE, Bailey M, Bellomo R, Beasley R, Brickell K, Eastwood GM, Gattas DJ, van Haren F, Litton E, Mackle DM, McArthur CJ, McGuinness SP, Mouncey PR, Navarra L, Opgenorth D, Pilcher D, Saxena MK, Webb SA, Wiley D, Rowan KM. Effect of Stress Ulcer Prophylaxis With Proton Pump Inhibitors vs Histamine-2 Receptor Blockers on In-Hospital Mortality Among ICU Patients Receiving Invasive Mechanical Ventilation: The PEPTIC Randomized Clinical Trial. *JAMA* 2020 Jan 17;323(7):616-626. doi: 10.1001/jama.2019.22190

Summary

Critically ill patients are often prescribed either proton pump inhibitors (PPIs) or histamine-2 receptor blockers (H2RBs) to help prevent the development of stress ulcers

in the upper gastrointestinal tract. However, the relative effect of PPIs vs H2RBs on mortality rates is unknown. The PEPTIC trial was conducted to compare these two approaches for stress ulcer prophylaxis among adults in the ICU requiring mechanical ventilation. The primary aim was to compare the risk of all-cause mortality during index hospitalization up to 90 days. In this cluster crossover randomized trial, 26,982 patients requiring invasive mechanical ventilation within 24 hours of ICU admission were randomized by site at 50 ICUs in 5 countries to either a PPI or H2RB strategy. Investigators found no statistically significant difference in in-hospital mortality among patients treated with PPIs vs H2RBs (18.3% vs 17.5%, risk ratio 1.05 [95% CI 1.00-1.10]; absolute risk difference 0.93 [95% CI -0.01 to 1.88] percentage points; $p = 0.054$). Clinically-important upper gastrointestinal bleeding occurred in 1.3% of the PPI group, compared to 1.8% of the H2RB group (risk ratio 0.73 [95% CI, 0.57 to 0.92]; absolute risk difference, -0.51 [95% CI -0.90 to -0.12] percentage points; $p = 0.009$). Among patients treated at sites randomized to PPIs, 4.1% received H2RBs; among patients treated at sites randomized to H2RBs, 20.1% received PPIs.

Comments

1. The default prescription of either a PPI or H2RB was determined by ICU randomization status, although treating physicians had the option to override the recommended choice and switch the patient to the nonpreferred strategy.
2. There was systematic nonadherence observed with a high rate of PPI use in the H2RB group; this degree of cross over in the use of assigned study treatment likely introduced bias and attenuated the signal of either benefit or harm of the drugs.
3. Even though there was no statistically significant difference in the 90-day in-hospital mortality rate between the two groups, the lower bound of the 95% CI for the risk ratio included 1 (1.00-1.00), suggesting that the PPI strategy may increase mortality.
4. Although there was a small, statistically significant reduction in clinically important gastrointestinal bleeding in the PPI group, there was no difference between treatment group in rates of other secondary outcomes, including *Clostridioides difficile* infection and ICU and hospital lengths of stay.
5. Although the pragmatic trial design used in this study offered several advantages, including increased trial efficiency, facilitation of enrollment of large cohorts (thereby improving generalizability), and the ability to generate evidence relevant to actual practice, the open-label cluster crossover design resulted in incomplete patient-level data, making it difficult to understand the true effects of the specific drugs among mechanically ventilated patients.

END OF LIFE CARE IN THE ICU

Rolnick JA, Ersek M, Wachterman MW, Halpern SD. The Quality of End-of-Life Care among Intensive Care Unit Versus Ward Decedents. *Am J Respir Crit Care Med* 2020 Jan 15[Online ahead of print].

Summary

Treatment in an ICU at the end of life is common and often considered to be a marker of low-quality care. However, for some patients, dying in an ICU may represent goal-concordant care. Rolnick and colleagues sought to better understand how ICU care affects the end-of-life experience for patients dying in the hospital and their families. Specifically, authors evaluated the association between ICU care during terminal hospitalization and family ratings of end-of-life care for patients who died in 106 Veterans Affairs hospitals between 2010-2016. The primary exposure was treatment setting, which was divided into 4 categories: no ICU care, ICU-only care, mixed care (died outside the ICU), and mixed care (died in the ICU). Multivariable linear regression models were adjusted for patient and hospital characteristics; patients receiving mixed care were also analyzed based on percentage of time in the ICU. Among 57,550 decedents, 28,062 (48.8%) had a survey completed by a surrogate. Compared to no ICU care, ICU-only care was associated with more frequent optimal ratings than no ICU care, including overall excellent care (56.6% vs. 48.1%, $p < 0.001$) and care consistent with preferences (78.7% vs. 72.4%, $p < 0.001$). Among patients with mixed care, increasing ICU time was associated with higher ratings on these same measures ($p < 0.001$ for comparisons of those spending $>75\%$ time in ICU vs. $\leq 25\%$ time).

Comments

1. This study suggests that quality of care may be viewed more favorably among family members of patients cared for in ICUs at the end of life, and highlights the need to better understand the mediators of high-quality end-of-life care for hospitalized patients.
2. Confidence in these results is enhanced by the finding that an increasing percentage of time in ICU care was associated with higher ratings across all measures among patients with mixed care.
3. The findings from the study challenge the belief that ICU care at the end of life is "low-quality care," and align with results from a recent study that found physicians at the end of life (who presumably have greater knowledge about death and dying) are more likely to die in an ICU compared to non-physicians (Wunsch et al JAMA Network Open 2019).
4. Approximately half of patients in the study had pain that was not well controlled, which is consistent with prior studies suggesting that there are substantial unmet needs for symptom management at the end of life.
5. Future research should seek to understand what elements of ICU-based care improve the end-of-life experience, so these findings can be extrapolated to other settings.

OTHER ARTICLES OF INTEREST

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LUNG TRANSPLANTATION

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LUNG TRANSPLANT REFERRAL

Ramos KJ, Smith PJ, McKone EF, Pilewski JM, Lucy A, Hempstead SE, Tallarico E, Faro A, Rosenbluth DB, Gray AL, Dunitz JM, and the CF Lung Transplant Referral Guidelines Committee. **Lung Transplant Referral for Individuals with Cystic Fibrosis: Cystic Fibrosis Consensus Guidelines.** *J Cyst Fibros.* 2019; 18(3), 321-333. PMID: PMC6545264

Summary

Compared with other lung diseases, individuals undergoing lung transplantation for Cystic Fibrosis-related lung disease derive the largest improvements in health-related quality of life and survival. The median survival for adults with CF undergoing transplantation is nearly 10 years. Nevertheless, a substantial proportion of individuals with CF die from respiratory failure without having been referred for transplant evaluation. To maximize the chance that every individual with advancing CF-related lung disease can learn about and consider lung transplantation, the Cystic Fibrosis Foundation (CFF) led an effort to develop consensus guidelines for referral. Through integrative meetings of experts in lung transplantation as well as a focus group of transplant recipients with CF and their spouses, 21 recommendations were generated that formed the new Referral Guidelines. Key categories of recommendations include 1) an emphasis for CF clinicians to destigmatize lung transplant by discussing periodically with patients with milder disease 2) obtaining specific testing to screen for risk factors for shortened survival that should trigger transplant referral 3) developing personal relationships between CF clinicians and partnering transplant center clinicians and 4) earlier referral to transplant centers to provide education, destigmatize transplant, and more opportunity to address modifiable barriers.

Comments

1. The CFF guidelines emphasize that CF clinicians should normalize and destigmatize lung transplantation by discussing it as one of several treatment options; these discussions should begin in those with mild lung disease and increase in frequency and detail as an individual's lung disease advances.
2. A key component of destigmatizing lung transplantation is for CF clinicians to use up-to-date CF-specific transplant information (such as 10-year median survival) to promote understanding of the transplant journey and to minimize misconceptions about outcomes

3. The Guidelines note that developing personal relationships between CF clinicians and peer transplant clinicians will optimize communication, facilitate continuity of care, and ensure a shared understanding of the clinical status and trajectory of individuals with CF referred for transplant evaluation.
4. For individuals with CF who are ≥ 18 years, the CF Foundation recommends lung transplant referral no later than when FEV1 is $< 50\%$ predicted and rapidly declining; OR when FEV1 is $< 40\%$ predicted with markers of shortened survival (i.e., 6MWD $< 400\text{m}$, or hypoxemia, or hypercarbia, or evidence of pulmonary hypertension); OR when FEV1 is $< 30\%$ predicted.
5. For individuals with CF who are < 18 years, the CF Foundation recommends lung transplant referral no later than when FEV1 is $< 50\%$ predicted and rapidly declining; OR when FEV1 is $< 50\%$ predicted with markers of shortened survival (i.e., 6MWD $< 400\text{m}$, or hypoxemia, or hypercarbia, or evidence of pulmonary hypertension); OR when FEV1 is $< 40\%$ predicted.

INCREASING THE LUNG TRANSPLANT DONOR POOL

Woolley AE, Singh SK, Goldberg HJ, Mallidi HR, Givertz MM, Mehra MR, Coppolino A, Kuszto AE, Johnson ME, Chen K, Haddad EA, Fanikos J, Harrington DP, Camp PC, Baden LR; DONATE HCV Trial Team. **Heart and Lung Transplants from HCV-Infected Donors to Uninfected Recipients.** *NEJM.* 2019 Apr 25;380(17):1606-1617. PMID: 30946553

Summary

The limited availability of donor lungs leads to an unacceptably waitlist mortality rate. Investigators in this single-center, open-label, pilot clinical trial examined whether hearts or lungs from donors with HCV viremia could be safely transplanted into uninfected adult recipients. The study enrolled adults who were actively listed for either heart or lung transplantation and eligible to receive an organ from a donor with an HCV NAT-positive test. Contemporary transplant recipients who received donor organs from NAT-negative donors formed the comparison group. Patients receiving organs from HCV NAT-positive donors were initiated on a 4-week course of sofosbuvir plus velpatasvir on the day of transplantation. The primary outcomes were sustained virologic response at 12-weeks after completion of antiviral therapy and 6-month graft survival. Forty-four patients (36 lung and 8 heart) underwent transplant from HCV-NAT + donors. No serious adverse effects were identified. 42 of 44 recipients had detectable viral loads immediately after transplant that soon became undetectable; the 35 recipients with

6-month follow-up all had sustained virologic response. HCV-infected recipients had more acute cellular rejection than their comparison group that was not significant after adjusting for confounders.

Comments

1. Approximately 1000 U.S. adults waitlisted for lung or heart transplantation die due to a shortage of available organs; some of these deaths could be avoided if individuals infected with hepatitis C virus could donate organs
2. The investigators used sofosbuvir/velpatasvir, a direct acting anti-viral medication active against all 6 HCV genotypes because HCV-infected donor organs were accepted before their HCV genotypes or viral loads were known.
3. 42 of the 44 transplant recipients had detectable HCV viral loads immediately after transplant which were proportional to the viral load in the donors; these viral loads all became undetectable by approximately two weeks after transplantation and remained undetectable thereafter.
4. This study, combined with similar studies published this year, provides strong rationale to consider transplanting organs from donors infected with HCV into HCV-negative lung transplant candidates provided early delivery of direct-acting pan-genotypic antiviral therapy can be ensured.

ACUTE REJECTION AFTER LUNG TRANSPLANTATION

Levy L, Huszti E, Tikkanen J, Ghany R, Klement W, Ahmed M, Husain S, Fiset PO, Hwang D, Keshavjee S, Singer LG, Juvet S, Martinu T. **The impact of first untreated subclinical minimal acute rejection on risk for chronic lung allograft dysfunction or death after lung transplantation.** *Am J Transplant.* 2020 Jan;20(1):241-249.

Summary

Acute cellular rejection after lung transplantation is common and is one of the most significant risk factors for chronic lung allograft dysfunction (CLAD). Because of its association with CLAD, many transplant programs perform routine allograft surveillance that includes transbronchial biopsy (TBBx) to screen for ACR. With the aim of reducing the risk of CLAD, higher grade ACR is generally treated with high dose corticosteroids, itself a somewhat risky therapy. Considerable uncertainty, however, surrounds whether minimal (A1 on a scale from A0-A4) rejection presenting without symptoms or graft dysfunction (i.e., “stable A1”) warrants treatment. To address this question, this single-center retrospective cohort study analyzed the outcomes of patient-cases who developed stable A1 rejection that was NOT treated in the first post-operative year to matched control patients who did not have episodes of ACR. Stable A1 rejection cases were defined as A1 ACR in the absence of clinical symptoms or decline in lung function (FEV1 drop of 10%). 173 cases were matched 1:2 from 410 controls based on the timing of TBBx relative to date of transplant. In multivariate analysis, stable A1 was not associated with

earlier time to CLAD (HR 1.15, 95%CI: 0.84-1.58) or death (HR 0.80, 95%CI: 0.57-1.12).

Comments

1. Of the one third of lung transplant recipients who have at least one episode of acute cellular rejection in the first post-operative year, a substantial proportion experience minimal (A1) ACR that is not associated with symptoms or clinical evidence of graft dysfunction which is termed “stable A1 rejection” in this manuscript.
2. Prior studies demonstrating a strong association between ACR and risk of CLAD did not distinguish stable A1 rejection from higher grade ACR or A1 rejection that was accompanied by symptoms or evidence of graft dysfunction
3. By carefully curating lung transplant recipients with untreated episodes of stable A1 ACR and time matching them to recipients who did not have ACR, the authors provide the most compelling evidence to date that minimal (A1) ACR not accompanied by evidence of graft dysfunction does not require treatment.
4. Notably, hazard ratio point estimate for time to CLAD of 1.15 and upper bounds of the 95% confidence interval of 1.58 means that this moderate sized study cannot exclude the possibility that stable A1 ACR is a real risk factor for CLAD, a point that the authors acknowledge.

TELOMERE-RELATED PULMONARY FIBROSIS AND LUNG TRANSPLANT OUTCOMES

Swaminathan AC, Neely ML, Frankel CW, et al. **Lung Transplant Outcomes in Patients With Pulmonary Fibrosis With Telomere-Related Gene Variants.** *Chest.* 2019;156(3):477-485.

Summary

The last decade has solidified the role of rare variants in telomere-related genes with resultant telomere shortening as a key contributor to pathogenesis and survival in patients with pulmonary fibrosis. Given the systemic nature of these telomeropathies, concern has arisen on whether gene variants or short telomeres themselves may explain some of the worse outcomes experienced by patients with pulmonary fibrosis undergoing lung transplantation. Until 2019, the literature examining these outcomes had been largely limited to small case series. In this single center cohort study, investigators analyzed whether patients with predominantly sporadic pulmonary fibrosis with rare variants in telomere-related genes were at increased risk for acute rejection, CLAD, and death after transplant. Among 262 pulmonary fibrosis patients who underwent lung transplantation and had whole exome sequencing, 31 (12%) had rare deleterious variants in the telomere-related genes TERT, RTEL1, or PARN. By Kaplan Meier analysis, an estimated 62% of the patients with gene variants developed CLAD by 5 years after transplant compared to only 34% in the rest of the cohort ($p=0.02$; adjusted HR 2.9, 95%CI: 1.4-5.9). Those with

rare variants also had an increased risk of death (adjusted HR 1.8, 95%CI: 1.07-3.08).

Comments

1. Compared to other diagnostic indications such as cystic fibrosis and pulmonary hypertension, patients undergoing lung transplantation generally have worse survival and improvement in HRQL.
2. The 12% prevalence of deleterious variants in telomere-related genes in this cohort of predominantly sporadic PF, rather than familial, undergoing transplantation underscores the importance of heightened focus on telomeres in examining lung transplant outcomes.
3. Patients with the rare variants developed more and earlier onset CLAD and, of those who developed CLAD, there was a trend towards the fibrotic sub-type of CLAD. These data were used to advance a hypothesis that short telomeres may impair cellular response to injury and, through abnormal donor-host interactions, stimulate a remodeling response to injury that results in fibrosis.
4. Since telomere length was not measured, it remains unclear whether the association between rare variants in telomere related genes and CLAD/mortality is mediated through shortened telomeres.

INNATE IMMUNE GENE POLYMORPHISMS AND THE RISK OF INFECTION, CLAD, AND DEATH AFTER LUNG TRANSPLANTATION

Calabrese DR, Wang P, Chong T, et al. Dectin-1 genetic deficiency predicts chronic lung allograft dysfunction and death. *JCI Insight*. 2019;4(22)

Summary

The association between colonization and infection with *Aspergillus* species with chronic lung allograft dysfunction (CLAD) is thought to be mediated through local tissue inflammation and injury with resultant innate immune system activation and allorecognition. Dectin-1 is an innate immune receptor for fungi and bacteria and important in cytokine regulation and CD4 T-cell differentiation. CLEC7A is a common SNP in the dectin-1 gene that results in a premature stop codon and a relative deficiency in Dectin-1. In this paper the authors hypothesized that lung transplant recipients with the CLEC7A polymorphism would have dectin-1 deficiency and would be at increased risk for fungal infection, CLAD, and death. In a deeply characterized single center subgroup, carriers of the CLEC7A polymorphism had decreased dectin-1 mRNA expression, soluble dectin-1 protein in BAL fluid and plasma, and dectin-1 expression on monocytes compared to wild-type recipients. They also had increased risk for viral and fungal infection as well as reduced CLAD-free survival (adjusted HR: 1.8, 95%CI: 1.2-1.8). To analyze the association between CLEC7A polymorphisms and death, a cohort of 1,129 genotyped lung transplant recipients enrolled in the

multicenter Lung Transplant Outcomes Group was also analyzed. In both the single center and LTOG cohorts, carriers of CLEC7A polymorphisms had an increased risk of death (adjusted HR 1.8, 95%CI: 1.1-3.8 and aHR 1.3, 95%CI: 1.1-1.6, respectively).

Comments

1. This paper provides novel insights into how a polymorphism in the dectin-1 gene, present in up to 10% of the general population, increases the risk of developing viral and fungal infections as well as risk of CLAD and death after lung transplantation.
2. The authors suggest that the CLEC7A polymorphism coupled with intense immune suppression may impair innate immune function in lung transplantation and other immunosuppressed populations.
3. A limitation of the clinical outcomes component of this paper was the lack of inclusion of other risk factors for CLAD and death in the statistical modeling.
4. This work provides supportive evidence that pre-transplant genotyping may allow for more tailored antimicrobial prophylaxis and surveillance strategies in the future.

OTHER ARTICLES OF INTEREST

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Glanville AR, Verleden GM, Todd JL, et al. Chronic lung allograft dysfunction: Definition and update of restrictive allograft syndrome-A consensus report from the Pulmonary Council of the ISHLT. *J Heart Lung Transplant*. 2019;38(5):483-492.

Gottlieb J, Neurohr C, Müller-Quernheim J, et al. A randomized trial of everolimus-based quadruple therapy vs standard triple therapy early after lung transplantation. *Am J Transplant*. 2019;19(6):1759-1769.

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COPD

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COPD TREATMENT

Pascoe S, Barnes N, Brusselle G, Compton C, Criner GJ, Dransfield MT, Halpin DMG, Han MLK, Hartley B, Lange P, Lettis S, Lipson DA, Lomas DA, Martinez FJ, Papi A, Roche N, van der Valk RJP, Wise R, Singh D. **Blood Eosinophils and Treatment Response with Triple and Dual Combination Therapy in Chronic Obstructive Pulmonary Disease: Analysis of the IMPACT Trial.** *Lancet Respir Med* 2019; 7:745-66.

Summary

This is a secondary analysis of data collected in the IMPACT Study. IMPACT was a Phase 3, randomized, placebo-controlled, double-blinded investigation of triple (ICS/LAMA/LABA) vs double therapy (ICS/LABA or LAMA/LABA) for the prevention of acute exacerbations of COPD (AECOPD). IMPACT found that triple therapy was superior to double therapy for those above or below a pre-specified threshold of 150 eosinophils per uL peripheral blood. This secondary analysis modeled the eosinophil count as a continuous independent covariable to examine outcomes such as AECOPD, lung function, the Transitional Dyspnoea Index and the SGRQ Total Score. The study investigators found that triple therapy (ICS/LAMA/LABA) or dual combination therapy containing ICS (ICS/LABA) was superior to LAMA/LABA in the prevention of AECOPD. This effect was greater in those with higher peripheral blood eosinophil counts and greater in former than current smokers. The effect of smoking status on the beneficial effect of ICS/LAMA/LABA over LAMA/LABA was observed for all AECOPD as well as severe AECOPD. One potential explanation for these latter findings was that the immunomodulatory effect of smoking on the lung could result in suppression of the associated corticosteroid responsive elements.

Comments

1. The results of IMPACT as well as these secondary analyses strongly suggest that patients with COPD at risk for acute exacerbations of disease who have increased blood eosinophil counts will benefit from the administration of inhaled corticosteroids.
2. Visual inspection of the data presented in these analyses suggest that patients have increasing benefit from the administration of inhaled corticosteroids for eosinophil counts exceeding 200 per uL.
3. Smoking cessation should continue to be a cornerstone of care for patients with COPD as these data objectively

demonstrate the beneficial impact it can have on the reduction of acute respiratory exacerbations.

TREATMENT

Criner GJ, Celli BR, Brightling CE, Agusti A, Papi A, Singh D, Sin DD, Vogelmeier CF, Sciruba FC, Bafadhel M, Backer V, Kato M, Ramirez-Venegas A, Wei YF, Bjermer L, Shih VH, Jison M, O'Quinn S, Makulova N, Newbold P, Goldman M, Martin UJ, for the GALATHEA and TERRANOVA Study Investigators. **Benralizumab for the Prevention of COPD Exacerbations.** *N Engl J Med* 2019; 381:1023-34.

Summary

The data for this publication are an aggregate of two randomized, placebo-controlled, double-blinded investigations, GALATHEA (n=1,120) and TERANOVA (n=1,545) examining the effect of benralizumab on the prevention of AECOPD. Benralizumab is an IL-5 alpha-directed cytolytic monoclonal antibody that induces eosinophil depletion. Study participants were 40-85 years of age, had moderate to very severe COPD with a greater than 10 pack-year tobacco history and must have had 2 moderate or 1 severe AECOPD in the year prior to enrollment despite being treated with dual or triple inhaled therapy. Enrollment was stratified by baseline blood eosinophil count (<220; 220-299, >299 per uL) and participants were randomized into 1 of 4 arms (benralizumab 10mg, 30mg, 100mg, or placebo). The primary outcome was the annualized exacerbation rate in participants with eosinophil counts greater than 220/uL. All doses of benralizumab resulted in marked reduction of blood eosinophil counts to near zero. There was, however, no consistent benefit of such add on therapy (to double or triple inhaled therapy) for the prevention of AECOPD in people with an eosinophil count of at least 220/uL at enrollment. The authors state that further studies may identify a higher dose of benralizumab that is efficacious but given the consistent and marked effects of such therapy on blood eosinophil count, "such a strategy may not be successful".

Comments

1. These data represent two large, well-controlled prospectively enrolled clinical investigations that comprehensively explore the use of benralizumab for the prevention of acute respiratory exacerbations.

2. A possible subgroup analysis of this work could focus on those study participants who were not taking inhaled corticosteroids at the time of enrollment.

Dransfield MT, Voelker H, Bhatt SP, Brenner K, Casaburi R, Come CE, Cooper JAD, Criner GJ, Curtis JL, Han MLK, Hatipoglu U, Helgeson ES, Jain VV, Kalhan R, Kaminsky D, Kaner R, Kunisaki KM, Lambert AA, Lammi MR, Lindberg S, Make BJ, Martinez FJ, McEvoy C, Panos RJ, Reed RM, Scanlon PD, Sciurba FC, Smith A, Sriram PS, Stringer WW, Weingarten JA, Wells JM, Westfall E, Lazarus SC, Connett JE, for the BLOCK COPD Trial Group. **Metoprolol for the Prevention of Acute Exacerbations of COPD.** *N Engl J Med* 2019;381:2304-14.

Summary

Data from several observational studies suggest that beta-blocker therapy is associated with a reduction in the risk for AECOPD even in those people with COPD who do not have a medical indication for such treatment. The data for this publication comes from the BLOCK COPD study. BLOCK was a randomized, placebo-controlled, double-blinded investigation of metoprolol XR (50mg). Participants were 40-85 years of age, had moderate or greater COPD and were at risk for having an AECOPD (had an exacerbation in the year prior to enrollment or were prescribed supplemental oxygen). People were excluded from participation if they had a proven indication for beta-blocker therapy. 532 people were enrolled before the study was stopped by the DSMB. At the time of study termination, there was no evidence of a difference in the risk of COPD exacerbation between the metoprolol and placebo group. Further, metoprolol use was associated with a higher risk of exacerbation leading to hospitalization.

Comments

1. These data do not support the use of beta-blocker therapy in patients with COPD without a proven indication for such treatment and further suggest that the use of metoprolol in these patients may put them at increased risk for more severe respiratory events.
2. This study cohort consisted of participants with moderate or severe COPD and the results cannot be generalized to include people with mild expiratory airflow obstruction or to people with COPD who have another clinical indication for beta-blocker therapy.
3. Because this study was stopped early, the cohort lacked enough subjects to enable additional analyses to determine factors associated with adverse outcomes in people randomized to metoprolol therapy.

Butler CC, Gillespie D, White P, Bates J, Lowe R, Thomas-Jones E, Wootton M, Hood K, Philips R, Melbye H, Llor C, Cals JWL, Naik G, Kirby N, Gal M, Riga E, Francis NA. **C-Reactive Protein Testing to Guide Antibiotic Prescribing for COPD Exacerbations.** *N Engl J Med.* 2019;381:111-20.

Summary

In this study, the investigative team sought to determine if point of care CRP testing may reduce unnecessary use of antibiotics in patients presenting to their physicians with an AECOPD. This was an open-label multicenter randomized controlled trial of patients with a diagnosis of COPD who sought care in 1 of 86 medical practices. 653 patients were randomized, 325 in the CRP-guided group and 324 into usual care. Additional inclusion criteria were age >40 and presentation with a least 1 Anthonisen criteria for an exacerbation (increased dyspnea, increased sputum volume, or increased sputum purulence). The primary outcome of this study was the use of antibiotics and evidence of harm. The CRP guidance provided to clinicians was the following: CRP levels less than 20mg/L – antibiotics unlikely to be beneficial; CRP level 20-40mg/L – antibiotics may be beneficial (primarily if purulent sputum is present); CRP>40mg/L – antibiotics are likely to be beneficial. There was no effect of POC CRP testing on the prescribing pattern for antibiotics if only a single Anthonisen criteria was present. If 2 or 3 criteria were present, POC CRP testing resulted in significant reductions in the use of antibiotics to treat AECOPD. Overall, POC CRP testing resulted in a lower percentage of patients using antibiotics after the initial presentation or during the subsequent 4 weeks of follow up compared to usual care. There was no difference in health care-seeking behavior or metrics of patient well-being at 6 months between those in the POC CRP arm vs usual care.

Comments

1. This investigation collected data on antibiotic prescription as well as actual antibiotic use should people have obtained antibiotics previously or not filled the prescription as advised by their physician.
2. Reductions in antibiotic use attributed to POC CRP testing were not associated with increased short- or longer-term adverse events.

DEFINITION

Bhatt SP, Balte PP, Schwartz JE, Cassano PA, Couper D, Jacobs DR Jr, Kalhan R, O'Connor GT, Yende S, Sanders JL, Umans JG, Dransfield MT, Chaves PH, White WB, Oelsner EC. **Discriminative Accuracy of FEV1:FVC Thresholds for COPD-Related Hospitalization and Mortality.** *JAMA.* 2019; 321:2438-47.

Summary

There is an ongoing debate about the spirometric threshold used to define expiratory airflow obstruction, a fixed ratio of the FEV1 to FVC (i.e. 0.70) or the lower limit of normal (LLN). This team of investigators sought to answer this debate by examining data pooled from 4 general population-based cohorts. The aggregate cohort for this investigation consisted of 24,307 subjects who ranged in age from 45 to 102 years with a follow up of 340,757 person-years. The presence of expiratory airflow

obstruction was defined as either a value less than a fixed threshold (0.65-0.75 tested in 0.01 increments) or a value less than the lower limit of normal as defined by Global Lung Initiative reference equations. The outcome of interest was a composite of COPD hospitalizations and COPD-related mortality. The optimal spirometric threshold to classify obstruction was defined by the best discrimination for events (Harrell C statistic) and compared to a fixed ratio of 0.7 and the LLN. The results of these analyses demonstrated that a fixed threshold of 0.7 provided discrimination of COPD-related hospitalization and mortality in all study participants and optimal discrimination in the subgroup of ever smokers. The authors conclude that a fixed threshold of 0.7 should be used to identify individuals at risk for clinically significant COPD.

Comments

1. This study establishes the FEV1/FVC ratio of < 0.7 as an easy to use diagnostic threshold for clinically significant COPD.
2. In smokers, no thresholds were significantly more accurate than 0.7 in multivariable models or sex-based strata suggesting that this fixed threshold is applicable in all adults.
3. The spirometric data collected for this investigation were obtained without the use of inhaled bronchodilator medications while standard guidelines from groups such as GOLD (Global Initiative for Chronic Obstructive Pulmonary Disease) recommend using post-bronchodilator values.

OTHER ARTICLES OF INTEREST

Paulin LM, Gassett AJ, Alexis NE, Kirwa K, Kanner RE, Peters S, Krishnan JA, Paine R, Dransfield MT, Woodruff PG, Cooper CB, Barr RG, Comellas AP, Pirozzi CS, Han MLK, Hoffman EA, Martinez FJ, Woo H, Peng RD, Fawzy A, Putcha N, Breyse PN, Kaufman JD, Hansel NN, for SPIROMICS Investigators. **Association of Long-term Ambient Ozone Exposure with Respiratory Morbidity in Smokers.** *JAMA Intern Med.* 2020;180(1):106-115.

Wang M, Pistenmaa CA, Madrigano J, Hoffman EA, Angelini E, Yang J, Laine A, Vetterli TM, Kinney PL, Sampson PD, Sheppard LE, Szpiro AA, Adar SD, Kirwa K, Smith B, Lederer DJ, Diez-Roux AV, Vedal S, Kaufman JD, Barr RG. **Association Between Long-term Exposure to Ambient Air Pollution and Change in Quantitatively Assessed Emphysema and Lung Function.** *JAMA.* 2019;322:546-56.

Celli BR, Wedzicha JA. **Update on Clinical Aspects of Chronic Obstructive Pulmonary Disease.** *N Engl J Med* 2019;381:1257-66.

Agusti A, Hogg JC. **Update on the Pathogenesis of Chronic Obstructive Pulmonary Disease.** *N Engl J Med* 2019;381:1248-56.

RESPIRATORY INFECTIONS

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FINDING MEANING IN THE MICROBIOME

Dickson RP, Schultz MJ, van der Poll T, Schouten LR, Falkowski NR, Luth JE, Sjoding MW, Brown CA, Chanderraj R, Huffnagle GB, Bos LDJ. **Lung Microbiota Predict Clinical Outcomes in Critically Ill Patients.** *Am J Respir Crit Care Med* 2020; 201: 555-563.

Summary

Although respiratory infections are the most common infectious cause of death, our understanding of the microbiology of the lung remains relatively poor. Recent advances in diagnostic capabilities have changed our understanding of the lung: previously thought to be a sterile space, the lung is now recognized as a complex ecosystem of microbes, with equally complex relationships to their host and each other. However, the meaning and the causal framework of these discovered ecosystems are yet to be fleshed out. Dickson et al extend their paradigm-shifting work in this area with this study, in which they prospectively evaluated relationships between patterns of the microbiome and clinical outcomes in 91 critically ill patients using droplet digital PCR and ribosomal RNA sequencing. Patients with increased lung bacterial burden had fewer ventilator-free days, and the detection of gut-associated bacteria was also associated with the presence of acute respiratory distress syndrome. Interestingly, these relationships help independently from the presence of a pneumonia diagnosis.

Comments

1. This is the first study to demonstrate relationships between patterns in the lung microbiota and clinical outcomes in critically ill patients.
2. The study supports the hypothesis that the presence of gut bacteria in the lung is associated with acute lung injury.
3. There was a lack of concordance between molecular characterization of the lung and clinical assessment of pneumonia, which raises questions about the meaning of a pneumonia diagnosis.
4. The study did not control for antibiotic exposure and had insufficient numbers of pneumonia-diagnosed patients to contrast patterns for pneumonia.

PRAGMATIC TRIALS AND GLUCOCORTICOIDS

Lloyd M, Karahalios A, Janus E, Skinner EH, Haines T, De Silva A, Lowe S, Shackell M, Ko S, Desmond L, Karunajeewa H, Improving Evidence-Based Treatment Gaps and Outcomes in Community-Acquired Pneumonia

(IMPROVE-GAP) Implementation Team at Western Health. **Effectiveness of a Bundled Intervention Including Adjunctive Corticosteroids on Outcomes of Hospitalized Patients With Community-Acquired Pneumonia: A Stepped-Wedge Randomized Clinical Trial.** *JAMA Intern Med.* 2019.

Summary

This year's ATS/IDSA Clinical Practice Guidelines for Community-acquired Pneumonia acknowledged that most recommendations were supported only by low quality evidence. Only 11 of the 43 recommendations stemming from randomized clinical trials, which can be difficult to generalize to clinical practice due to difficulties including representative patients. One major area of uncertainty is the effectiveness of steroids. Lloyd et al conducted a stepped-wedge randomized clinical trial that compared a bundled intervention that included adjunctive glucocorticoids, routine early mobilization, switching from IV to oral antibiotics, and dietary interventions to usual care. 89% of all patients diagnosed with CAP were successfully enrolled in the study, and the intervention group had high adherence to the treatments. When comparing 416 patients who received the intervention to 401 controls, they found no difference in hospital length of stay, mortality, or readmissions, but did find a higher rate of gastrointestinal bleeding in the intervention group (2% versus 0.7%).

Comments

1. The overall lack of difference in outcomes raises the possibility that there was a combination of benefit and harm.
2. The finding of gastrointestinal bleeding in the intervention group reinforces some concerns about the use of steroids in some patients.
3. The bundled nature of the intervention makes it difficult to draw conclusions about the effectiveness of separate interventions.
4. The pragmatic trial design included more representative patients than traditional approaches, including the elderly and patients with uncertain diagnoses.

ENGINEERED BACTERIOPHAGES

Dedrick RM, Guerrero-Bustamante CA, Garlena RA, Russell DA, Ford K, Harris K, Gilmour KC, Soothill J, Jacobs-Sera D, Schooley RT, Hatfull GF, Spencer H. **Engineered bacteriophages for treatment of a patient with a disseminated drug-resistant Mycobacterium abscessus.** *Nat Med.* 2019; 25: 730-733.

Summary

The emergence of multidrug resistant organisms in both community- and hospital-acquired infections is a major public health threat. Phage therapy – which works by targeting bacteriophages toward specific pathogens -- is a promising new tool for combatting antibiotic resistant infections. Bacteriophages are very selective in the strains of bacteria they are effective against, reducing side effects and risk of resistance; however, the difficulty of finding an effective phage for a particular infection has been a major limitation to their use. In this case report, Dedrick et al report the first therapeutic use of engineered phages, which leverage advances in genome sequencing and computational biology, for the treatment of disseminated *Mycobacterium abscessus* in a 15-year old cystic fibrosis patient with bilateral lung transplant who had failed antimicrobial treatment. The use of engineered bacteriophages allowed the team to rapidly identify and produce a 3-phage cocktail, which was well tolerated by the patient and was associated with clinical improvement.

Comments

1. This was the first therapeutic use of phages for mycobacterial infection in a human patient and the first use of engineered phages.
2. The patient tolerated the treatment well, with only a mild antibody response to phage proteins.
3. The identification and genomic sequencing of 1,800 candidate phages was accomplished through the work of phage-hunting students in the SEA-PHAGES program.
4. Engineered phages will likely continue to be more widely available with future computational advances, bringing us closer to truly personalized antimicrobial therapies.

THE COVID (HOST) RESPONSE

McElvaney OJ, McEvoy N, McElvaney OF, Carroll TP, Murphy MP, Dunlea DM, O'NC, Clarke J, O'Connor E, Hogan G, Ryan D, Sulaiman I, Gunaratnam C, Branagan P, O'Brien ME, Morgan RK, Costello RW, Hurley K, Walsh S, de Barra E, McNally C, McConkey S, Boland F, Galvin S, Kiernan F, O'Rourke J, Dwyer R, Power M, Geoghegan P, Larkin C, O'Leary RA, Freeman J, Gaffney A, Marsh B, Curley GF, McElvaney NG. **Characterization of the Inflammatory Response to Severe COVID-19 Illness.** *Am J Respir Crit Care Med* 2020.

Summary

The clinical consequences of respiratory infection are increasingly recognized as the result of a complex interplay between patient hosts and pathogens. Particularly for a novel respiratory virus such as COVID-19, understanding the role of a patient's immune response is crucial to rapidly establishing effective therapy. In this

study, McElvaney et al took an important first step by contrasting the cytokine profiles between concurrent patients with 1) hospitalized-but-stable COVID-19, 2) ICU-admitted COVID19, 3) ICU-admitted, COVID-negative community-acquired pneumonia, and 4) healthy controls. While pro-inflammatory cytokines IL-1b, IL-6, IL-8, and sTNFR1 were elevated for all groups compared to healthy controls, the cytokine pattern for ICU-admitted with COVID-19 was distinct from that of patients with pneumonia, with a blunted anti-inflammatory responses of anti-IL-10 and AAT and profound increases in the ratios of IL-6:IL-10, IL-1b:IL-10, and IL-6:AAT. This finding suggests that patients with critical illness due to COVID-19 may demonstrate a pattern of altered immunometabolism that could predict outcomes and response to targeted immunomodulatory therapies. Other inflammatory lab values were all similar between ICU-admitted patients with COVID-19 versus severe pneumonia, with the exception of higher lactate dehydrogenase.

Comments

1. This is the first in-depth characterization of the immune profile in patients with COVID-19.
2. The inclusion of concurrent patients with non-COVID-19 community-acquired pneumonia allowed us to place the findings into the context of our previous understanding of the immune response in pneumonia.
3. The number of subjects within each group (15) was small with substantial individual variation, suggesting heterogeneity of the host response that needs further study.
4. The findings support a concept that the immune profile represents a specific immune response in patients with severe disease, but whether this profile is a cause or effect of severe disease is not known.
5. Similar analyses of future patients may need to be conducted to evaluate immune profiles after the introduction of vaccines and herd immunity.

THE DEXAMETHASONE RECOVERY TRIAL

Group RC, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. **Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report.** *N Engl J Med* 2020.

Summary

The swift global rise of the COVID-19 pandemic has demanded rapid knowledge generation and dissemination as we grapple for better understanding and treatment of patients suffering from this new player in respiratory infection. Glucocorticoids are clinically plausible as a potential modulator of the immune response to lung

infection that could mitigate acute lung injury in acute respiratory distress syndrome and have been extensively studied in community-acquire pneumonia, including viral pneumonias such as SARS, Middle East respiratory syndrome (MERS), and severe influenza. Studies have demonstrated disappointingly mixed results, raising the possibility of both benefit and harm. In response to the need for rapid but high-quality evaluation of adjunctive therapies, the RECOVERY collaborative group launched a multi-armed, adaptive, randomized open-label clinical trial designed to compare effects of multiple investigative treatments to usual care in a population of patients admitted to 176 National Health Service hospitals across the United Kingdom. In the dexamethasone arm, investigators randomized 2104 patients to receive dexamethasone compared to 4321 who received usual care. Significant reductions in 28-day mortality with dexamethasone were found among patients undergoing mechanical ventilation (absolute risk reduction 12%) and those receiving oxygen (absolute risk reduction 3%), but no benefit was established among those not receiving oxygen.

Comments

1. Due to the results this trial, guidelines issued by the U.K. and the U.S. National Institutes of Health recommended the use of glucocorticoids in select patients hospitalized with COVID-19 –less than 4 months after the study began.
2. The study was not placebo-controlled, not all data were actively collected, patients were not followed after hospital discharge, and no surrogate endpoints were collected, limiting our full understanding of the mechanism of the findings.
3. The average in the group receiving mechanical ventilation was 59 years, younger than most patients in United States critical care settings.
4. The authors stressed that the benefit of glucocorticoids is likely dependent on the right dose, at the right time, in the right patient.
5. If the mechanism of dexamethasone's treatment benefit is mitigation of the patient's immune response, future populations that are vaccinated or not naïve to SARS-CoV-2 may not experience the same treatment benefit, as host immune responses may change.

THE HOLY GRAIL: VACCINE DEVELOPMENT AGAINST SARS-COV-2

Jackson LA, Anderson EJ, Roupheal NG, Roberts PC, Makhene M, Coler RN, McCullough MP, Chappell JD, Denison MR, Stevens LJ, Pruijssers AJ, McDermott A, Flach B, Doria-Rose NA, Corbett KS, Morabito KM, O'Dell S, Schmidt SD, Swanson PA, 2nd, Padilla M, Mascola JR, Neuzil KM, Bennett H, Sun W, Peters E, Makowski M, Albert J, Cross K, Buchanan W, Pikaart-Tautges R, Ledgerwood JE, Graham BS, Beigel JH. **An mRNA Vaccine against SARS-CoV-2 - Preliminary Report.** *N Engl J Med* 2020.

Summary

The urgent need of a vaccine against SARS-CoV-2 stimulated a rapid global effort of vaccine development. This study reports preliminary results of a phase 1, dose-escalation clinical trial establishing the immunogenicity and tolerability of a mRNA-1273 SARS-CoV-2 vaccine developed by researchers at Kaiser Permanente Washington Health Research Institute. Targeted to produce neutralizing antibodies against the spike protein of SARS-CoV, the vaccine was tested in 45 subjects ages 18-55 who were randomized to 3 different doses. Two administrations of the vaccine 28 days apart generated an immune response in 100% of the subjects, and the vaccine was generally well tolerated, although most participants developed mild systemic symptoms and one patient was excluded after developing vaccine-related urticaria after the first dose. The level of neutralizing antibody production was related to dose, although a moderate dose was sufficient. While seroconversion occurred within 2 weeks after the first vaccine, low levels of neutralizing antibodies were found prior to the second dose, which suggests that a 2-dose vaccination schedule will likely be needed.

Comments

1. The mRNA-1273 SARS-CoV-2 vaccine was developed at warp speed, with the first trial participants only 66 days after the genome of SARS-CoV-2 was sequenced, thanks in part to the scientific community's experience with other viruses of the same family. Vaccines typically take years to develop.
2. The authors reported preliminary results and were not able to assess the durability of the immune response.
3. Phase 3 trial is ongoing, which will evaluate clinical protection against COVID-19 infection in a wider range of patients.

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Sibila O, Laserna E, Shoemark A, Keir HR, Finch S, Rodrigo-Troyano A, Perea L, Lonergan M, Goeminne PC, Chalmers JD. **Airway Bacterial Load and Inhaled Antibiotic Response in Bronchiectasis.** *Am J Respir Crit Care Med* 2019; 200: 33-41.

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Nahid P, Mase SR, Migliori GB, Sotgiu G, Bothamley GH, Brozek JL, Cattamanchi A, Cegielski JP, Chen L, Daley CL, Dalton TL, Duarte R, Fregonese F, Horsburgh CR, Jr., Ahmad Khan F, Kheir F, Lan Z, Lardizabal A, Lauzardo M, Mangan JM, Marks SM, McKenna L, Menzies D, Mitnick CD, Nilsen DM, Parvez F, Peloquin CA, Raftery A, Schaaf HS, Shah NS, Starke JR, Wilson JW, Wortham JM, Chorba T, Seaworth B. **Treatment of Drug-Resistant Tuberculosis. An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline.** *Am J Respir Crit Care Med* 2019; 200: e93-e142.

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Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL. **A pneumonia outbreak associated with a new coronavirus of probable bat origin.** *Nature* 2020; 579: 270-273.

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MECHANICAL VENTILATION

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VENTILATOR STRATEGIES

ICU-ROX Investigators, the Australian and New Zealand Intensive Care Society Clinical Trials Group, Mackle D, Bellomo R, Bailey M, Beasley R, Deane A, Eastwood G, Finfer S et al. **Conservative oxygen therapy during mechanical ventilation in the ICU.** *N Engl J Med* 2020; 382:989-998

Summary

Supplemental oxygen therapy for critically ill patients was considered benign until recent data suggested the harms of liberal oxygen use. In this randomized clinical trial of 1000 mechanically ventilated patients, Mackle and colleagues compared conservative to usual oxygen therapy. All patients had a default lower limit of oxygen saturation of 90% by pulse oximetry (SpO₂). Patients assigned to the conservative oxygen group had an upper SpO₂ alarm of 97%, for which the fraction of inspired oxygen (FiO₂) was decreased to 21% if the SpO₂ remained above 90%. In the usual oxygen group, there were no protocol to limit FiO₂ or SpO₂. There was a good separation of groups as the conservative-oxygen group spent more time at an FiO₂ of 21% (29 versus 1 hour) and less time with an SpO₂ saturation above 96% (27 versus 49 hours) than the usual-oxygen group. However, there was no difference in the primary outcome of 28-day ventilator-free days (21.3 [0-26.3] vs 22.1 [0-26.2] days; p=0.8) or secondary outcome of 180-day mortality (35.7% versus 34.5%). In a pre-specified subgroup analysis, patients with hypoxic-ischemic encephalopathy more ventilator free days (21.1 versus 0 days), improved 180-day mortality (43% versus 59%) and less functional impairment (55% vs 68%) in the conservative-oxygen group.

Comments

1. In this multicenter randomized study, there was no difference in ventilator free days, 180-day mortality, or cognitive outcomes between mechanically ventilated patients assigned to the conservative or usual-oxygen therapy groups.
2. These findings are in contrast to a preliminary study demonstrating a survival benefit with conservative oxygen use which may be explained by the difference in oxygen targets in the control group, as saturations above 96% were targeted and premature stoppage of the preliminary study likely exaggerated the effect size.

3. Patients in the conservative oxygen group had a lower frequency of severe problems with mobility and personal care with the caveat that about 14% of the follow-up data were missing, which was not accounted for in the statistical analysis.
4. The heterogeneity of treatment effect of conservative oxygen therapy improving outcomes in patients with suspected hypoxic-ischemic encephalopathy aligns with prior literature which suggests that hyperoxemia in this context is harmful.
5. These interesting results suggest that although conservative oxygen therapy has no additional advantage over standard oxygen therapy, there may be benefits in those vulnerable to hyperoxia which warrants further investigation.

Writing Committee for the PROBESE Collaborative Group of the PROtective VEntilation Network (PROVENet) for the Clinical Trial Network of the European Society of Anaesthesiology. **Effect of intraoperative high positive end-expiratory pressure (PEEP) with recruitment maneuvers vs low PEEP on postoperative pulmonary complications in obese patients: a randomized clinical trial.** *JAMA.* 2019;321(23):2292–305.

Summary

Obese patients are at high risk for postoperative pulmonary complications (PPC) but the benefits of intraoperative positive end-expiratory pressure (PEEP) remain unclear. In this randomized clinical trial, 2013 obese patients (body mass index >35) at moderate to high risk of PPC undergoing surgery with general anesthesia were randomized to receive high or low levels PEEP while on volume-controlled ventilation with a tidal volume of 7mL/kg of ideal body weight (IBW). The high PEEP group received a PEEP level of 12cm H₂O with alveolar recruitment maneuvers that consisted of increasing tidal volume by 4mL/kg of IBW until the plateau pressure reached 40-50cm H₂O, after which three breaths were given and the tidal volume was set back to baseline. The low PEEP group had a PEEP level of 4cm H₂O. Oxygen supplementation was titrated to maintain a peripheral oxygen saturation of >92% for all patients. The primary outcome was the incidence of PPC within a 5-day postoperative period. There was no difference in the incidence of PPCs between groups (high PEEP 21.3 vs low PEEP 23.6%; p=0.23). Hypoxemia was more common in the low PEEP group and hypotension and bradycardia were more common in the high PEEP group.

Comments

1. Intraoperative high PEEP with recruitment maneuvers did not improve the incidence of postoperative pulmonary complications (PPC) as compared with a low PEEP strategy.
2. Interestingly, the lack of benefit of high PEEP intraoperatively in obese patients was similar to results of a previous clinical trial performed in non-obese adults.
3. The proportion of patients at high risk for PPC was only 16%, which led to a lower rate of PPC than the expected 40% requiring an adjustment of the power calculation and possibly contributed type II error.
4. A standard high PEEP is a “one size fits all” approach to PEEP titration which may be beneficial to some but harmful to others suggesting that an individualized approach to PEEP titration tailored to physiologic parameters may have been more successful.
5. The stepwise titration of tidal volume during the recruitment maneuver may have led to overdistension and increase in driving pressure in the high PEEP group.

SEDATION STRATEGIES

Shehabi Y, Howe BD, Bellomo R, Arabi Y, et al. **Early sedation with dexmedetomidine in critically ill patients.** *N Engl J Med.* 2019;380(26):2506–17.

Summary

Choosing the best sedative for mechanically ventilated patients has been an evolving target. In an open-label randomized clinical trial, 4000 mechanically ventilated patients were assigned to receive dexmedetomidine as the sole primary sedative or usual care (with propofol or benzodiazepines) within 12 hours of mechanical ventilation. Sedation was targeted to lightly sedated to restless stage corresponding to a Richmond Agitation and Sedation Scale of -2 to +1. The primary outcome was 90-day mortality. Unfortunately, over half of the patients were deemed by the treating physician to require deep sedation for the first two days of the study, resulting in 75% of the patients in the dexmedetomidine group receiving supplemental sedation, most commonly with propofol. The usual care group was sedated with propofol most commonly (60%), followed by midazolam (11.9%), or both (20%). There was no difference in 90-day mortality with early use of dexmedetomidine. Bradycardia and hypotension were more common in the dexmedetomidine group. Patients in the dexmedetomidine group had one more ventilator free day and coma/delirium free day than the usual care group. There was a heterogeneity of treatment effect on mortality as patients who were younger than the median age of 63.7 years demonstrated higher mortality with dexmedetomidine.

Comments

1. This study demonstrated no difference in 90-day mortality in mechanically ventilated patients with the use of early dexmedetomidine in comparison to usual care in mechanically ventilated patients.
2. However, the additional sedative use in the dexmedetomidine group and deep sedation in both groups prevented

- differentiation of the sedation strategies to identify any meaningful clinical differences between each approach.
3. Given that other best practices in ICU management such as daily interruption of sedation or combining trials of awakening with spontaneous breathing were not mandated, it is unclear if sedative choice would have additional impact on clinical outcomes without this foundational standard of care.
 4. Although there was a heterogeneity of treatment effect suggesting increased mortality with early dexmedetomidine in younger patients, it remains unclear if early dexmedetomidine is the sole driver of this risk or rather the combined use of other sedatives with dexmedetomidine.
 5. This clinical trial highlights the challenges of behavioral change as deep sedation was employed in the absence of clear indications such as paralysis or status epilepticus.

LIBERATION FROM MECHANICAL VENTILATION

Subira C, Hernandez G, Vazquez A, Rodriguez-Garcia R, et al. **Effect of Pressure Support vs T-Piece Ventilation Strategies During Spontaneous Breathing Trials on Successful Extubation Among Patients Receiving Mechanical Ventilation: A Randomized Clinical Trial.** *JAMA.* 2019;321(22):2175–2182.

Summary

The best approach for performing spontaneous breathing trials (SBT) has been the subject of much debate. Subira and colleagues conducted a randomized clinical trial of 1153 mechanically ventilated patients comparing two strategies for the initial SBT: a “more demanding” two-hour T-piece trial and a “less demanding” 30-minute pressure support ventilation (PSV) trial with 8 cm H₂O of inspiratory pressure and 0 cm H₂O of positive end expiratory pressure. All patients met weaning criteria prior to randomization and thus were liberated if they passed an SBT. The primary outcome was successful extubation defined as remaining off mechanical ventilation for 72 hours after the SBT. Successful extubation was more common in the PSV group (82.3%) in comparison to the T-piece group (74%; p=0.001). There were no differences in reintubation rates, ICU, or hospital length of stay between groups. Patients in the PSV group had improved hospital and 90-day mortality in comparison to the T-piece group.

Comments

1. In this clinical trial, the “less demanding” SBT using a thirty-minute pressure support ventilation trial was associated with more successful extubations and improved hospital and 90-day mortality in comparison to a “more demanding” SBT with a 2-hour T-piece trial.
2. Interestingly, although the work of breathing with T-piece is thought to be similar to spontaneous breathing, it was less well tolerated.
3. Even though the authors were comparing both duration and mode of SBT, each group represents the philosophical approach of clinicians at the bedside with those who are risk averse choosing a more demanding prolonged SBT to minimize the chance of extubation failure versus those who

are accepting of the risk of extubation failure to minimize the chance unnecessarily prolonged mechanical ventilation.

4. The authors did not standardize the post-extubation ventilation strategy and notably the “less demanding” SBT group were more likely to receive prophylactic noninvasive ventilation or high flow nasal cannula, which may in part explain the improved extubation success rates.
5. It remains unclear what mode of SBT is associated with extubation success in a higher risk population of patients who failed an initial SBT.

LONG-TERM OUTCOMES WITH MECHANICAL VENTILATION

Jubran A, Grant BJB, Duffner LA, Collins EG, Lanuza DM, Hoffman LA, Tobin MJ. Long-Term Outcome after Prolonged Mechanical Ventilation: A Long-Term Acute-Care Hospital Study. *Am J Resp Crit Care* 2019; Jun 15;199(12):1508-1516.

Summary

Preliminary observational data suggest that survivors of prolonged mechanical ventilation have poor long-term survival and functional outcomes. In this prospective, longitudinal study of 315 patients being weaned from mechanical ventilation at a long-term acute care hospital (LTACH), Jubran and colleagues sought to investigate the effects of prolonged mechanical ventilation on survival, muscle weakness, and quality of life at 6 months and a year after discharge. Patients were also enrolled in a clinical trial comparing weaning methods in LTACH patients. Over half of the patients (53.7%) were able to liberate from the ventilator and two-thirds of the patients (66.9%) were alive at one-year. In terms of muscle function, handgrip strength and respiratory muscle strength improved from discharge to six months. The proportion of patients needing assistance with activities of daily living fell from 95.6% to 26% at one year. At 12 months, quality of life scores in the physical and mental domains returned to pre-critical illness values. When survivors were asked if they would go through the process of mechanical ventilation again, 84.7% indicated that they would. Sensitivity analyses accounting for missing values, death as a competing risk, and confounding due to randomization to a specific weaning method, yielded similar results.

Comments

1. This study suggests that the long-term outcomes of patients on prolonged mechanical ventilation requiring long-term acute care hospitalization are favorable especially if patients are able to successfully detach from the ventilator.
2. Forty percent of the strength assessments after LTACH discharge were not completed and may affect the reliability of the reported findings.
3. All patients were enrolled in a clinical trial of ventilator weaning strategies in prolonged mechanical ventilation which likely

affected the high successful liberation rates and as such may represent the “best case scenario” for long-term outcomes.

4. The use of surrogates for assessment of pre-illness quality of life and physical function scores may have overestimated the baseline degree of functional dependence.
 5. These data can inform expectant guidance for patients and their families and emphasizes that successful detachment from the ventilator is crucial to the long-term survival and recovery of patients with prolonged mechanical ventilation.
- Garroute-Orgeas M, Flahault C, Vinatier I, Rigaud J-P, et al. Effect of an ICU Diary on Posttraumatic Stress Disorder Symptoms Among Patients Receiving Mechanical Ventilation: A Randomized Clinical Trial. *JAMA*. 2019;322(3):229-239.

Summary

Survivors of critical illness often suffer from psychological sequelae characterized by posttraumatic stress, anxiety, and depression possibly due to poor recollection of the intensive care unit (ICU) stay. In a multicenter randomized clinical trial, 657 mechanically ventilated patients and their families were randomized to use an ICU diary detailing the events of their care or usual ICU care without a diary. The primary outcome was the presence of posttraumatic stress disorder (PTSD) symptoms in patients at 3 months. Follow-up at three months was completed in 51.6% of the patients and 85.6% of their family members. There was no difference in the PTSD symptoms in patients between the intervention and control groups at 3 months. There was also no difference in secondary outcomes including depression/anxiety in patients and family members, or PTSD in family members. Patients only read their ICU diary a median of three times. A content analysis of the ICU diaries revealed that a third of the randomly sampled diaries were unreadable and the majority of the meaningful entries were written by family members.

Comments

1. Poor implementation of the ICU diary program may have contributed to the lack of clinical benefit as most of the participating ICUs had no prior experience with ICU diaries and consequently a third of the randomly sampled diaries were unreadable and had limited contribution from the physician.
2. Only half of the patients completed the 3-month follow-up, which may have contributed to type II error.
3. Interestingly, the rates of PTSD symptoms and anxiety were much more common in the family members than in patients highlighting the need for family/caregiver directed interventions.
4. Given that baseline psychopathology increases the risk of PTSD in critical illness survivors, it is unknown if both groups had the same proportion of baseline psychiatric disease and may represent an unmeasured confounder.
5. Finally, the lack of standardization of sedation practices such as daily interruption, which was shown to reduce the PTSD symptoms adds further uncertainty to this finding.

OTHER ARTICLES OF INTEREST

LIBERATION FROM MECHANICAL VENTILATION

Dres M, Younes M, Rittayamai N, Kendzerska T, et al. **Sleep and Pathological wakefulness at time of liberation from mechanical ventilation.** *Am J Respir Crit Care Med* . 2019 May 1;199(9):1106-1115.

Vivier E, Muller M, Putegnat JB, Steyer J, et al. **Inability of diaphragm ultrasound to predict extubation failure.** *Chest*. 2019 Jun;155(6):1131-1139.

COMPLICATIONS OF MECHANICAL VENTILATION

Shinn JR, Kimura KS, Campbell BR, Lowery AS, et al. **Incidence and outcomes of acute laryngeal injury after prolonged mechanical ventilation.** *Crit Care Med* 2019; 47:1699–1706.

Hamilton M, Tomlinson G, Chu L, Robles P, et al. **Determinants of depressive symptoms at 1 year following ICU discharge in survivors of >7days of mechanical ventilation: Results from the RECOVER Program, a secondary analysis of a prospective multicenter cohort study.** *Chest* 2019; 156(3):466-476

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